Clinical Study Protocol

AN OPEN-LABEL SINGLE-ARM STUDY OF DUPILUMAB IN ADOLESCENT AND ADULT SKIN OF COLOR PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	REGN668 (dupilumab)
Study Name:	DISCOVER – Dupilumab In Skin of Color: Open-label moderate-to-seVere Eczema tRial
Clinical Phase:	4
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Amendment 2 Date of Issue	*See appended electronic signature page*
Amendment 1 Date of Issue:	14 Mar 2024
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AMENDMENT HISTORY

Amendment 2

The purpose of this protocol amendment is to add language stating that a data snapshot and/or interim analysis may occur.

Description of Change	Brief Rationale	Section # and Name
Language has been added stating that a data snapshot and/or interim analysis may be performed.	This change has been made to allow for interim data to be analyzed and presented.	Section 6.2 Planned Interim Analysis

Amendment 1

The purpose of this protocol amendment is to delete the requirement for similar proportions of Fitzpatrick skin types (4, 5, and 6) to be enrolled. In addition, the nomenclature of the analysis set names was corrected to remove references to "registry".

Description of Change	Brief Rationale	Section # and Name
Deletion of requirement for similar proportions of Fitzpatrick skin types (4, 5, and 6) to be enrolled	At the time of this amendment, too few participants of type 6 have been enrolled relative to the current total study population, such that it is no longer possible to achieve similar proportions across the skin types.	Clinical Study Protocol Synopsis: Target Population Clinical Study Protocol Synopsis: Statistical Plan Section 7.2 Study Population Section 11.2 Justification of Sample Size
Remove 'registry' from analysis set names, and the registry evaluation analysis set, together with references to effectiveness	Registry was included in error: this is not a registry study	List of Abbreviations and Definitions of Terms Clinical Study Protocol Synopsis: Statistical Plan Section 9.2 Study Procedures Section 11.3.1 Full Analysis Set Section 11.3.2 Safety Analysis Set Section 11.3.3 Registry Evaluation Analysis Set (deleted)
Update to risk section	Updated to maintain consistency with the main ICF, following updates to the dupilumab safety information	Section 3.3.1.2 Risk
Minor editorial updates	For clarification	Throughout the protocol

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
aOR	Adjusted odds ratio
BSA	Body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CICU	Chronic Inducible Cold Urticaria
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CSU	Chronic Spontaneous Urticaria
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EDC	Electronic data capture
FAS	Full Analysis Set
FBR	Future biomedical research
FDA	US Food and Drug Administration
FST	Fitzpatrick Skin Type
GCP	Good Clinical Practice
GPS	Global Patient Safety
HADS	Hospital Anxiety and Depression Scale
IAF	Informed assent form
ICF	Informed consent form
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	IL-4 receptor alpha subunit
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web responses system

MI	Multiple imputation
NRS	Numerical Rating Scale
OCT	Optical Coherence Tomography
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGID	Patient Global Impression of Disease
PHSS	Post-inflammatory hyperpigmentation severity scale
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PP	Peak Pruritus
PRO	Patient-Reported Outcome
PT	Preferred term
QOL	Quality of life
Q2W	Once every 2 weeks
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
SP NRS	Skin Pain NRS
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	An Open-Label Single-Arm Study of Dupilumab in Adolescent and Adult Skin of Color Patients with Moderate-to-Severe Atopic Dermatitis
Site Locations	This study will be conducted at approximately 30 US sites.
Objectives	**Primary Objective** The primary objective of the study is: • To describe further the efficacy of dupilumab on extent and severity of eczematous lesions in skin of color participants, ≥12 years old, with moderate-to-severe AD **Secondary Objectives** The secondary objectives of the study are: • To describe further the efficacy of dupilumab on pruritus and other AD symptoms in skin of color participants, ≥12 years old, with moderate-to-severe AD • To describe further the efficacy of dupilumab on measures of mental health (anxiety and depression) and quality of life in skin of color participants, ≥12 years old, with moderate-to-severe AD • To describe further the safety of dupilumab administered to skin of color participants, ≥12 years old, with moderate-to-severe AD • To assess dupilumab modulation of type 2 biomarkers in skin of color participants, ≥12 years old, with moderate-to-severe AD • To evaluate further the systemic exposure of dupilumab in skin of color participants, ≥12 years old, with moderate-to-severe AD
Study Design	This is a phase 4 US-only multicenter open-label monotherapy study to describe further the efficacy and safety of dupilumab treatment for 24 weeks, with dosing per United States Prescribing Information (USPI) in adolescent and adult (≥12 years old) skin of color participants with moderate-to-severe AD.
Study Duration	The duration of the study for a participant is approximately 24 weeks, excluding the screening period.
End of Study Definition	The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator).

Population

Sample Size:	Up to 120 participants
Target Population:	The study population includes adolescent and adult participants (≥12 years of age) with skin of color (Fitzpatrick skin type ≥4) and with moderate-to-severe atopic dermatitis (EASI ≥16, IGA ≥3, Pruritus NRS ≥4) that cannot be adequately controlled with topical AD medications. The enrolled population will attempt to approximate the US census bureau data on proportions of self-reported races that comprise the skin of color population in the United States– to this end all self-reported races representing skin of color will be included, however a cap at approximately 40% will be set for non-black / non-African American participants. A participant must meet the following criteria to be eligible for inclusion in the study: 1. Male or female adolescent or adult (≥12 years of age at time of screening visit) 2. Skin of color, defined as Fitzpatrick skin type ≥4 at screening visit 3. Diagnosis of AD according to American Academy of Dermatology consensus criteria at time of screening visit 4. EASI ≥16 at screening and baseline visits 5. IGA score ≥3 at screening and baseline visits 6. ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits 7. Peak Pruritus NRS ≥4 at baseline visit (weekly average over prior 7 days)

Treatments

Study Drug	dupilumab
Dose/Route/Schedule:	Dosed over 24 weeks as per the USPI for AD in adults and adolescents
Background Treatment	Topical emollient (moisturizer)
Dose/Route/Schedule:	Topical emollient (moisturizer) should be applied twice daily, as per physician's recommendation starting at the screening visit. Participants should continue to apply moisturizers throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the day of the study visit. All types of moisturizers will be permitted, but participants should not initiate treatment with prescription moisturizers or moisturizers containing additives (ceramide, hyaluronic acid, urea, filaggrin degradation products, hydrocortisone) during the screening period or during the study. Participants will be permitted to continue using stable doses of such moisturizers if initiated before the screening visit, unless specifically prohibited (eg, hydrocortisone or other topical corticosteroid).

Endpoints

Primary:

Proportion of participants with Eczema Area and Severity Index (EASI)-75 (≥75% reduction from baseline in EASI) at week 24

Secondary:

Secondary Efficacy Endpoints:

- Proportion of participants with Investigator's Global Assessment (IGA) = 0 to 1 at each visit through week 24
- Percent change from baseline in EASI at each visit through week 24
- Absolute change from baseline in EASI at each visit through week 24
- Proportion of participants with EASI-50 (≥50% reduction from baseline in EASI) at each visit through week 24
- Proportion of participants with EASI-75 (≥75% reduction from baseline in EASI) at each visit through week 24
- Proportion of participants with EASI-90 (≥90% reduction from baseline in EASI) at each visit through week 24
- Percent change from baseline in total SCORing AD (SCORAD) and SCORAD component scores at each visit through week 24
- Proportion of participants with SCORAD-50 (≥50% reduction in SCORAD from baseline) at each visit through week 24
- Proportion of participants with improvement (reduction) of weekly average of daily peak Pruritus (PP) NRS ≥3 from baseline at each visit through week 24
- Proportion of participants with improvement (reduction) of weekly average of daily PP NRS ≥4 from baseline at each visit through week 24
- Percent change from baseline in weekly average of daily PP NRS at each visit through week 24
- Absolute change from baseline in weekly average of daily PP NRS at each visit through week 24
- Change from baseline in percent BSA at each visit through week 24
- Change from baseline in health-related quality of life as measured by Dermatology Life Quality Index (DLQI; age ≥16), Children's Dermatology Life Quality Index (CDLQI; age <16) at each visit through week 24
- Change from baseline in Patient Oriented Eczema Measure (POEM) at each visit through week 24
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) at each visit through week 24
- Change from baseline in Skin Pain NRS at each visit through week 24

	• Change from baseline in weekly average Sleep Quality NRS at each visit through week 24 • Proportion of participants with PGID response as No symptoms at each visit through week 24 • Proportion of participants with PGID response as No symptoms or Mild symptoms at each visit through week 24 • Proportion of participants who rate their eczema symptoms in PGIC as "Much better" at each visit through week 24 • Proportion of participants who rate their eczema symptoms in PGIC as "Much better" or "Moderately better" at each visit through week 24 **Safety Endpoint:** • Incidence of non-herpetic skin infection treatment-emergent adverse events (TEAEs) through the last study visit **Biomarkers Endpoint:** • Change and percent change in total and allergen-specific IgEs from baseline to weeks 4, 12 and 24 **Clinical Pharmacology Endpoint:** • Trough concentration of functional dupilumab in serum at various time points through week 24
Procedures and Assessments	**Efficacy assessments** for the primary and secondary endpoints include the following: Patient- Reported Outcome Measures: Peak Pruritus NRS, Sleep Quality NRS, Skin Pain NRS, Dyspigmentation NRS, Xerosis NRS, Children's Dermatology Life Quality Index, Dermatology Life Quality Index, Hospital Anxiety and Depression Scale, POEM, PGID, PGIC Investigator- Reported Outcome Measures: EASI, IGA, SCORing Atopic Dermatitis, Body Surface Area Involvement of Atopic Dermatitis, AD phenotypic description (primary morphologies, and distribution), Post-inflammatory hyperpigmentation severity scale Substudies: Photography (select sites), Colorimetry measurement (select sites), Optical Coherence Tomography (OCT) and additional optional non-invasive in vivo imaging (single site) at AD lesional, hyperpigmentation lesional, and non-lesional targets **Safety procedures and assessments:** adverse event (AE), physical examination, and clinical laboratory testing **Pharmacokinetics (PK)**: Serum samples will be collected at specified time points for assay of dupilumab concentration.

Statistical Plan	**Justification of Sample Size** Due to the descriptive character of this study, no formal sample size calculation will be performed. The sample size of this study is chosen empirically to support descriptive analysis of efficacy and safety in the overall skin of color population. With up to a potential 15% drop out rate based on prior studies, 120 participants would yield 105 participants overall. **Analysis Sets:** ***Full Analysis Set (FAS)*** The full analysis set (FAS) includes all participants who are enrolled in the study and have at least 1 post-baseline efficacy assessment. The FAS is the main analysis population for the study and will be used to summarize baseline characteristics and disposition and to analyze efficacy variables. ***Safety Analysis Set (SAF)*** The safety analysis set (SAF) includes all participants in the FAS who are enrolled and received at least one dose of dupilumab during the study. Treatment compliance and administration, and all safety variables will be analyzed using the SAF. ***Pharmacokinetic Analysis Sets*** The PK analysis population includes all participants who received any study drug and who had at least 1 non-missing result following the first dose of study drug. **Statistical Methods:** All statistical analyses will be descriptive. For continuous variables, descriptive statistics will include the following information: the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

1. INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a pruritic skin condition characterized by a chronic, relapsing form of skin inflammation. The pathophysiology of AD is complex and is influenced by genetic, immunologic, and environmental factors which lead to a dysfunctional skin barrier and dysregulation of the immune system (Bieber, 2008) (Eichenfield, 2014). Altered epidermal barrier function, together with immune changes in the skin, lead to the development of eczematous lesions with erythema, edema, xerosis, erosions/excoriations, oozing/crusting, and lichenification that may vary by patient age, disease chronicity, as well as race and/or ethnicity.

AD usually presents during early infancy or childhood, though it can persist into or start in adulthood (Kay, 1994). The disease affects 15% to 30% of children and 2% to 10% of adults in industrialized countries, but variation related to geographic region and racial and/or ethnic origin has been described (Bieber, 2008). Population-based studies in the US have demonstrated a higher prevalence of AD in African American children (19.3%) than in European American children (16.1%) (Brunner, 2019) (Kaufman, 2018b) (Kaufman, 2018a) with similar disparities observed in Europe (Alexis, 2019) (Williams, 1995). After adjusting for sociodemographic characteristics, compared to non-Hispanic whites, non-Hispanic blacks were more likely to have incident AD (adjusted odds ratio [aOR] 2.71, 95% confidence interval [CI]: 1.75, 4.19) and both non-Hispanic blacks (aOR 6.26, 95% CI: 2.32, 16.88) and Hispanics (aOR 6.42, 95% CI: 1.93, 21.41) with early childhood AD were more likely to have persistent AD (Kim, 2019). Examining AD severity by self-identified racial subgroups has furthermore suggested greater severity among black children compared to white children by common outcome measures assessing AD signs and symptoms (Ben-Gashir, 2002). In particular, pruritus has been found to have a disproportionate impact on black patients (McColl, 2021) (Whang, 2019). A cross sectional study leveraging the National Ambulatory Medical Care Survey (NAMCS) in the US reported that the numbers of per capita visits for AD among black patients and Asian/Pacific Islanders were 2-fold and 6-fold higher, respectively, compared to whites, suggesting a disproportionate impact on healthcare resource utilization (Janumpally, 2002).

The clinical pattern of AD is generally heterogeneous and may additionally vary by racial subgroup. Predominant areas of involvement classically described across adolescents and adults with AD include the flexural folds, such as the posterior neck, and antecubital and popliteal fossae of the upper and lower extremities, respectively, as well as the trunk. Asian patients are observed to present with more sharply demarcated 'psoriasiform' AD lesions with prominent scaling. Patients of African descent are less likely to present with flexural distribution patterns and rather may present with involvement of extensor surfaces or localized disease. Furthermore, in black patients, unique primary lesional morphologies are more frequently reported including follicular AD, lichenoid AD, and papular AD. Black patients are also more likely than white patients to develop prurigo nodularis, a common AD comorbidity (Boozalis, 2018). Certain secondary cutaneous changes including xerosis, lichenification, and dyspigmentation are also more common in populations comprising skin of color (Kaufman, 2018a) (Kaufman, 2018b). Finally, a key difference in the clinical presentation of AD, relevant across skin of color AD phenotypes, relates to the distinct appearance of erythema. Specifically, where erythema is pink or red in fairly complected skin, erythema in darker skin pigmentation may be more subtle, appearing violaceous or grey or hyperpigmented (Kaufman, 2018b). Because erythema is frequently incorporated into

AD scoring systems as a central indicator of inflammatory activity, there is concern that disease severity in skin of color is often underestimated (Ben-Gashir, 2002).

AD has been shown to have a marked impact on the quality of life (QOL) of patients, greater than that seen in other common skin disorders like psoriasis and acne (Lewis-Jones, 1995). Often severe, pruritus is a universal finding in AD and often results in sleep disruption, irritability, and generalized stress for both the affected patients as well as family members (Kim, 2012). In addition to causing discomfort, sleep loss, and psychosocial challenges, AD can impose major financial burdens on families for direct medical care, household accommodations, and missed work (Su, 1997) (Verboom, 2002) (Williams, 2005). In patients with skin of color, xerosis and post-inflammatory pigment alteration are both more common and more apparent on a background of rich pigmentation, thereby adding to the burden of AD for these patients (Alexis, 2021) (Kaufman, 2018b) (Poladian, 2019).

Several studies have suggested that different racial and/or ethnic populations have distinct skin barrier physiology that may relate to heightened genetic susceptibility to AD, leading to observed differences in prevalence, severity, xerosis, and burden of pruritus (Alexis, 2021). For example, black skin may have a thicker and more compact stratum corneum, differences in corneocyte desquamation, decreased ceramide content, variations in transepidermal water loss (TEWL), and larger mast cell granules. However the clinical relevance of these findings has not been established (Alexis, 2019). Moreover, these observations are drawn from small studies, and several assays of barrier function by TEWL have shown conflicting results (Muizzuddin, 2010) (Berardesca, 1998). The skin lesions of AD are characterized by increased expression of proinflammatory Type 2 helper T cell (Th2) cytokines, such as IL-4 and IL-13, and by skin infiltration of Th2 cells. The elevated IgE responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the Th2 cytokines IL-4 and IL-13 (Leung, 1999). Type 2 helper T cell mediated immune response is believed to play a central role in the pathogenesis of AD across racial subgroups; however, distinct molecular signatures relating to innate and adaptive immunity and skin barrier structure/function by race have been described (Nomura, 2020). For example, in Asian patients, high involvement of IL-17 has been found; in contrast, low involvement of IL-17 has been reported in African American/black patients (Chan, 2018) (Noda, 2015) (Sanyal, 2019). Lower rates of filaggrin loss of function mutations are seen in AD patients of African ancestry compared to patients of European ancestry (Margolis, 2012). It has been hypothesized that immune influenced downregulation of barrier genes, including acquired filaggrin deficiency mediated by IL-4 and IL-13 signaling, may in part drive the appearance of AD in the absence of FLG null mutations. Type 2 helper T cell-associated cytokines also regulate the production of antimicrobial proteins and inhibit the production of major terminal differentiation proteins, such as loricrin, filaggrin, involucrin, and the antimicrobial proteins human beta defensin 2 and 3, which in turn, is associated with development of AD (Guttman-Yassky, 2011a) (Guttman-Yassky, 2011b) (Howell 2007). The Th2 cytokines also act on keratinocytes and induce production of chemokines, including chemokine (C-C motif) ligand 17 (also known as thymus and activation-regulated chemokine [TARC]), and chemokine (C-C motif) ligand 26 (also known as eotaxin-3), which are chemo-attractants for Th2 cells and eosinophils; thus, perpetuating the inflammatory response. Since activation of IL-4 and IL-13 signaling precedes the release of proinflammatory mediators, antagonism of these cytokines has the potential to reduce the Th2 response and provide therapeutic benefit.

Dupilumab is a human monoclonal antibody that targets the IL-4 receptor alpha subunit (IL-4Rα), a component of IL-4 receptors Type I and Type II, as well as the IL-13 Type II receptor system. The binding of dupilumab to IL-4Rα results in the blockade of both IL-4 and IL-13 signal transduction. As a biologic product that selectively targets the Th2 inflammatory pathway, dupilumab has shown to be a safe and efficacious option for the treatment of AD in children, adolescents, and adults, with regulatory approvals down to 6 months of age. The development program leading to regulatory approvals in AD consisted of global randomized controlled trials and included patients of diverse racial and ethnic background; however, non-white patients corresponded to less than a quarter or the enrolled with less than 10% representing self-reported black/African American patients. Existing data on the use of dupilumab in self-reported racial and ethnic subgroups comprising skin of color supports efficacy and safety profiles that are consistent with overall studied populations, though sample sizes with dosing per United States Prescribing Information (USPI) are further limited in the minority subgroups (Alexis, 2019). Rigorous prospective characterization of AD presentations in skin of color as well as dupilumab treatment responses in a large number of skin of color patients has not been performed to date.

In summary, the primary purpose of this study is to provide additional data on the use of dupilumab in adolescent and adult skin of color patients with moderate-to-severe AD. AD presents with distinct clinical manifestations in skin of color that may contribute to diagnostic uncertainty and complicate assessment of disease activity and severity (Kaufman, 2018b). Information regarding unique clinical features and mechanisms of disease progression specifically characterizing skin of color AD as well as dupilumab treatment responses will support advancements of AD management in this subpopulation with disproportionate disease burden.

Additional background information on the study drug and development program can be found in the Investigator's Brochure and USPI.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To describe further the efficacy of dupilumab on extent and severity of eczematous lesions in skin of color participants, ≥12 years old, with moderate-to-severe AD

2.2. Secondary Objectives

The secondary objectives of the study are:

- To describe further the efficacy of dupilumab on pruritus and other AD symptoms in skin of color participants, ≥12 years old, with moderate-to-severe AD
- To describe further the efficacy of dupilumab on measures of mental health (anxiety and depression) and QOL in skin of color participants, ≥12 years old, with moderate-to-severe AD
- To describe further the safety of dupilumab administered to skin of color participants, ≥12 years old, with moderate-to-severe AD
- To assess dupilumab modulation of type 2 biomarkers in skin of color participants, ≥12 years old, with moderate-to-severe AD
- To evaluate further the systemic exposure of dupilumab in skin of color participants, ≥12 years old, with moderate-to-severe AD

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To describe and photograph clinical phenotypes of moderate-to-severe AD in skin of color participants, ≥12 years old and associated dupilumab treatment responses
- To assess erythema and pigmentation changes related to moderate-to-severe AD in skin of color participants ≥12 years old through clinical assessments, patient-reported severity and impact, and direct colorimetric measurement in AD lesional, hyperpigmentation lesional, and non-lesional skin
- To assess skin dryness changes in moderate-to-severe AD in skin of color participants, ≥12 years old through clinical assessment of dryness and patient-reported severity and impact
- To assess pre and post dupilumab structural changes in skin of color AD lesional, hyperpigmentation lesional, and non-lesional skin via Optical Coherence Tomography (OCT) with possible additional non-invasive imaging at the discretion of the investigator (including line field confocal OCT and/or reflectance confocal microscopy)
- To study dupilumab mechanism of action (related to efficacy and/or safety), the biology of IL-4R, IL-4, IL-13, and related pathways, AD, and related diseases.

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

In adolescent and adult skin of color participants ≥12 years old with moderate-to-severe AD inadequately responsive to topical therapies, treatment with dupilumab will be associated with clinically relevant improvements in extent and severity of eczematous lesions, pruritus and associated symptoms and will demonstrate acceptable safety in open-label treatment for 24 weeks.

3.2. Rationale

3.2.1. Rationale for Study Design

The primary purpose of this study is to provide additional data on the use of dupilumab in adolescent and adult skin of color participants ≥12 years old with moderate-to-severe AD. Existing data on the use of dupilumab in self-reported racial and ethnic subgroups comprising skin of color support efficacy and safety profiles that are consistent with overall studied AD populations, though sample sizes with dosing per USPI are limited in minority subgroups (Alexis, 2019). Epidemiologic data suggest that AD may be more prevalent, persistent, and severe in skin of color participants even when controlling for geographic and socioeconomic factors (Brunner, 2019) (Kim, 2019). Moreover, AD presents with distinct clinical manifestations in the skin of color population that may contribute to diagnostic uncertainty and complicate assessment of disease activity and severity (Kaufman, 2018b). Information regarding unique clinical features and mechanisms of disease progression specifically characterizing skin of color AD as well as dupilumab treatment responses have not yet been prospectively collected and will support advancements of AD management in this subpopulation with disproportionate disease burden and evidence for undertreatment.

This study was designed with a 24-week treatment duration because this period of time is considered sufficient to assess near maximal extended treatment effects across AD phenotypes in adolescent and adult skin of color participants treated with dupilumab. Additionally, this period of treatment is sufficiently long to observe participants after appropriate steady-state drug concentrations are achieved. Based on pharmacokinetic (PK) simulations, in the absence of a loading dose, the time to steady-state is expected to be 12 weeks for a 200 or 300 mg Q2W regimen, and the use of a loading dose in this study will reduce the time to steady-state for the Q2W regimen, as has been observed previously. Our intent is to continue to observe participants for a period of approximately 16 weeks beyond attaining steady-state drug concentrations. This will ensure capture of treatment effects on subtypes of AD that more commonly appear in skin of color that are reported to be more treatment refractory (ie, nummular AD). Additionally, an extended treatment period is required to describe changes in pigmentation and xerosis related to AD improvement but known to lag in time course.

The primary endpoint in the study (proportion of participants with ≥75% reduction in EASI from baseline [EASI-75]) is the same as those used in the adult and adolescent pivotal studies (R668-AD-1334, R668-AD-1416, and R668-AD-1526). This endpoint is an investigator-assessed outcome measure of objective AD signs, which has been broadly validated in drug development for this indication and is broadly recognized as a clinically meaningful categorical responder

definition of treatment benefit. EASI has been validated in the adult and pediatric population, including in participants aged 12 to 17 years old.

3.2.2. Rationale for Dose Selection

The dose regimen of dupilumab selected for this study is a loading dose of 600 mg administered SC, followed by 300 mg administered SC Q2W for adults and for adolescents weighing ≥60 kg. The dose regimen of dupilumab for adolescents weighing ≥30 to <60 kg is a loading dose of 400 mg administered SC, followed by 200 mg administered SC Q2W. This is the approved posology in adults and adolescents with moderate-to-severe AD. These dose regimens have proven to be effective and have demonstrated an acceptable safety profile in adult and adolescent participants ≥12 years old with moderate-to-severe AD. Prior analyses of mean functional dupilumab trough concentrations by self-reported race support similar drug exposure over 16 weeks of treatment across subgroups.

3.3. Risk-Benefit

3.3.1. Risk-Benefit for Participants in the Study

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

For information regarding the permitted timing of COVID-19 vaccinations, see Section 7.2.2 Exclusion Criteria, criterion #19 and Section 8.9 Concomitant Medications.

3.3.1.1. Benefit

The efficacy and safety of dupilumab in patients with AD has been demonstrated in randomized, double-blind, placebo-controlled trials (R668-AD-1224, R668-AD-1334, and R668-AD-1416) in adults, (R668-AD-1526) in adolescents, and (R668-AD-1539 and R668-AD-1652) in pediatrics (6 months ≤12 years of age). In all studies, dupilumab demonstrated robust and consistent efficacy in completed clinical studies, across a variety of clinical outcomes, reflecting clinically meaningful and statistically significant improvements compared to placebo in AD disease activity outcomes including objective measures of AD signs (eg, IGA, EASI, BSA affected by AD), measures of symptoms (eg, Pruritus NRS), and QOL in adults, adolescents, and pediatrics. These results formed the basis for approval of dupilumab in the treatment of moderate-to-severe AD whose disease in not adequately controlled with topical prescription therapies or when those therapies are not advisable in adults and pediatric patients ages 6 months and older in the US. The efficacy of dupilumab across skin of color populations was supported by the pivotal studies even though the sample sizes were limited and the trials were not powered for significance in subgroups. The clinical benefit of dupilumab treatment in moderate-to-severe AD adolescent and adult skin of color participants will be investigated in this study.

3.3.1.2. Risk

The identified adverse drug reactions (ADR) across all indications are injection site reactions (ISRs), serum sickness-like reaction/serum sickness and anaphylactic reaction.

In the AD clinical studies, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, blepharitis, dry eye, eye pruritus, herpes simplex (primarily mucocutaneous in nature), eosinophilia, and oral herpes were identified ADRs. The eye and herpes related ADRs appear to be predominantly AD indication specific. Conjunctivitis is also considered an ADR for CRSwNP and PN indications. Most events were mild in intensity, transient in nature, and did not necessitate treatment discontinuation.

In the completed AD studies in children aged 6 months to 17 years, the safety profile was consistent with that reported in adults and no new safety concerns were identified. In a study in patients aged 6 -11 years with asthma, Enterobiasis and Eosinophilia were identified as additional ADRs. Angioedema, arthralgia, keratitis, ulcerative keratitis and facial rash have been identified as ADRs in the post-marketing setting.

“Systemic hypersensitivity” and “Conjunctivitis and keratitis related events in AD patients” are considered important identified risks for dupilumab. Eosinophilia associated with clinical symptoms in patients with asthma or CRSwNP and comorbid asthma is an important potential risk, based on cases of eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia reported in asthma clinical trials (as well as in adult patients with comorbid asthma in the CRSwNP development program). These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy. A causal association between dupilumab and these conditions has not been established.

For full details of dupilumab safety information, please refer to the current version of dupilumab Investigator’s Brochure.

3.3.1.3. Risk-Benefit Conclusion

The safety data available to date across multiple indications, in conjunction with the clinical benefit of dupilumab demonstrated in trials in adults, adolescents, and children with AD, support a favorable benefit-risk profile for dupilumab.

Further information on the risks and benefits of dupilumab with respect to the overall development program is provided in the Investigator’s Brochure and USPI.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

- Proportion of participants with EASI-75 (≥75% reduction from baseline in EASI) at week 24

4.1.2. Secondary Endpoints

Secondary Efficacy Endpoints:

- Proportion of participants with Investigator's Global Assessment (IGA) = 0 to 1 at each visit from baseline through week 24
- Percent change from baseline in EASI at each visit through week 24
- Absolute change from baseline in EASI at each visit through week 24
- Proportion of participants with EASI-50 (≥50% reduction from baseline in EASI) at each visit through week 24
- Proportion of participants with EASI-75 (≥75% reduction from baseline in EASI) at each visit through week 24
- Proportion of participants with EASI-90 (≥90% reduction from baseline in EASI) at each visit through week 24
- Percent change from baseline in total SCORing AD (SCORAD) and SCORAD component scores at each visit through week 24
- Proportion of participants with SCORAD-50 (≥50% reduction in SCORAD from baseline) at each visit through week 24
- Proportion of participants with improvement (reduction) of weekly average of daily Peak Pruritus (PP) NRS ≥3 from baseline at each visit through week 24
- Proportion of participants with improvement (reduction) of weekly average of daily PP NRS ≥4 from baseline at each visit through week 24
- Percent change from baseline in weekly average of daily PP NRS at each visit through week 24
- Absolute change from baseline in weekly average of daily PP NRS at each visit through week 24
- Change from baseline in percent BSA at each visit through week 24
- Change from baseline in health-related QOL as measured by Dermatology Life Quality Index (DLQI; age ≥16), Children's Dermatology Life Quality Index (CDLQI; age <16) at each visit through week 24
- Change from baseline in Patient Oriented Eczema Measure (POEM) at each visit through week 24

- Change from baseline in Hospital Anxiety and Depression Scale (HADS) at each visit through week 24
- Change from baseline in Skin Pain NRS (SP NRS) at each visit through week 24
- Change from baseline in weekly average Sleep Quality NRS at each visit through week 24
- Proportion of participants with PGID response as No symptoms at each visit through week 24
- Proportion of participants with PGID response as No symptoms or Mild symptoms at each visit through week 24
- Proportion of participants who rate their eczema symptoms in PGIC as "Much better" at each visit through week 24
- Proportion of participants who rate their eczema symptoms in PGIC as "Much better" or "Moderately better" at each visit through week 24

Safety Endpoint:

- Incidence of non-herpetic skin infection treatment-emergent adverse events (TEAEs) through the last study visit

Biomarkers Endpoint:

- Change and percent change in total and allergen-specific IgEs from baseline to weeks 4, 12 and 24

Clinical Pharmacology Endpoint:

- Trough concentration of functional dupilumab in serum at various time points through week 24

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Proportion of participants with each category of AD phenotypes, including morphological features, at each visit through week 24
  -Localized AD
  -Flexural AD
  -Extensor AD
  -Nummular AD
  -AD with prurigo nodules
  -Follicular AD
  -Papular AD
  -Lichenoid AD
  -Psoriasiform AD
- Change from baseline in post-inflammatory hyperpigmentation severity scale (PHSS) at each visit through week 24

- Change from baseline in patient-reported Dyspigmentation NRS at each visit through week 24
- Change from baseline in patient-reported Xerosis NRS at each visit through week 24
- Change from baseline in SCORAD dryness component at each visit through week 24
- Photography substudy at selected sites; 2D/3D/dermoscopic, at AD lesional, hyperpigmentation lesional, and non-lesional sites, baseline, week 16, and end of treatment
- Colorimetry substudy at selected sites: change from baseline in erythema index and change from baseline in melanin index at AD lesional, non-lesional, and hyperpigmentation lesional skin, at each visit through week 24
- OCT substudy with possible additional non-invasive in vivo imaging including line field confocal OCT and/or reflectance confocal microscopy at a single study site; non-invasive in vivo imaging performed at AD lesional, hyperpigmentation lesional, and non-lesional sites at baseline, week 4, week 16, and week 24

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description of corresponding study procedures, refer to Section 9.2.

5.1. Demographic and Baseline Characteristics

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

Demographic and baseline characteristics will be summarized descriptively.

5.2. Efficacy Variables

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

- Patient-Reported Outcomes:

  NRS for:

  – Peak Pruritus

  – Skin pain

  – Sleep Quality

  – Dyspigmentation

  – Xerosis

  Score of:

  – CDLQI or DLQI

  – HADS

  – POEM

  – PGID

  – PGIC

- Investigator-Reported Outcomes:

  Score of:

  – EASI

  – IGA

  – SCORAD

  – BSA

  – AD phenotypic description (primary morphologies, and distribution) including Localized AD, Flexural AD, Extensor AD, Nummular AD, AD with prurigo nodules, Follicular AD, Papular AD, Lichenoid AD, and Psoriasiform AD

  - PHSS
- Substudies:
  - Photography: Two-dimensional, 3-dimensional (2D, 3D), and dermoscopic photographs of AD lesional, hyperpigmentation lesional, and non-lesional targets (select sites)
  - Colorimetry measurement: colorimetry for melanin index and erythema index at AD lesional, hyperpigmentation lesional, and non-lesional targets (select sites)
  - OCT substudy with possible additional non-invasive in vivo imaging including line field confocal OCT and/or reflectance confocal microscopy at AD lesional, hyperpigmentation lesional, and non-lesional targets (single site)

5.3. Safety Variables

Safety variables include AEs, physical examination findings, body weight and height, and pregnancy test. Participants will be asked to report all AEs experienced from the time of informed consent/assent until their last study visit.

5.4. Pharmacokinetic Variables

The pharmacokinetic variable is the concentration of functional dupilumab at each time point. Samples in this study will be collected using a sparse sampling schedule, eg, only 1 blood sample for drug concentration measurement is collected at any single clinic visit. These sampling time points are specified in Table 1.

5.5. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and biomarker variables include laboratory test results for individual participants of the following: total serum IgE and allergen-specific IgEs.

These biomarkers are believed to be relevant to the pathophysiology of AD, response to treatment (ie, assessment of type 2 inflammation), and baseline predictors of response and dupilumab mechanism of action.

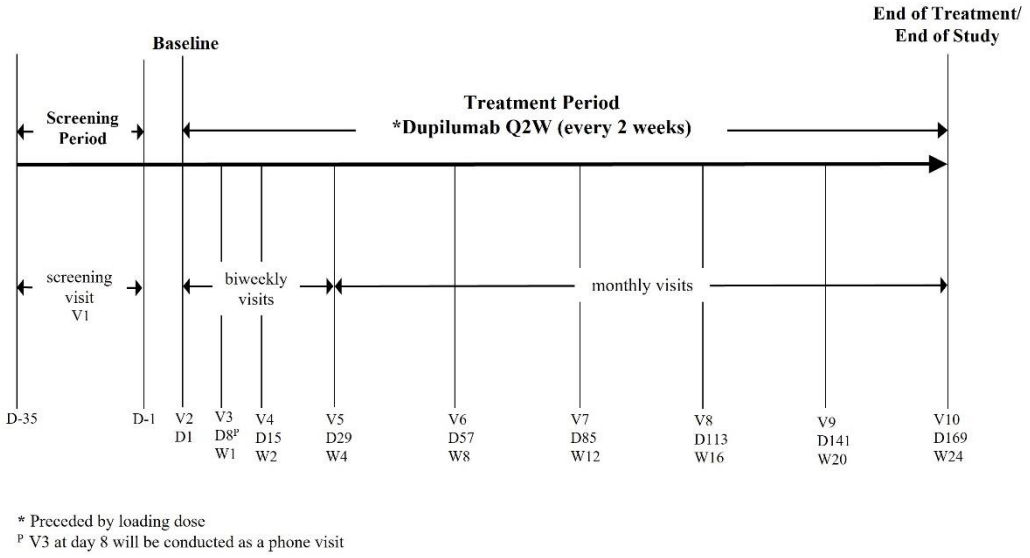
6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 4 US-only multicenter open-label monotherapy study to describe further the efficacy and safety of dupilumab treatment for 24 weeks, with dosing per USPI in adolescent and adult (≥12 years old) skin of color participants with moderate-to-severe AD.

The study flow diagram is provided in Figure 1.

Figure 1: Study Flow Diagram



* Preceded by loading dose
P V3 at day 8 will be conducted as a phone visit

The study will consist of the following 2 periods:

1. Screening of up to 35 days
2. Treatment period of 24 weeks

After adult participants provide informed consent and adolescent participants and/or their legal parents/legal guardians provide informed consent and informed assent (as appropriate), participants will be assessed for study eligibility at the screening visit. During the screening period, topical and systemic treatments for AD will be washed out, as applicable, according to the eligibility requirements. Topical emollient (moisturizer) should be applied twice daily, as per physician's recommendation starting at the screening visit. Participants should continue to apply moisturizers throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the day of the study visit. All types of moisturizers will be permitted, but participants should not initiate treatment with prescription moisturizers or moisturizers containing additives (ceramide, hyaluronic acid, urea, filaggrin degradation products, hydrocortisone) during the screening period or during the study. Participants will be permitted to continue using stable doses of such moisturizers if initiated before the screening visit, unless specifically prohibited (eg, hydrocortisone or other topical corticosteroid).

Participants who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be initiated on Q2W subcutaneous (SC) injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 for adults and adolescents weighing ≥60 kg, and

Q2W SC injections of 200 mg dupilumab following a loading dose of 400 mg on day 1 for adolescents weighing ≥30 to <60 kg. During the treatment period, participants will have a phone visit on week 1 and a clinic visit on week 2 and week 4, followed by monthly clinic visits through the end of treatment. Participants and/or parents/caregivers (as deemed appropriate based on age of participant), will be trained on injecting study drug at visit 2. Safety, laboratory, and clinical assessments will be performed at specified clinic visits, as noted in the Schedule of Events (SoE) Table 1. The end of treatment period visit occurs at week 24, 2 weeks after the last dose of study drug.

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

6.1.1. End of Study Definition

The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

A data snapshot and/or interim analysis may be performed.

A description of the statistical methods to be employed is in Section 11.4.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

7.1. Number of Participants Planned

Up to 120 participants will be enrolled at approximately 30 US sites.

7.2. Study Population

The study population includes adolescent and adult participants (≥12 years of age) with skin of color (Fitzpatrick skin type ≥4) and with moderate-to-severe atopic dermatitis (EASI ≥16, IGA ≥3, Pruritus NRS ≥4) that cannot be adequately controlled with topical AD medications.

The enrolled population will attempt to approximate the US census bureau data on proportions of self-reported races that comprise the skin of color population in the United States. As such, all self-reported races representing skin of color will be included; however a cap at approximately 40% will be set for non-black/non-African American participants.

7.2.1. Inclusion Criteria

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

1. Male or female adolescent or adult (≥12 years of age at time of screening visit)
2. Skin of color, defined as Fitzpatrick skin type ≥4 at screening visit
3. Diagnosis of AD according to American Academy of Dermatology consensus criteria at time of screening visit
4. EASI ≥16 at screening and baseline visits
5. IGA score ≥3 at screening and baseline visits
6. ≥10% BSA of AD involvement at the screening and baseline visits
7. PP NRS ≥4 at baseline visit (weekly average over prior 7 days)

NOTE:

- Baseline PP NRS for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding baseline. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For participants who do not have at least 4 daily scores reported during the 7 days immediately preceding baseline, the baseline visit may be postponed until this requirement is met, but without exceeding the 35-day maximum duration for screening

8. Recent history (within 6 months before screening visit) of inadequate response of atopic dermatitis to topical prescription therapies or those therapies were inadvisable (eg, intolerance, because of important side effects or safety risks)

NOTE:

- Participants who are unable to achieve and/or maintain remission and low disease activity (comparable to IGA 0 = clear to 2 = mild) despite treatment with a daily regimen of medium to higher potency TCS (±TCI as appropriate), applied for at least 28 days of use, or for the maximum duration recommended by the product prescribing information, whichever is shorter, will meet the definition of inadequate response for the purpose of this study.
- Participants with documented systemic treatment for AD in the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with dupilumab after appropriate washout.
- Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the participant's treating physician. If documentation is inadequate, potential participants may be offered a course of treatment with a daily regimen of TCS of medium potency (±TCI as appropriate), applied for at least 28 days during the screening period or for the maximum duration recommended by the product prescribing information, whichever is shorter. Participants who demonstrate inadequate response, as defined above, or develop important side effects (eg, significant skin atrophy, systemic effects) during this period will still be eligible for inclusion in the study.

9. Willing and able to comply with clinic visits and study-related procedures
10. Has applied a stable dose of topical emollient (moisturizer) twice daily as per physician recommendation starting at screening visit (see exclusion criterion 10 regarding restrictions on the kind of emollients permitted during the study)
11. Participant or, in the case of minors, parent/legal guardian must provide signed informed consent and assent (as appropriate). Participants who are minors must also provide separate informed assent to enroll in the study, and sign and date either a separate informed assent form (IAF) or the informed consent form (ICF) signed by the parent/legal guardian (as appropriate based on local regulations and requirements).
12. Able to understand and complete study requirements and study-related procedures and questionnaires

7.2.2. Exclusion Criteria

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

1. Self-reported Caucasian or White race
2. Adolescent body weight less than 30 kg at screening
3. Prior use of dupilumab within 6 months of screening
4. Known hypersensitivity to any of the ingredients in the study drug
5. Concomitant skin diseases that could confound AD assessments
6. Concomitant skin diseases or other pigmentary disorder that, in the investigator's judgment, could confound assessment of dyspigmentation
7. Current or prior use, within 12 weeks before the screening visit, of phototherapy or tanning beds
8. Active helminthic infections; suspected or high risk of helminthic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before baseline
9. At baseline, presence of any conditions listed as criteria for permanent study drug discontinuation
10. Treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) within 7 days prior to baseline
11. Treatment with systemic cyclosporine A, systemic corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, or anti-IL-13 treatments within 4 weeks prior to baseline visit
12. Treatment with biologics as follows:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit, or until lymphocyte count returns to normal, whichever is longer
    - Other immune-modulating biologics: within 5 half-lives (if known) or 16 weeks prior to screening visit, whichever is longer
13. For Janus Kinase (JAK) inhibitors, the following applies;
    - For topical JAK inhibitors: treatment within 2 weeks or within 5 half-lives, whichever is longer, before the baseline visit
    - For systemic JAK inhibitors: within 4 weeks or within 5 half-lives, whichever is longer, before the baseline visit
14. Treatment with a topical investigational drug within 4 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
15. Treatment with a systemic investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to screening
16. Planned or anticipated use of any prohibited medications and procedures

17. Planned or anticipated major surgical procedure during the participant's participation in this study
18. Treatment with live (attenuated) vaccine within 4 weeks before baseline
19. Has received a COVID-19 vaccination within 1 week of planned start of study medication or for which the planned COVID-19 vaccinations would not be completed 1 week prior to start of study drug
20. Acute infection requiring systemic treatment within 1 week before the screening visit

NOTE:

- Participants may be rescreened, but not sooner than 1 week after the infection resolves, and with permission of the sponsor's medical monitor.

21. Any malignancy in the past 3 years, except for non-melanoma skin cancer or cervical/anus in-situ, that has been treated and resolved, with no evidence of recurrence (deemed 'cancer free' currently)
22. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study
23. Presents any concern to the study investigator that might confound the results of the study or poses an additional risk to the subject by their participation in the study
24. Was hospitalized (ie, >24 hours) for any reason within 30 days of the screening visit
25. Any other medical or psychological condition, as well as personal or social circumstances, which in opinion of investigator may present an unreasonable risk to the study participant because of his/her participation in clinical trial, may make participant's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, CRFs, etc)
26. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor
27. Pregnant or breastfeeding women
28. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation (occlusion)
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)

e. and/or sexual abstinence†, ‡.

*Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women who are postmenopausal or permanently sterile (including hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Pregnancy testing and contraception are required for WOCBP.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

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

7.3. Premature Withdrawal from the Study

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

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

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

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

7.4. Replacement of Participants

Participant prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational Treatments

Dosing of dupilumab will be for 24 weeks and in accordance with the USPI. Participants will receive 1 of 2 dose regimens based on age and body weight:

For adults and for adolescents (weighing ≥60 kg): initial dose of 600 mg (2 x 300 mg injections), followed by 300 mg Q2W

Dupilumab drug product is supplied for this dose in the following concentration:

- Dupilumab 150 mg/mL: Each 2.25 mL single-use prefilled syringe with needle shield delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)

For adolescents weighing ≥30 to <60 kg: initial dose of 400 mg (2 x 200 mg injections), followed by 200 mg Q2W

Dupilumab drug product is supplied for this dose in the following concentration:

- Dupilumab 175 mg/mL: Each 1.14 mL single-use prefilled syringe with needle shield delivers 200 mg of study drug (1.14 mL of a 175 mg/mL solution)

Instructions on dose preparation are provided in the pharmacy manual. Subcutaneous (SC) injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and optionally upper arms, so that the same site is not injected for 2 consecutive weeks. To allow for adequate assessment of possible ISRs, study drug should be administered only into areas of normal looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual.

Participants and/or parents/caregivers (as deemed appropriate based on age of participant), will be trained on injecting study drug at visit 2 and may self-inject study drug during weeks in which no clinic visit is scheduled.

Detailed instructions for transport, storage, preparation, and administration of study drug will be provided by the site to the participant (or caregiver). Participants and/or parents/caregivers will document/report compliance with self-injection of study drug in a diary.

8.2. Background Treatments

Topical emollient (moisturizer) should be applied twice daily, as per physician's recommendation starting at the screening visit. Participants should continue to apply moisturizers throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the day of the study visit. All types of moisturizers will be permitted, but participants should not initiate treatment with prescription moisturizers or moisturizers containing additives (ceramide, hyaluronic acid, urea, filaggrin degradation products, hydrocortisone) during the screening period or during the study. Participants will be permitted to continue using stable doses of such moisturizers if initiated before the screening visit, unless specifically prohibited (eg, hydrocortisone or other topical corticosteroid).

8.3. Rescue Treatments

For participants who receive rescue treatment during treatment period, observed efficacy results will be analyzed in this study.

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study participants at the discretion of the investigator. Although the use of rescue medications is allowed at any time during the study, the use of rescue medications should be delayed, if possible, for at least 14 days following the initiation of the investigational treatment. If possible, investigators are encouraged to consider rescue initially with topical treatment (eg, medium/high potency TCS) and to escalate to systemic medications only for participants who do not respond adequately after at least 7 days of topical treatment. Topical calcineurin inhibitors may be used for rescue, alone or in combination with TCS, but the use of TCI should be reserved for problem areas only (eg, face, neck, intertriginous and genital areas, etc). Investigators may also consider rescue with crisaborole. Rescue treatment for these topical therapies should be used as per prescribing information and local guidelines. Participants may continue study treatment if rescue consists of topical medications.

Participants who receive systemic corticosteroids or systemic nonsteroidal immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc) as rescue medication during the study will be discontinued permanently from the study drug. All participants will be asked to complete the scheduled study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety laboratory tests) before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary. For the purpose of efficacy analysis, participants who receive rescue treatment during the study will be considered treatment failures.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

Dose modification for an individual participant is not allowed.

8.4.2. Study Drug Discontinuation

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

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

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met (FDA, 2009)
- Participant or legal parent/legal guardian withdraws assent or consent
- If, in the investigator's opinion, continuation in the study would be detrimental to the participant's well-being
- In the event of a protocol deviation, at the discretion of the investigator or the Sponsor
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin. Participant must be withdrawn for these latter malignancies if they cannot be adequately treated by local resection.
- Other intercurrent illnesses or major surgery which could, in the opinion of the investigator, present an unreasonable risk to the participant as a result of his/her continued participation in the study
- Any infection that is opportunistic, such as tuberculosis and other infections whose nature or course may suggest an immunocompromised status

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron medical monitor.

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the participant's best interest. However, the Regeneron medical monitor should be contacted as soon as possible. The Regeneron medical monitor should be consulted prior to the resumption of study drug dosing.

If a participant requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.5. Management of Acute Reactions

8.5.1. Acute Injection Reactions

8.5.1.1. Systemic Injection Reactions

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

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

8.5.1.2. Local Injection Site Reactions

Local ISRs must be reported as AEs and graded according to Section 10.2.4.

8.6. Method of Treatment Assignment

This is an open-label study; all participants will receive dupilumab.

8.7. Blinding

This is an open-label study, without a reference treatment.

8.8. Treatment Logistics and Accountability

8.8.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

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

8.8.2. Supply and Disposition of Treatments

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

8.8.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

8.8.4. Treatment Compliance

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

8.9. Concomitant Medications and Procedures

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

- If a participant intends to receive a COVID-19 vaccine (initial series or booster), before the start of study drug administration, day 1 of the study and the events associated with day 1, should not occur until at least 1 week after any COVID-19 vaccination dosing.
- During the treatment period, it is recommended to delay COVID-19 vaccination, either as an initial series or as a booster dose, until participants are receiving and tolerating a steady dose of study drug.
  - COVID-19 vaccination, either as an initial series or as a booster dose, received during the study, will be treated as a concomitant medication. As noted, administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product (at least 72 hours, ideally by at least 1 week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

8.9.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study. Study drug will be immediately discontinued if any of the following are used during the study:

- Treatment with a live (attenuated) vaccine; below is a list of examples of such vaccines; refer to study manual for a current, comprehensive list of prohibited vaccines.

Chickenpox (Varicella)
FluMist-Influenza
Intranasal influenza
Measles (Rubeola)
Measles-mumps-rubella combination
Measles-mumps-rubella-varicella combination
Mumps
Oral polio (Sabin)
Oral typhoid
Rubella
Smallpox (Vaccinia)
Monkeypox
Yellow fever
Bacillus Calmette-Guerin
Rotavirus
Varicella Zoster (shingles)

- Treatment with an investigational drug (other than dupilumab)
- Treatment with immunomodulating biologics
- Treatment with systemic nonsteroid immunosuppressant (may be used as rescue, see Section 8.3 for details)
- Treatment with systemic corticosteroids (may be used as rescue, see Section 8.3 for details)
  - Treatment with TCS or TCI (may be used as rescue, see Section 8.3 for details)
- Treatment with crisaborole (may be used as rescue, see Section 8.3 for details)
- Initiation of treatment of AD with prescription moisturizers

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Tanning in a bed/booth
  - Phototherapy (UVA, UVB, nbUVB, high dose UVA and PUVA)

8.9.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 8.9.1, treatment with concomitant medications is permitted during the study. This includes basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration.

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

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

Study assessments and procedures are presented by study period and visit in Table 1 (screening period, baseline visit, treatment period, ET visit, and EOT/EOS visit).

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
Screening/Baseline:											
Inclusion/Exclusion[4]	X	X									
Fitzpatrick skin type	X										
Informed consent/assent[5]	X										
Informed consent/assent for optional pharmacogenomics substudy[5]	X										
Informed consent/assent for optional future biomedical research substudy[5]	X										
Informed consent/assent for optional use of photographs (selected study sites only)[5]	X										
Informed consent/assent for optional colorimetry substudy (selected study sites only)[5]	X										
Informed consent/assent for optional OCT and non-invasive in vivo imaging substudy (single study site only)[5]	X										
Skin-type characterization questionnaire[6]		X									
Medical history	X										

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
Medication history	X										
Demographics	X										
Patient diary training[7]	X										
Treatment:											
Injection training of study drug		X									
Administer dupilumab[8,9,10]		X		X	X	X	X	X	X		
Patient diary recording dosing information		X	X	X	X	X	X	X	X		
Concomitant Medications/procedures	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[10]											
Patient Reported:											
Peak Pruritus NRS[6,11]		X (daily)									
Sleep Quality NRS[6,11]		X (daily 7 days prior to each visit)									
Skin Pain NRS[6]		X		X	X	X	X	X	X	X	X
Dyspigmentation NRS[6]		X		X	X	X	X	X	X	X	X
Xerosis NRS[6]		X		X	X	X	X	X	X	X	X
CDLQI[6,12], DLQI[6,12]		X		X	X	X	X	X	X	X	X
HADS[6]		X		X	X	X	X	X	X	X	X

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
POEM[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Disease[6]		X		X	X	X	X	X	X	X	X
Patient Global Impression of Change[6]				X	X	X	X	X	X	X	X
Investigator Reported:											
EASI	X	X		X	X	X	X	X	X	X	X
IGA	X	X		X	X	X	X	X	X	X	X
SCORAD		X		X	X	X	X	X	X	X	X
BSA	X	X		X	X	X	X	X	X	X	X
AD phenotypic description[13]		X		X	X	X	X	X	X	X	X
Post-inflammatory hyperpigmentation severity scale (PHSS)		X		X	X	X	X	X	X	X	X
Photography (select sites)[14]		X						X		X	X
Colorimetry measurement (select sites)[15]		X		X	X	X	X	X	X	X	X
Optical Coherence Tomography and non-invasive in vivo imaging (single site)[16]		X			X			X		X	X

Table 1: Schedule of Events[1]		**TREATMENT PERIOD**									
Study Procedure	**SCNV1[2]**	**BL V2**	**Ph V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET Visit[3]**	**EOT / EOS V10**
Week (W)			W1	W2	W4	W8	W12	W16	W20		W24
Day (D)	D-35 to D-1	D1	D8	D15	D29	D57	D85	D113	D141		D169
Visit Window (Days [d])			±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d		±7 d
Safety:[10]											
Physical Examination	X									X	X
Weight / Height	X									X	X
Adverse Events[17]	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[10, 19a]											
Pregnancy Test (Urine, WOCBP only)		X		X	X	X	X	X	X	X	X
Pharmacokinetics Sampling:[18]											
Drug conc. sample[19]		X					X			X	X
Biomarkers:[19]											
Total serum IgE and allergen-specific IgEs		X			X		X			X	X
Exploratory Research Serum/Plasma		X			X		X			X	X
Future Biomarker Serum/Plasma (optional)		X			X		X			X	X
Pharmacogenomics:											
Whole blood for DNA (optional)[20]		X									

Abbreviations: BL = baseline; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; IgE = Immunoglobulin E; NRS = numerical rating scale; Ph = Phone; SCN = screening; SCORAD = SCORing Atopic Dermatitis; WOCBP = women of childbearing potential

9.1.1. Footnotes for the Schedule of Events Table

9.1.1.1. Table 1 Schedule of Events

1. In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.
2. The length of the screening period is not fixed but must not exceed 35 days.
3. All visit 10 assessments should be performed if a participant terminates the study after the baseline visit and prior to the visit 10 window (early termination visit).
4. Eligibility based on age and weight at time of screening visit.
5. Assent collected from participant, if applicable, based upon the age of the participant.
6. The questionnaires will be administered only to those participants who speak fluently the language(s) in which the questionnaire is presented (based on availability of validated translations). Patient-reported assessments are completed only by the participant.
7. Training of participants/parents/caregivers regarding completion of diary at visit 1 to record assessment of PP NRS and Sleep Quality NRS. Provide additional training as necessary based on review of diary use.
8. Dupilumab to be dosed as per USPI. Study drug administration will occur Q2W. Q2W study drug administrations must be separated by at least 11 days. At the baseline visit, study drug will be administered at the clinic and thereafter study medication will be provided to participants for administration at home. If the investigator and participants (± parent/guardians as appropriate) agree, participants may return to the clinic for dupilumab administration (as prescribed) instead.
9. Last scheduled dose of dupilumab during the treatment period will be at week 22.
10. Assessments/procedures should be conducted in the following order: Patient-Reported Outcomes (PROs), investigator assessments, safety and laboratory assessments, administration of study drug. Clinical sites will check participant data collected on the diary. Topical emollient (moisturizer) should be applied twice daily, as per physician's recommendation starting at the screening visit. Participants should continue to apply moisturizers throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the day of the study visit.

11. These assessments are to be completed by study participants in their diaries: Peak Pruritus NRS will be conducted daily starting 7 days prior to baseline. Sleep Quality NRS is to be collected daily for 7 days immediately preceding the baseline visit and all subsequent visits.
12. CDLQI for participants <16 years of age, DLQI for participants ≥16 years of age.
13. AD phenotypic description (primary morphologies, and distribution) includes the following: Localized AD, Flexural AD, Extensor AD, Nummular AD, AD with prurigo nodules, Follicular AD, Papular AD, Lichenioid AD, and Psoriasiform AD
14. A photography substudy will be performed at a subset of study sites. Site training will be provided. Participant/parents or legal guardians who agree to participate in the substudy will be required to sign a separate substudy informed consent/assent form for use of photographs for educational/marketing purposes before the procedure is performed.
15. A colorimetry substudy will be performed at a subset of study sites. Site training will be provided. Participant/Parents or legal guardians who agree to participate in the substudy will be required to sign a separate substudy informed consent/assent form before the measurements are performed.
16. An OCT substudy with additional non-invasive in vivo imaging including line field confocal OCT and/or reflectance confocal microscopy at the discretion of the investigator will may be performed at a single study site. Participant/Parents or legal guardians who agree to participate in the substudy will be required to sign a separate substudy informed consent/assent form before the procedure is performed.
17. Any participant who experiences an AESI related to an eye disorder will be referred to an ophthalmologist if deemed necessary by the investigator.
18. Any unused serum samples collected for dupilumab concentrations measurements will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations) and may be used for exploratory biomarker research related to AD, inhibition of the IL-4Rα pathway with an antibody, treatment response (PD and/or predictive), as well as to investigate unexpected AEs or to identify markers associated with adverse reactions. The results of these exploratory research analyses will not be presented in the clinical study report (CSR).
19. Blood samples will be collected prior to administration of study drug. In the event of suspected serious adverse events (SAEs), such as anaphylaxis or hypersensitivity, PK samples may be collected at or near the event when possible.
    a. If COVID-19 restrictions limit the availability of staff or the participant to have in-clinic visits:
        – Procedures/sample collection should occur at the next available in-clinic visit. Pregnancy testing must be performed as indicated (in-clinic or at-home) monthly (at a minimum) and results reported in a timely manner.
20. Whole blood sample for DNA as part of the pharmacogenomics substudy should be collected on day 1/baseline (predose) but can be collected at a later study visit.

9.1.2. Early Termination Visit

Participants who are withdrawn from the study before the primary endpoint visit (week 24) will be asked to return to the clinic: once for an early termination visit consisting of the end of study assessments described in Table 1 and again at select visits (eg, the primary endpoint visit [day x/visit y] and key secondary endpoint visit(s), as applicable).

9.1.3. Unscheduled Visits

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

9.2. Study Procedures

A variety of parameters will be collected during the study to assess efficacy of dupilumab in skin of color participants, including measures of AD severity, use of concomitant treatment for AD, and participant reported measures of AD symptoms and QOL.

Assessments/procedures should be conducted in the following order:

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

Please see study manual for instructions on the administration and use of all patient-reported instruments.

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

- Inclusion/Exclusion criteria
- Fitzpatrick skin type
- Skin-type characterization questionnaire
- Medication history
- Demographics

9.2.1.1. Fitzpatrick Skin Type (FST)

The Fitzpatrick skin type (FST), also sometimes referred to as Fitzpatrick skin phototype, is a system to classify skin by its melanin content and its reaction to ultraviolet (UV) radiation (Roberts, 2009). It is determined by constitutional pigmentation and the patient-reported effect of UV with regard to burning and tanning. Training and a pictural guide will be provided for reference. The FST delineates 6 skin types (1 to 6), with lower numbers indicating more fairly complected skin with less melanin content and ≥4 serving as a generally accepted designation for skin of color.

9.2.1.2. Skin-Type Characterization Questionnaire

At the baseline visit the participant will complete a questionnaire consisting of items relating to functional/practical characterization of skin pigmentation type.

9.2.2. Efficacy Procedures

9.2.2.1. Patient-Reported Outcome Measures

Questionnaire will be administered only to those participants who speak fluently the language in which the questionnaire is presented (based on availability of validated translations). Patient-reported assessments are completed only by the participant.

9.2.2.1.1. Peak Pruritus NRS (PP NRS)

The PP NRS is a simple assessment tool that participants will use to report the intensity of their pruritus (itch) during a 24-hour recall period. Participants will be asked the following question:

For maximum itch intensity: “On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being the ‘worst itch imaginable’, how would you rate your itch at the worst moment during the previous 24 hours?”

Participants will be instructed on using the participant diary to record their PP NRS at the screening visit. Participants will complete the rating scale daily throughout the entire study (baseline and preceding 7 days and treatment period; see Table 1). Clinical sites will check and remind the participant to complete the diary according to the time points in Table 1.

9.2.2.1.2. Sleep Quality NRS

Study participants will be asked to rate their sleep quality on their past night upon awakening, using the Sleep Quality NRS, ranging from 0 (“Worst possible sleep”) to 10 (“Best possible sleep”). Sleep Quality NRS are to be collected daily including 7 days immediately preceding the baseline visit and then daily during the week before each planned visit.

Participants will be instructed on using the participant diary to record their Sleep Quality NRS at the screening visit. Clinical sites will check and remind the participant to complete the diary according to the time points in Table 1.

9.2.2.1.3. Skin Pain NRS (SP NRS)

Skin pain will be assessed using a skin pain NRS with 7-day recall period (Silverberg, 2021). Study participants will be asked to report if they experience any pain of skin over the past week and if yes, rate the severity of pain on a 11-point scale (0 to 10) in which 0 indicates no pain while 10 indicates worst imaginable pain. SP NRS can be categorized as: no pain (0), mild (1 to 3), moderate (5 to 6), severe (7 to 9), and very severe (10). The threshold for minimally clinically important difference for SP NRS is between 2.2 to 2.9 (Silverberg, 2021). The SP NRS will be performed at time points according to Table 1.

9.2.2.1.4. Dyspigmentation NRS

Dyspigmentation will be assessed using a numeric rating scale. This assessment will be administered when the scale becomes available.

The Dyspigmentation NRS will be performed per the SoE in Table 1.

9.2.2.1.5. Xerosis NRS

Xerosis will be assessed using a numerical rating scale. This assessment will be administered when the scale becomes available.

The Xerosis NRS will be performed per the SoE in Table 1.

9.2.2.1.6. Children's Dermatology Life Quality Index (CDLQI)

The CDLQI is a questionnaire designed to measure the impact of skin disease on the QOL in children 4 years to <16 years old (Lewis-Jones, 1995). The aim of the questionnaire is to measure how much a participant's skin problem has affected the participant over a recall period of the past week. To complete the questionnaire, participants need to provide responses to 10 questions (the questions focus on domains such as symptoms feelings associated with disease, the impact of the disease on leisure, school or holidays, personal relationships, sleep, and side effects of treatment for the skin disease). The instrument has a recall period of 7 days. Nine of the 10 questions are scored as follows:

- Very much = 3
- Quite a lot = 2
- Only a little = 1
- Not at all = 0
- Question unanswered = 0

Question 7 has an additional possible response (prevented school), which is assigned a score of 3.

The CDLQI for a participant is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on the QOL. The CDLQI can also be expressed as a percentage of the maximum possible score of 30.

This questionnaire measures concept(s), which are known only/best to the participant suffering from AD. As such the questionnaire is designed for self-report. Where possible the participant should read and complete the questionnaire alone. This information will be transferred to the eCRF. Participants will undergo this assessment at time points according to Table 1.

9.2.2.1.7. Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL in participants ≥16 years old (Badia, 1999). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. The DLQI will be performed at time points according to Table 1.

9.2.2.1.8. Hospital Anxiety and Depression Scale (HADS)

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a participant's emotional state (Herrmann, 1997) (Zigmond, 1983). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. The questionnaire will be administered at time points according to Table 1.

9.2.2.1.9. Patient Oriented Eczema Measure (POEM)

The POEM is a 7-item, questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency of these disease symptoms during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity. The questionnaire will be administered at time points according to Table 1.

9.2.2.1.10. Patient Global Impression of Disease (PGID)

The PGID is an assessment instrument used by the participant in clinical studies to rate their eczema symptoms during the past 7 days.

Participants will rate their disease based on the 5-level scale as follows:

"Overall, how would you rate your eczema symptoms during the past 7 days?"

- No symptoms
- Mild
- Moderate
- Severe
- Very severe

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

9.2.2.1.11. Patient Global Impression of Change (PGIC)

PGIC will be measured using a participant administered tool.

Participants will respond to the following question based on the 7-level scale as follows:

"Compared to before you started the study, how would you rate your eczema now?"

- Much better
- Moderately better
- A little better
- No change
- A little worse
- Moderately worse
- Much worse

The PGIC is an instrument used by the participant in clinical studies to compare their eczema symptoms from the beginning of the study to when they completed the assessment.

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

9.2.2.2. Investigator-Reported Outcome Measures

9.2.2.2.1. Eczema Area and Severity Index (EASI)

The EASI is a 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 time points according to Table 1.

9.2.2.2.2. Investigator's Global Assessment (IGA)

The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed at time points according to Table 1.

9.2.2.2.3. SCORing Atopic Dermatitis (SCORAD)

SCORAD is a tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (European Task Force, 1993). There are 3 components to the assessment: A = extent or affected BSA, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see Section 9.2.2.2.4) and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, and dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the participant or relative on a Visual Analogue Scale, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: $A/5 + 7B/2 + C$ where the maximum is 103. Participants will undergo this assessment at time points according to Table 1.

9.2.2.2.4. Body Surface Area (BSA) Involvement of Atopic Dermatitis

BSA affected by AD will be assessed for each section of the body using the rule of nines (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. Participants will undergo this assessment at time points according to Table 1.

9.2.2.2.5. AD Phenotypic Description (Primary Morphologies and Distribution)

A total body skin exam will be performed to qualitatively assess for pre-specified morphological subtypes of AD (listed below). Pictorial guidance and/or morphological descriptors will be included in the study reference manual. Dominant morphology will be captured and additional morphologies will be indicated as 'present' or 'absent.'

AD subtypes:

- -Localized AD
- -Flexural AD
- -Extensor AD
- -Nummular AD
- -AD with prurigo nodules
- -Follicular AD
- -Papular AD
- -Lichenoid AD
- -Psoriasiform AD

Participants will undergo this assessment at time points according to Table 1.

9.2.2.2.6. Post-Inflammatory Hyperpigmentation Severity Scale (PHSS)

PHSS is an assessment tool that investigators will use to rate the severity of dyspigmentation on a 9 point scale ranging from 0 (normal) to 9 (severe). Investigators are asked to consider 'overall pigmentary change severity', 'pigmentary intensity of hyperpigmented lesions', 'area of hyperpigmented lesions', 'degree of hypopigmentation', and 'presence/extent of erythema, burning, peeling, dryness'.

Participants will undergo this assessment at time points according to Table 1.

9.2.2.3. Substudies

Site training will be provided for photography and colorimetry substudies. Study reference manuals will be provided to standardize data acquisition procedures. Additional exploratory analyses will be specified in the statistical analysis plan (SAP).

9.2.2.3.1. Photography: 2D, 3D, and Dermoscopic Photographs of AD Lesional, Hyperpigmentation Lesional, and Non-Lesional Targets (Select Sites)

At select study sites, photographs will be taken of a representative area of AD (EASI erythema and papulation severity subscore each >0) , a representative area of hyperpigmentation (PHSS >1 and EASI erythema and papulation severity subscore each = 0), and a representative area of background non-lesional skin (PHSS ≤1 and EASI erythema and papulation severity subscore each = 0). Efforts should be made to select photoprotected targets (to minimize confounding from UV exposure) and targets within the same anatomical region (trunk, upper extremity, lower extremity) or on the contralateral side. Images will be captured with conventional non-polarized and cross-polarized flash photography, high resolution 3D photography, and dermoscopic photography techniques on the identified target areas. Subsequent images of the same sites will be taken at time points according to Table 1.

9.2.2.3.2. Colorimetry Measurement: Colorimetry for Melanin Index and Erythema Index at AD Lesional, Hyperpigmentation Lesional, and Non-Lesional Targets (Select Sites)

Colorimetry for melanin index and erythema index at AD lesional, hyperpigmentation lesional, and non-lesional targets (select sites) – At select study sites, melanin and erythema indices will be measured by handheld colorimeter probe applied to a representative area of AD (EASI erythema and papulation severity subscore each >0), a representative area of hyperpigmentation (PHSS >1 and EASI erythema and papulation severity subscore each = 0), and a representative area of background non-lesional skin (PHSS ≤1 and EASI erythema and papulation severity subscore each = 0). Efforts should be made to select photoprotected targets (to minimize confounding from UV exposure) and targets within the same anatomical region (trunk, upper extremity, lower extremity) or on the contralateral side. Subsequent measurements of the same sites will be taken at time points according to Table 1.

9.2.2.3.3. Optical Coherence Tomography and Additional Optional Non-Invasive In Vivo Imaging at AD Lesional, Hyperpigmentation Lesional, and Non-Lesional Targets (Single Site)

Optical Coherence Tomography at AD lesional, hyperpigmentation lesional, and non-lesional targets (single site) – At a single study site, OCT images will be captured from a representative area of AD (EASI erythema and papulation severity subscore each >0), a representative area of hyperpigmentation (PHSS >1 and EASI erythema and papulation severity subscore each = 0), and a representative area of background non-lesional skin (PHSS ≤1 and EASI erythema and papulation severity subscore each = 0). Change in lesional and non-lesional and hyperpigmentation lesional skin thickness, by measuring epidermal thickness, changes in anatomy or appearance of the dermo-epidermal junction and the dermis, and changes in vascular flow patterns, including the number and size of vessels in lesional and non-lesional skin will be assessed. Additional exploratory analyses will be specified in the SAP. Week 4 evaluation of structural skin components at near histologic resolution via OCT± line field confocal OCT and/or reflectance confocal microscopy may provide early evidence of skin normalization and allow for identification of cellular and architectural changes with prognostic significance. Efforts should be made to select photoprotected targets (to minimize confounding from UV exposure) and targets within the same anatomical region (trunk, upper extremity, lower extremity) or on the contralateral side. Subsequent images of the same sites will be taken at time points according to the SoE. Additional non-invasive in vivo images may be captured with line field confocal OCT and/or reflectance confocal microscopy at the discretion of the investigator. Participants will undergo this assessment at time points according to Table 1.

9.2.3. Safety Procedures

9.2.3.1. Body Weight and Height

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

9.2.3.2. Physical Examination

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

9.2.3.3. Laboratory Testing

Pregnancy testing samples using urine sticks will be analyzed by each study site. Detailed instructions for urine sample collection are in the package insert available at study sites.

9.2.4. Drug Concentration and Measurements

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Table 1. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional blood samples may be collected at or near the event for PK assessment. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused or residual samples may be used for exploratory biomarker research.

9.2.5. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore AD, how dupilumab may modify the underlying the disease process in AD, type 2 inflammation, and predictors of dupilumab safety and efficacy.

Samples for total IgE and allergen-specific IgEs will be collected at time points according to in Table 1. The biomarkers studied are believed to be relevant to the pathophysiology of AD in participants with skin of color, response to treatment (ie, assessment of type 2 inflammation) and baseline predictors of response and dupilumab mechanism of action.

IL-4 and IL-13 regulate B cell class switching to, as well as production of, IgE. Dupilumab has been shown to suppress IgE (total and allergen-specific) in AD, asthma, and nasal polyposis patients. Serum concentrations of IgE (total and a panel of allergen-specific) will be measured at time points indicated in Table 1. Modulation of IgE is a known pharmacodynamic marker for dupilumab in AD. Data analysis will be described in the SAP and the results will be provided in the CSR.

9.2.5.1. Residual Samples

Residual samples for study-related research (eg, blood, serum, plasma) will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for exploratory research that may or may not be related to dupilumab safety and/or efficacy, the progression and clinical outcomes of AD and related diseases, the biology of IL-4R, IL-4, IL-13, and related pathways and/or for assay development and/or validation. The results of these exploratory research analyses will not be presented in the CSR.

9.2.5.2. Serum and Plasma for Exploratory Research

Serum and plasma for exploratory research will be collected and banked for exploratory research related to dupilumab safety and/or efficacy, the progression, disease activity and clinical outcomes of AD and related diseases, and the biology of IL-4Rα and related pathways.

9.2.6. Future Biomedical Research (Optional)

Participants/parents or legal guardians who agree to participate in the future biomedical research (FBR) substudy will be required to consent to this optional substudy before samples are banked for FBR. Additional samples will be collected for FBR according to Schedule of Events Table 1. Residual biomarker samples for study-related research will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these FBR analyses will not be presented in the CSR.

9.2.7. Pharmacogenomic Analysis (Optional)

Participants/parent or legal guardians who agree to participate in the genomics substudy will be required to consent to this optional substudy before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose), but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of AD and related diseases. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

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

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

Research findings from the optional genomic substudy will not be disclosed to the participant or principal investigator, even if they have implications for a participant's health and management. Genetic results from this substudy are for research purposes only and not for medical diagnosis or for reproductive decision-making.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of on-treatment period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

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

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

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

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

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

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

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

10.1.2. Reporting Procedure

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

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

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**
- **Adverse Events of Special Interest** (AESIs; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Anaphylactic reactions
  - Systemic hypersensitivity reactions
  - Helminthic infections
  - Any severe type of conjunctivitis or blepharitis
  - Keratitis
  - Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Any participant who experiences an AESI related to an eye disorder will be referred to an ophthalmologist if deemed necessary by the investigator. Further evaluation of these AESIs will be performed including any additional tests, as per the discretion of the ophthalmologist.
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female, during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study participant and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH, 1994).

For studies with PROs, the PRO data are generally not reportable as individual AEs and thus will not be reported or reconciled as such.

10.2.2. Serious Adverse Event

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

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

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

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

10.2.4. Severity

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

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

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

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

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

Injection Site Reactions

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

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

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

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

10.2.5. Causality

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

Include the following when applicable] For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses

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

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

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

  or

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

Causality to the study conduct (protocol specified procedure):

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

10.3. Safety Monitoring

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

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

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

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IEC/IRB unless delegated to the sponsor.

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

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

11. STATISTICAL PLAN

11.1. Statistical Hypothesis

There is no formal statistical hypothesis testing and no planned inferential comparisons in this study.

11.2. Justification of Sample Size

The enrolled population will attempt to approximate the US census bureau data on proportions of self-reported races that comprise the skin of color population in the United States– to this end all self-reported races representing skin of color will be included, however a cap at approximately 40% will be set for non-black/non-African American participants.

Due to the descriptive character of this study, no formal sample size calculation will be performed. The sample size of this study is chosen empirically to support descriptive analysis of efficacy and safety in the overall skin of color population. With up to a potential 15% drop out rate based on prior studies, 120 participants would yield approximately 105 participants overall.

11.3. Analysis Sets

11.3.1. Full Analysis Set

The full analysis set (FAS) includes all participants who are enrolled in the study and have at least 1 post-baseline efficacy assessment. The FAS is the main analysis population for the study and will be used to summarize baseline characteristics and disposition and to analyze efficacy variables.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all participants in the FAS who are enrolled and received at least 1 dose of dupilumab during the study. Treatment compliance and administration, and all safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

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

11.4. Statistical Methods

All statistical analyses will be descriptive.

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

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

11.4.1. Participant Disposition

The number and percentage of participants screened, enrolled, and the primary reasons for screening failure and discontinuation will be summarized.

11.4.2. Demography and Baseline Characteristics

Demographic variables (eg, age, race, and gender), baseline characteristics, medical history, and prior and concomitant mediations and procedures will be summarized. See Section 5.1 for a full list of demographic and baseline variables.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The primary endpoint will be summarized descriptively with no hypothesis testing planned. Subgroup analysis will be performed. Details with be specified in the SAP.

11.4.3.2. Secondary Efficacy Analysis

For continuous variables, descriptive statistics will include the following information: number of participants reflected in the calculation (n), mean, median, 25% percentile, 75% percentile, 75% percentile, standard deviation, minimum and maximum.

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

Primary Imputation Method:

- For continuous endpoints: Data after rescue or drop-out due to lack of efficacy, will be assigned by post baseline last-observation carried forward (LOCF); MI will be applied for all other missing data.
- Binary/responder endpoints will be calculated based on the corresponding continuous assessments (based on the values after imputation)

Other sensitivity analyses with different imputation methods will be planned and detailed in the study SAP.

11.4.4. Control of Multiplicity

Not applicable since no statistical inferential analyses are planned.

11.4.5. Safety Analysis

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety data (ie, physical exam).

A descriptive summary of safety results will be presented for each study part.

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the end of study.

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

Analysis

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of participants with at least 1 TEAE by system organ class (SOC) and preferred term (PT)
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs, presented by SOC and PT
- Treatment-emergent AESIs
- Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Laboratory Tests

Listings will be provided for pregnancy test results.

11.4.5.3. Treatment Exposure

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

Q2W dosing: (Date of last study drug injection – date of first study drug injection) + 14 days

The number (%) of participants exposed to study drug will be presented by specific time periods. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized using number of participants, means, standard deviation, minimums, medians, and maximums.

A summary of the number of doses will be provided.

11.4.5.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

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

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

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of functional/total dupilumab over time will be summarized by descriptive statistics for all participants.

No formal statistical hypothesis testing will be performed.

No formal statistical analysis will be performed. Trough functional dupilumab concentration in serum ($C_{trough.time\ point}$) will be summarized at each time point using descriptive statistics. The data may be combined with data from other studies for analysis using population methods. Any population PK analysis will be reported separately.

11.4.7. Analysis of Pharmacodynamic and Exploratory Biomarker Data

All exploratory biomarker data analyses will be performed on the RAS and no multiplicity adjustment is planned. Analyses of exploratory endpoints will be provided in the SAP.

11.5. Statistical Considerations Surrounding the Premature Termination of a Study

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, concomitant medications. medical history and procedures) will be done using internationally recognized and accepted dictionaries.

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

12.1.2. Electronic Systems

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

- IVRS/IWRS system –study drug supply
- EDC system – data capture – Medidata RAVE
- Statistical Analysis System (SAS) – statistical review and analysis
- Sanofi-Genzyme Pharmacovigilance safety database
- AWARE, Business Objects XI – pharmacovigilance activities (Sanofi)
- Digital archive system for photographic and video images
- Electronic diary - collection of PP NRS and Sleep Quality NRS

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

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

12.2.2. Source Document Requirements

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

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

12.2.3. Case Report Form Requirements

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

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

12.3. Audits and Inspections

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

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

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

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

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

13.3. Participants Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

13.5. Clinical Study Data Transparency

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

- The investigator has received all items and information necessary to perform the study, but has not enrolled any participant within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of participants required for the study are enrolled earlier than expected

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: An Open-Label Single-Arm Study of Dupilumab in Adolescent and Adult Skin of Color Patients with Moderate-to-Severe Atopic Dermatitis and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: An Open-Label Single-Arm Study of Dupilumab in Adolescent and Adult Skin of Color Patients with Moderate-to-Severe Atopic Dermatitis

Protocol Number: Protocol R668-AD-2217

Protocol Version: Protocol R668-AD-2217 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00345039 v1.0

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