Protocol for

Official Title of Study

A PHASE 2, MULTICENTER, GLOBAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CENDAKIMAB (CC-93538) IN ADULT SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

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PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, Global, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Cendakimab (CC-93538) in Adult Subjects with Moderate to Severe Atopic Dermatitis.

Indication

CC-93538 is a recombinant humanized, high-affinity neutralizing (immunoglobulin G1 kappa [IgG1κ]) monoclonal antibody (mAb) selective for interleukin-13 (IL-13). CC-93538 binds to IL-13, thus preventing its interaction with both IL-13 receptors, IL-13 receptor alpha 1 (IL-13Rα1) and IL-13 receptor alpha 2 (IL-13Rα2). Atopic dermatitis (AD) is a common and chronic type 2 immunity driven inflammatory skin disorder. Type 2 cytokines have a strong impact on the skin immune response and barrier function. Interleukin-4 (IL-4) and IL-13 are both key cytokines involved in type 2 inflammatory conditions; however, evidence continues to emerge that supports IL-13 as a primary cytokine involved in AD (Bieber, 2019). The assumed central role of IL-13 in allergic and type 2 inflammatory conditions strengthens the position for CC-93538 as a potential treatment option for patients with moderate to severe AD.

Objectives

Primary Objective

- To evaluate the clinical efficacy of 3 dosage regimens of CC-93538 [([redacted]mg once weekly (QW), [redacted]mg every other week (Q2W), and [redacted] mg (Q2W)], compared with placebo on the change in the core clinical outcome measure, Eczema Area and Severity Index (EASI), in subjects with moderate to severe AD

Secondary Objective

- To evaluate the effect of 3 CC-93538 dosage regimens, compared with placebo on additional clinical outcome measures and patient reported outcomes in subjects with moderate to severe AD
- To evaluate the safety and tolerability, including characterization of the immunogenicity profile of 3 dosing regimens of CC-93538, compared with placebo in subjects with moderate to severe AD
- To assess the trough serum concentration of CC-93538 in subjects with moderate to severe AD

Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, 4 arm, parallel-group, dose-ranging, Phase 2 study to evaluate the efficacy and safety of CC-93538 in approximately 200 adult subjects with moderate to severe AD. Subjects participating in the study must be candidates for systemic therapy, defined as having an intolerance or inadequate response to treatment with topical medications for at least 4 weeks, or who have required at least 1 systemic therapy to control their disease.

After completion of an up to 4-week screening period, approximately 200 eligible subjects (50 subjects per arm) will be randomized (1:1:1:1) to receive either CC-93538 ([redacted] mg QW, [redacted] mg Q2W, or [redacted] mg Q2W) or placebo for 16 weeks. Treatment assignment will be stratified by geographic region (Japan versus rest of world). Within the rest of world region only, randomization will also be stratified by disease severity based on the Day 1 baseline validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score (3 [moderate] or 4 [severe]). Randomization will occur on Day 1 (Baseline) through the use of Interactive Response Technology (IRT) system.

Starting at Day 1 (Baseline), subjects will receive a total of 16 doses investigational product (IP), administered QW, via 2 subcutaneous (SC) injections. Following the last dose of IP administered (Week 15), subjects will continue to be evaluated at the site for safety and clinical status. Subjects will return to the site for an End of Treatment Visit (EOT) at Week 16, to undergo efficacy and safety assessments. Subsequently, subjects will return to the site for 2 additional visits. The Initial Follow Up Visit (Week 24) will occur 8 weeks after the End of Treatment Visit. The Final Follow Up Visit/End of Study Visit (Week 32) will occur 16 weeks after the after the End of Treatment Visit.

Clinical laboratory tests, vital signs, physical examinations (including height and weight), pregnancy tests, clinical symptom assessments, subject-reported outcomes, serum CC-93538 concentrations, serum antibodies to CC-93538 (to assess immunogenicity), concomitant medications, and adverse event (AE) assessments will be performed according to the Table of Events. Relevant biomarkers including but not limited to peripheral blood eosinophils, immunoglobulin E (IgE), lactate dehydrogenase, IL-13,interleukin-22 (IL-22), chemokine (C-C motif) ligand 17 (CCL17)/thymus- and activation-regulated chemokine (TARC), and chemokine (C-C motif) ligand 18 (CCL18)/ pulmonary and activation-regulated chemokine (PARC) will be measured pre- and post-treatment, as outlined in the Table of Events. Further details regarding the timing and scheduling of the protocol specific assessments and procedures outlined in the Table of Event are described in Section 5, Table 3, Table 4, and Table 5, respectively.

The overall benefit/risk profile of the CC-93538 [redacted] mg SC QW dose will be initially explored in this study. [redacted] additional safety assessments, such as increased onsite visit frequency, ongoing blinded safety reviews of the study data, oversight from an internal Safety Management Team (SMT), and oversight from an external independent Data Monitoring Committee (DMC), further described in Section 6.6) will be conducted during the study to ensure that the safety of the subjects is adequately monitored.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

The study population will consist of approximately 200 male and female subjects aged 18 to 75 years with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy (ie, have AD which has not been adequately controlled by topical medications).

Subjects must have a diagnosis of AD for ≥ 12 months, and present with signs and symptoms consistent with moderate to severe AD, defined as ≥ 10% body surface area (BSA) involvement,

an EASI score ≥ 16, vIGA-AD ≥ 3, and a Pruritus Numeric Rating Scale (NRS) severity score ≥ 4 at Baseline.

Length of Study

The maximum duration of subject participation in this study is approximately 36 weeks. Subjects will participate up to 4 weeks in the Screening Period. Upon randomization, subjects will enter the Treatment Phase of the study, and will receive a total of 16 doses of IP starting at Day 1 (Baseline) and ending at Week 15. At Week 16, subjects will return for the End of Treatment Visit for safety and efficacy assessments. Following the Week 16 End of Treatment Visit, subjects will enter a 16 Week Follow Up Period, and will return for 2 additional visits to assess safety, clinical status, pharmacokinetic (PK)/pharmacodynamics (PD), and serum antibodies to CC-93538. The Initial Follow Up Visit will be conducted 8 weeks after the End of Treatment Visit (Week 24) and the Final Follow Up/End of Study Visit will be conducted 16 weeks after the End of Treatment Visit (Week 32).

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Two injections at a volume of [redacted] mL will be administered SC QW using a pre-filled syringe (PFS) of CC-93538 [redacted] or matching placebo. Subjects will be randomized 1:1:1:1 to 1 of the following treatment arms:

- CC-93538 [redacted] mg SC QW for 16 weeks
- CC-93538 [redacted] mg SC Q2W for 16 weeks. Matching placebo will be administered every other week on alternate weeks to maintain the blind.
- CC-93538 [redacted] mg SC Q2W for 16 weeks. Matching placebo will be administered weekly to maintain the blind.
- Matching placebo SC QW for 16 weeks

Overview of Key Efficacy Assessments

- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)
- Pruritus Numeric Rating Scale (NRS)
- Body Surface Area % (BSA)
- SCORing Atopic Dermatitis (SCORAD) Index

Overview of Key Safety Assessments

- Type, frequency, severity, seriousness, and relationship of AEs to IP
- Adverse Events of Special Interest (AESI)

- Clinically significant changes in vital signs, physical examinations, and laboratory findings.
- Ongoing safety surveillance of AE/serious adverse events (SAEs) related to COVID-19
- Presence of and clinical effects of anti-drug antibodies (ADAs)

Statistical Methods

Sample Size Determination

Approximately 200 subjects will be randomized in this Phase 2 dose ranging study. Randomization will be equal among the 4 dose groups of placebo, [redacted] mg Q2W, [redacted] mg Q2W, and [redacted] mg QW (approximately 50 subjects per group). Assuming a 10% dropout rate, a sample size of 45 subjects per group will provide approximately 90% power to detect a treatment difference relative to placebo (difference in means) of 35% with respect to the primary endpoint of percentage change from baseline in EASI scores at Week 16.

The sample size calculations are based on the following considerations for comparing mean percentage changes from baseline in EASI scores at Week 16 versus placebo. In particular, the recent Phase 2b study of dupilumab trial reported an observed mean for placebo of 18.1% and corresponding treatment differences of 50.1% (standard error [SE] = 6.7%) and 55.7% (SE = 6.7%), for the doses of 300 mg Q2W, and 300 mg QW, respectively (Thaçi, 2016).

This study evaluating CC-93538 is designed to detect a (true) treatment difference relative to placebo of 35%. We assume a (true) mean of 20% for placebo, and means for the active dose groups corresponding to treatment differences of 25% ([redacted] mg Q2W), 30% ([redacted] mg Q2W), and 35% ([redacted] mg QW), with a common standard deviation (SD) of 50%. We note that the common SD assumption of 50% for the percentage change from baseline in EASI scores at Week 16 was also assumed in the dupilumab Phase 2b study design (Thaçi, 2016). Under these assumptions, it is estimated that with a sample size of 45 subjects per group the study provides approximately 90% power to detect superiority relative to placebo for at least 1 dose at the overall type-1 error of $\alpha = 0.05$ (two-sided) using a hierarchical testing approach (in the order of [redacted] mg QW versus placebo, [redacted] mg Q2W versus placebo, and [redacted] mg Q2W versus placebo).

Statistical Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint of percentage change from baseline in EASI scores at Week 16 will be analyzed using an analysis of covariance(ANCOVA) model, based on the modified intent to treat (mITT) population, with treatment group indicators as the main effects adjusting for baseline EASI scores, and the stratification factors of vIGA-AD score (3[moderate] or 4 [severe]) and region (Japan versus rest of the world [RoW]) as covariates. For each of the active treatment arms, the adjusted mean percentage changes from baseline and corresponding differences versus placebo in EASI scores at Week 16 will be estimated (based on Least-Squares Means) along with 95% Wald confidence intervals (CIs) and p-values.

To adjust for multiplicity (with respect to the 3 active doses), a standard hierarchical approach will be utilized by conducting comparisons, each at the 2-sided 0.05 alpha-level (based on the aforementioned adjusted p-values), in the order of [redacted] mg QW versus placebo, [redacted] mg Q2W versus placebo, and [redacted] mg Q2W versus placebo.

Key Secondary Endpoints

There are 2 key secondary endpoints: (1) proportion of subjects with both an vIGA-AD score of 0 (clear) or 1 (almost clear) and a reduction ≥ 2 points in vIGA-AD score from Baseline at Week 16; and (2) proportion of subjects with at least a 75% improvement from baseline in Eczema Area and Severity Index (EASI-75) at Week 16. These endpoints will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test at a two-sided 5% significance level.

The randomization stratification levels are:

- Japan region,
- RoW region and vIGA-AD score 3, and
- RoW region and vIGA-AD score 4

Differences in proportions versus placebo and associated 95% confidence intervals will also be provided along with p-values.

The hierarchical testing approach used for the primary endpoint will be utilized to adjust for multiplicity with respect to the 3 active doses for each of these key secondary endpoints. However, multiplicity adjustments are not implemented across the primary and 2 key secondary endpoints simultaneously.

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1. INTRODUCTION

1.1. Disease Background

Atopic dermatitis (AD) is a common and chronic inflammatory skin disorder that affects a broad demographic, with an increasing prevalence worldwide. Although reported prevalence rates of AD vary, it is estimated that AD affects between 3% to 10% of the United States (US) population, and worldwide, AD affects up to 20% of children and 3% of adults (Sacotte, 2018). Of those affected, about 40% have moderate to severe disease, consistent with high disease burden, resulting in a significant impact on a patient's quality of life (Chiesa, 2019). Atopic dermatitis is associated with increased anxiety, depression, sleep disorders, reduced productivity, and impaired activity, all of approximately equivalent magnitude to those observed in psoriasis (Eckert, 2017). In addition, patients with AD have increased risk of other atopic disorders, including asthma, allergic rhinitis, and chronic sinusitis with nasal polyposis (Chandra, 2011; Mallol, 2013; Schneider, 2013) highlighting the need for more advanced therapies and treatment options within this evolving field. A recent study performed in the United States focused on the costs and treatment patterns associated with more advanced therapies such as dupilumab (anti-interleukin 4 receptor [IL-4R] monoclonal antibody), systemic corticosteroids, systemic immunosuppressants, and phototherapy. This study estimated that almost two-thirds of patients with moderate to severe AD who initiated systemic immunosuppressants, and a quarter of those who initiated dupilumab, discontinued treatment within 6 months. These patients represent a significant burden to the healthcare system, with costs in the United States representing approximately $20,000 per patient per year (Eichenfield, 2020). As such, there remains a clear unmet need for additional advancements in treatment options to address the complex medical and societal needs of patients with moderate to severe AD.

A multiplicity of factors, including epidermal barrier defects, dysregulation of innate immune responses, and altered type 2 immunity, are implicated in the pathogenesis of AD, culminating in a series of complex inflammatory responses involving multiple cell types, cytokines and chemokines. Enhanced allergen/antigen penetration through an impaired skin barrier resulting in a type 2 T helper (Th2)-type milieu has been proposed as a critical link between the primary barrier defect in patients with AD and Th2 polarization (Boguniewicz, 2011). Type 2 T helper differentiation of naive CD4+ T cells predominates in AD, causing an increased production of interleukins (IL), primarily interleukin-4 (IL- 4), interleukin-5 (IL-5), and interleukin-13 (IL-13), which then leads to an increased level of immunoglobulin E (IgE) (Alexander, 2019). IL- 4 and IL-13are both key cytokines involved in type 2 inflammatory conditions; however, evidence continues to emerge that supports IL-13 as a primary cytokine involved in AD. (Bieber, 2019).

Until recently, treatment for moderate or severe AD involved hydration of the skin, and/or application of topical treatments such as corticosteroids, calcineurin inhibitors, nonsteroidal phosphodiesterase 4 inhibitors, tar, vitamin D, or dilute bleach. First line therapy for moderate to severe AD is treatment with topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI), are typically used as second line therapy, or as an alternative therapy for patients with TCS intolerance. Although topical therapies remain a mainstay in the treatment in AD, these treatments continue to be associated with limited efficacy. In addition, long-term application of TCS carries the risk of side-effects, such as acneiform eruptions, dyspigmentation, skin atrophy, and risks associated with systemic absorption (Sidbury, 2014).

Moderate or severe cases of AD not adequately controlled by topical treatments are typically treated with phototherapy or other systemic treatment (eg, oral corticosteroids, cyclosporine, methotrexate, mycophenolate, and azathioprine). For most patients, long term treatment with these agents only provide modest efficacy and carries the potential for significant safety issues and long-term complications, such as organ toxicities (Schneider, 2013; Simpson 2017).

More recently, biologic and small molecule therapies have proven to be promising investigational treatments for AD. In particular, the recent European Medicines Agency and the U.S. Food and Drug Administration approval of dupilumab represents a significant treatment advance for AD patients (Ariëns, 2018). Nevertheless, AD exhibits biological and clinical heterogeneity (Muraro, 2016; Czarnowicki, 2019), where even novel therapeutic agents such as dupilumab, have displayed variable efficacy responses in subjects with moderate to severe AD. Results from dupilumab's Phase 3 registrational program (SOLO 1 and SOLO 2), demonstrated efficacy in treating patients moderate to severe AD. However less than half of the subjects (38% to 36% respectively) enrolled in the pivotal studies experienced a reduction of Investigators' Global Assessment (IGA) to either 1 (almost clear) or 0 (clear) after 16 weeks of treatment. These data highlight some of the challenges physicians face in treating patients with moderate to severe disease, as even with advanced therapeutic agents such as dupilumab, a majority of the patients do not have adequate control of their disease. As such, there remains a high unmet need for novel targeted therapies to improve patient outcomes, lessen disease burden, and further expand the current treatment paradigms available for AD patients with more advanced disease. (Simpson, 2016; 2017).

1.2. Compound Background

1.2.1. Mechanism of Action

CC-93538 (nonproprietary name, cendakimab) is a recombinant, humanized, high-affinity neutralizing (immunoglobulin G1 kappa [IgG1κ]) monoclonal antibody (mAb). CC-93538 is highly selective for human IL-13 and was generated by humanization of a rodent anti-human IL-13 mAb, which was identified using hybridoma technology through immunization of mice with human Q110 variant recombinant IL-13. [redacted] CC-93538 is produced by mammalian cell expression.

IL-13 is a cytokine that is expressed by a large number of cell types including most leukocytes, mast cells, epithelial cells, fibroblasts, and smooth muscle cells (Brightling, 2010). CC-93538 has high affinity for wild-type IL-13 and a common variant of IL-13, Q110, which is associated with and enhances human allergic inflammation (Vladich, 2005). CC-93538 binds an IL-13 epitope, comprised of residues in [redacted]. This binding in turn prevents IL-13 from binding to both IL-13 receptor alpha 1 (IL-13Rα1) and IL-13 receptor alpha 2 (IL-13Rα2) (Ying, 2010).

IL-13, IL-13Rα1 and IL-13 Rα2 are overexpressed in the lesional skin of AD (Tsoi, 2019; Esaki, 2015). In addition, mechanical scratching, as well as IL-13 itself, also upregulates IL-13 Rα2 expression (Ulzii, 2019).

The scratch-induced IL-13 Rα2 upregulation may attenuate the IL-13-mediated epidermal barrier dysfunction and dermal fibrosis. However, further research is needed to better understand the role of IL-13 Rα2 in atopic skin inflammation. (Furue, 2020)

1.2.2. Clinical Studies

As of 03 Oct 2020, CC-93538 has been investigated in approximately 202 subjects. Although this will be the first placebo-controlled efficacy and safety study of CC-93538 in subjects with AD, CC-93538 has been investigated in a Phase 1 clinical study in healthy adults and adults with mild-to-moderate controlled asthma, Study M10-378, and a Phase 2 clinical study in adults with EoE, Study RPC02-201. Two additional Phase 1 single-dose pharmacokinetic (PK) studies in adult healthy volunteers, RPC02-1901 and CC-93538-CP-001, were also conducted. One additional study, CC-93538-CP-002, is a single dose PK comparability study assessing CC 93538 using 2 different drug concentrations, 180 mg/mL and 150 mg/mL, in healthy adult subjects, and is currently ongoing.

[redacted]

1.2.2.4. Phase 2 Study, RPC02-201

Study RPC02-201 was a Phase 2, multicenter, multinational, randomized, double-blind, placebo-controlled parallel-group clinical study to evaluate the efficacy and safety of CC-93538 in 99 adult subjects with EoE over 16 weeks of treatment (Hirano, 2019). Subjects were stratified 1:1 by previously defined steroid refractory status, as determined by the Investigator.

Subjects were randomized to receive either CC-93538 180 mg (N = 31), CC-93538 360 mg (N = 34), or placebo (N = 34) weekly for 16 weeks during the double-blind (DB) Treatment Period. On the first day of dosing subjects received an IV load of either CC-93538 (5 mg/kg or 10 mg/kg) or placebo prior to SC dosing. An optional Open-Label Extension (OLE) for an additional 52 weeks where all subjects received 360 mg CC-93538 SC weekly was available for subjects completing the DB Treatment Period. Of the 99 subjects randomized and dosed, 86 entered the OLE and 66 subjects completed Week 52 of the OLE.

In Study RPC02-201, the primary endpoint (changes in esophageal eosinophil count at Week 16) was met. CC-93538 also improved inflammatory features of EoE including the endoscopic appearance of the esophageal mucosa and improvements in histologic changes including fibrosis parameters characteristic of EoE. Mean reductions in the subject's and clinician's global assessment of disease severity score were significant with the 360 mg dose.

Long-term treatment with CC-93538 360 mg showed sustained improvements in esophageal eosinophil count and other inflammatory features of EoE at Week 68. In the OLE, the treatment of subjects with weekly CC-93538 360 mg SC doses demonstrated continued improvement in subjects who transitioned from placebo and those who originally received the CC-93538 180 mg or 360 mg dose in the DB Treatment Period of the study.

Results from the Phase 2 Study, RPC02-201, suggest that CC-93538 at doses of 180 mg and 360 mg weekly was well tolerated and had an acceptable safety profile in subjects with EoE. The most frequently occurring related TEAEs (> 5% in the total CC-93538 group) in the DB Treatment Period, shown with incidences in the placebo, CC-93538 180 mg, and CC-93538 360 mg groups, respectively, were upper respiratory tract infection (2.9%, 9.7%, 11.8%), headache (8.8%, 9.7%, 8.8%), and arthralgia (0%, 12.9%, 2.9%). Injection site reaction TEAEs, were reported for 17.6% of placebo subjects, 12.9% subjects in the 180 mg CC-93538 group, and 26.5% of subjects in CC-93538 360 mg group. The most frequently occurring TEAEs in the OLE assessed as at least possibly related to study drug (> 3%) were headache and injection site hematoma (4.7% each), and injection site erythema, nasopharyngitis, and upper respiratory tract infection (3.5% each). Injection site reaction TEAEs were reported for 18.6% of subjects in the OLE Population. Anti-drug antibodies were assessed throughout the DB and OLE periods of the study and were not associated with any safety findings.

No deaths were reported throughout the study (inclusive of DB and OLE periods). Three subjects experienced 1 SAE each in the DB Treatment Period, including 2 subjects in the placebo group (1 with appendicitis and 1 with umbilical hernia, both moderate) and 1 subject in the CC-93538 360 mg group (severe appendicitis). All SAEs in the DB Treatment Period were assessed as unrelated to study drug. Six subjects experienced 1 SAE each in the OLE, of which 2 had severe, possibly related events (cholecystitis acute and abortion spontaneous) and 4 had unrelated or unlikely related events (moderate asthma, diverticulitis with perforation, schizophrenia, and femur fracture due to motorcycle accident).

Mean CC-93538 serum trough concentration (C_{trough}) values for subjects in the 360 mg dose group were approximately 2-fold of mean CC-93538 C_{trough} values for subjects in the 180 mg dose group at each visit, suggesting a dose-proportional increase in exposure. During the OLE, mean CC-93538 C_{trough} values were similar across double-blind randomized treatment groups by OLE at Week 12, with these levels sustained through OLE at Week 52.

CC 93538 trough concentration data showed steady state was reached between Weeks 12 and 16 of dosing, consistent with the $t_{½}$.

These Phase 2 data indicate that targeting IL-13 with CC-93538 significantly improves many of the important disease and symptomatic features of EoE and is well tolerated. The data support the further study of CC-93538 as a novel treatment for EoE, and a Phase 3 program is planned to be initiated in the first half of 2021.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

1.3. Rationale

1.3.1. Study Rationale and Purpose

Continuous advances have been made in understanding AD pathophysiology over the years. Evidence continues to emerge that supports IL□13 as a primary cytokine involved in AD, including its central role in the generation and maintenance of the inflammatory reaction and epidermal barrier function. (Bieber, 2019). The frequency of type 2 (IL-13+) T cells is significantly increased in lesional AD skin compared to both healthy and non-lesional AD skin. This IL-13 signals via the IL-13 receptor, through the heterodimer of IL-13Rα1 and IL-4Rα on multiple cells types including fibroblasts, pericytes, and vascular smooth muscle cells in the AD skin (He, 2020). Moreover, biologic therapies specifically targeting IL-13, such as lebrikizumab and tralokinumab, have demonstrated potential therapeutic benefit, and an acceptable safety profile in subjects with moderate to severe AD.

Tralokinumab is an anti-IL-13 mAb that has similar binding properties to CC-93538. Tralokinumab binds to the IL-13 cytokine at an epitope that overlaps with the binding site of the IL□13Rα receptor, preventing IL-13 from binding to both IL-13Rα1 and IL-13Rα2 (Popovic, 2017). Positive results were generated from 3 pivotal Phase 3 studies (ECZTRA 1, 2 and ECZTRA 3) evaluating tralokinumab in subjects with moderate to severe AD. Recent acceptance of the EU Marketing Authorisation Application (MAA) and US Biologics License Application (BLA) for tralokinumab in the treatment of adults with moderate-to-severe AD further validates the potential therapeutic benefit of IL-13 in this disease.

Tralokinumab when dosed at 300 mg every other week (Q2W) demonstrated superiority over placebo in all primary and secondary endpoints at Week 16. For the primary endpoint, an IGA 0/1 was achieved for subjects treated with tralokinumab was 15.8% for versus 7.1% for placebo in ECZTRA 1 and 22.2% versus 10.9% for ECZTRA 2. Reduction of the worst daily average of Pruritus Numeric Rating Scale (NRS) ≥ 4 from baseline to Week 16 was 20·0% with tralokinumab versus 10·3% with placebo in ECZTRA 1 and by 25·0% versus 9·5% with placebo in ECZTRA 2. The overall frequency and severity of AEs over 16 weeks was comparable between tralokinumab and placebo. Of the most frequently reported AEs (≥ 5% in any treatment group), upper respiratory tract infection and conjunctivitis occurred more frequently with tralokinumab versus placebo, and dermatitis atopic and skin infection occurred more frequently with placebo (Wollenberg, 2020). Tralokinumab demonstrated in Phase 3 studies that targeting IL-13 alone in is both a safe and effective therapy; however, is the overall efficacy profile does not appear to be superior to biologic agents already on the market. When compared to the results

reported from dupilumab Phase 3 SOLO 1 and SOLO 2 induction studies, response rates for achieving IGA 0/1were as high as 38% to 36% in the dupilumab 300 mg Q2W arm, compared to 10% to 8% in subjects treated with placebo (Simpson, 2016). Although tralokinumab is anticipated to the first anti-IL-13 approved for the treatment of moderate to severe AD, there remains a need to further evaluate other biologic agents targeting IL-13 pathway, to further assess anti-IL-13's potential of achieving an optimized efficacy profile in subjects with moderate to severe AD.

Lebrikizumab is an anti-IL-13 mAb, with a different mechanism of action (MOA) than tralokinumab, as it selectively targets IL-13 and prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex (Ultsch, 2013). In recently published data from the Phase 2b study, lebrikizumab demonstrated efficacy across all key clinical outcome measures (eg, IGA, and EASI scores) in subjects with moderate to severe AD, particularly at the highest dose level evaluated (eg, loading doses of 500 mg at baseline and week 2, followed by 250 mg of lebrikizumab administered every other week for a total of 16 weeks). Robust efficacy was observed with lebrikizumab treatment on pruritus, with improvement in Pruritus NRS score of ≥ 4 points from baseline in 70% of subjects on treatment compared with 27.3 % of subjects on placebo at Week 16. In addition, changes of at least 4 points in the Pruritus NRS score were seen as early as Day 2 in 15.3% [9 of 59] subjects treated with lebrikizumab at the highest dose level, as compared to 4.5% [2 of 44] subjects treated with placebo. These promising clinical observations associated with itch reduction in subjects treated with lebrikizumab support the preclinical evidence that IL-13 directly sensitizes sensory neurons to respond to pruritogens (Miron 2018). In addition to the enhanced efficacy profile demonstrated by the Phase 2 results, lebrikizumab was generally well tolerated, and had a favorable safety profile consistent with previous lebrikizumab studies conducted in AD and the extensive asthma Phase 2b and Phase 3 programs which enrolled over 1000 subjects (Hanania, 2016, Korenblat, 2018). Common TEAEs (≥ 5% in any lebrikizumab group) included upper respiratory tract infection, nasopharyngitis, headache, injection site pain, and fatigue. Serious TEAEs including peripheral edema, chronic obstructive pulmonary disease, and pulmonary embolism were reported by 2 of 52 placebo subjects (3.8%) and by 4 of 228 lebrikizumab subjects (1.8%), which include reports of chest pain, periprosthetic fracture, hernial eventration, and panic attack (Guttman-Yassky, 2020).

Phase 3 studies with lebrikizumab in AD are currently ongoing; therefore, it is too soon to tell if the efficacy profile observed in the Phase 2b study will be replicated in registrational programs. However, lebrikizumab's efficacy and safety profile observed in the high dose arm in Phase 2b are encouraging, and support the hypothesis that higher dosing with therapeutic agents targeting IL-13 may be able to provide improved disease outcomes for patients with AD.

CC-93538 will be the most recent anti-IL-13 mAb to be evaluated as a potential therapeutic option for subjects moderate to severe AD. Although CC-93538 shares a similar MOA to tralokinumab, as it prevents IL-13 binding to both IL-13Rα1 and IL-13Rα2 (Tripp, 2017), further research is needed to better understand the role of IL-13 Rα2 in atopic skin inflammation and fibrosis (Furue, 2020). As response rates in AD studies vary across the current biologic agents, clinical investigations with new therapies, like CC-93538, provide a unique opportunity to potentially optimize efficacy, by leveraging existing knowledge available from similar compounds.

The concept of [redacted] his Phase 2 dose ranging study to evaluate the potential of CC-93538 as a highly effective and well tolerated treatment option for AD.

1.3.1.1. Benefit-Risk Assessment

As few advanced treatment options exist for patients with moderate to severe AD, there is an unmet need for new pharmacotherapies targeting the pathophysiology of AD with a safety and tolerability profile acceptable for long-term treatment. Based on the clinical safety and efficacy data with CC-93538 reported to date, the benefit-risk assessment of CC-93538 supports further development in AD and other inflammatory conditions.

CC-93538 a biologic immunomodulator targeting IL-13, was generally well tolerated in the Phase 2 study conducted in EoE subjects, without an increased risk of serious infection. Other immunomodulatory biologics in development or marketed for type 2 inflammatory diseases with a related mechanism of action, for example, dupilumab (targeting the IL-4 receptor, blocks IL-4Rα (alone) and blocks IL-13/IL-13Rα1 signaling (Harb, 2020), lebrikizumab (targeting IL-13), and tralokinumab (targeting IL-13), also have not been associated with an increased risk of serious viral infections based on data observed in the extensive Phase 2 and Phase 3 clinical program. Although targeted corona virus disease (COVID) related research with these agents is limited, small studies conducted in patients with AD from high endemic areas (eg, Lombardy, Italy) provides supplemental, real-world evidence, that that there does not appear to be an increased risk for COVID□19 infection in patients being treated dupilumab (Carugno, 2020), which has a MOA similar to CC-93538.

In order to minimize the overall risk to subjects, this protocol has inclusion and exclusion criteria appropriate to the population and proposed treatments (see Section 4.2 and Section 4.3). Exclusionary screening tests will be used to identify latent tuberculosis (TB), viral hepatitis, human immunodeficiency virus (HIV), and other risk assessment, such as a detailed assessment of medical history, will be performed. Each study visit will include an assessment for AEs, and subjects who develop an intercurrent illness between study visits are encouraged to contact the Investigator, who will determine if a clinical assessment is required. The Sponsor has also developed guidance for Investigators on how to manage a subject with a clinical suspicion of, or a diagnosis of, COVID-19. This includes criteria for temporarily interrupting or permanently discontinuing IP (Section 7.2.5 and Section 7.2.6), and criteria for reinitiating IP on resolution of a COVID-19 infection (Section 7.2.5). In order to facilitate reporting of COVID-19 events that occur during the study, all AEs and SAEs related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 must be reported from the time of consent (Section 10.1). In addition, such AEs or SAEs will also trigger additional data collection through specialized eCRF pages, which will allow the Sponsor to further evaluate these events.

While the global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general, and it may particularly affect individuals with underlying chronic diseases. Based on the available safety data with CC-93538, and the established safety profile established other biologic immunomodulator targeting the IL-13 pathway, the overall benefit-risk for participation in this AD study with CC-93538 is considered favorable. The individual benefit-risk considerations regarding COVID-19 infection remains the responsibility of the Investigator.

Testing to exclude COVID-19 infection prior to enrollment and to inform decisions about subject care during the study should follow local standard practice and requirements.

1.3.2. Rationale for the Study Design

This is a randomized double-blind, placebo controlled, 4 arm, parallel-group study to evaluate the efficacy and safety of 3 doses, as compared to placebo, of CC-93538 in subjects with moderate to severe AD who are candidates for systemic therapy (ie, not adequately controlled by a stable regimen [≥ 4 weeks] of topical corticosteroids or calcineurin inhibitors or not eligible for topical therapy due to side effects or safety risks).

Although this will be the first placebo-controlled efficacy and safety study of CC-93538 in subjects with AD, the pathophysiology of IL-13 as a key cytokine involved in type 2 inflammatory conditions well supported throughout the literature. CC-93538 is a mAb which is highly selective for human IL-13, and as such, has a potential therapeutic benefit in treating subjects with moderate to severe AD. Furthermore, the positive data observed in with other IL-13 mAb (tralokinumab and lebrikizumab) summarized in section Section 1.3.1, have demonstrated that targeting IL-13, is an effective, and well tolerated treatment option in subjects with moderate to severe AD, warranting further exploration of CC-93538 as alternative anti-IL-13 treatment option in this disease state.

In the Phase 1 clinical studies, single doses up to 10 mg/kg IV have shown CC-93538 to have acceptable safety and tolerability, and PK properties consistent with other IgG1 mAbs. The Phase 2 study (RPC02-201) in subjects with EoE, further demonstrated the safety and tolerability of CC-93538, and showed continued clinical, endoscopic, and histologic improvements in subjects treated with 360 mg SC for up to 68 weeks of treatment. The risk/benefit profile of CC-93538, as demonstrated in the Phase 2 EoE Study, RPC02-201, supports further development in additional type 2 inflammatory conditions, such as AD.

The 16-week treatment duration was selected based on an assessment of the efficacy and safety results from similar Phase 2 and Phase 3 AD studies, evaluating mAb (eg, dupilumab, lebrikizumab, and tralokinumab) with similar MOA, and terminal elimination half-life ($t_{½}$) to CC-93538. These studies showed that 16 weeks is an appropriate treatment duration to achieve a clinical response, across an array of standard efficacy measures in subjects with moderate to severe AD. In addition, the 16 week treatment duration, is further supported by the efficacy results obtained in the double-blind portion of Study RPC02-201 summarized in Section 1.2.2.4. This study also demonstrated efficacy at the Week 16 time point by a reduction in esophageal eosinophil count in subjects with EoE. In addition, the follow-up period of an additional 16 weeks is based the mean terminal elimination half-life ($t_{½}$) for CC-93538, which ranged from 16.4 to 26.7 days, similar to other mAbs.

The primary efficacy endpoint is the percentage change from baseline in EASI score at Week 16. The EASI is a validated and widely used clinical trial endpoint in AD. Thus, it allows contextualization with the full spectrum of approved and experimental drugs offering maximum opportunity for benchmarking and modeling of the relationships between PK, PD, safety, and efficacy. This study will use it on a continuous scale to maximize statistical efficiency, as well as categorical endpoint of at least a 75% improvement Eczema Area and Severity Index (EASI-75) that will be assessed as a key secondary endpoint.

In addition, the validated Investigator Global Assessment for AD (vIGA-AD), a well-established endpoint recommended for inclusion in AD studies by the Food and Drug Administration (FDA) and other health agencies, will be evaluated as a key secondary endpoint. This endpoint is an important adjunct to the EASI score and can provide insight into the registrational plausibility of the study drugs.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

The 3 SC doses of CC-93538 ([redacted] mg once weekly [QW], [redacted] mg Q2W, or [redacted] mg Q2W) were selected based on an evaluation the existing nonclinical and clinical data, which includes external data from other biologic agents with similar MOA, with an objective to explore the therapeutic potential of CC-93538 [redacted] in subjects with moderate to severe AD.

Although [redacted] mg of CC93538 administered SC QW is the proposed highest dose in this study, substantially higher exposures (both AUC and C_{max}) were attained at steady state in the 26 week chronic toxicity studies in monkeys in doses up to [redacted] mg/kg. There were no CC-93538-related adverse effects in this study, and the no observed adverse effect level (NOAEL) was established at the highest dose tested, [redacted] mg/kg when administered SC or IV QW for 26 consecutive weeks. In comparison to the estimated exposure at the proposed highest dose in adults ([redacted] mg of CC-93538 dosed SC QW), the attained exposures in monkey at the NOAEL were 23-fold (C_{max}) and 13-fold (AUC 0-168) higher. Further data related to the pre-clinical pharmacology studies and the toxicology studies are summarized in the Investigator Brochure

[redacted] In the Phase 2 EoE clinical study (RPC02-201) administration of CC-93538 as a single 10mg/kg IV loading dose followed by 360 mg SC QW for up to 68 weeks was well tolerated and demonstrated efficacy versus placebo in histologic, clinical and endoscopic measures. Although an exposure/response (E/R) model could not be fully established from this study (as both the 180 mg and 360 mg QW dose cohorts demonstrated comparable efficacy on the primary endpoint of histological improvement), the higher dose of 360 mg was associated with greater improvements in endoscopic and clinical symptom parameters in EoE patients. Consequently, investigation of higher doses of CC-93538 (up to 720 mg SC QW) in this Phase 2 AD study is warranted, to more fully explore the therapeutic potential and better understand the E/R relationship of CC-93538 in AD.

The evaluation [redacted] of CC-93538 in this study is further supported by published data from AD clinical trials with other agents targeting the IL-13 pathway (eg, lebrikizumab and tralokinumab). Data published from the lebrikizumab Phase 2b AD study demonstrated rapid, dose-dependent efficacy with a favorable safety profile in adult patients with moderate to severe AD using a broad range of doses, including up to 4 times the target efficacious dose evaluated in their previously completed Phase 2b and Phase 3 asthma studies (Guttman-Yassky, 2020; Hanania, 2016; Korenblat 2018).

Based on the external data observed with other anti-IL-13 mAbs, it is important to understand whether treatment with CC-93538 [redacted] can optimize the potential for clinical improvement in subjects with AD.

1.3.4. Rationale for Choice of Comparator Compounds

The study design employs a comparison to placebo which is intended to minimize bias and to provide an accurate determination of efficacy and safety findings attributable to CC-93538 administration. Placebo is an acceptable control commonly used in AD studies to allow an assessment of clinical improvement related to a therapeutic candidate. The ongoing use of non-medicated topical emollient, as well as the allowance for rescue for intolerable AD symptoms further described in Section 8.4 has been employed in the study to ensure that all subjects enrolled in the study, including those on the placebo arm have symptom management interventions available within the context of the study.

1.3.5. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

Epidermal barrier defects, dysregulation of innate immune responses, and altered type 2 immunity are implicated in the pathogenesis of AD, culminating in complex inflammatory responses involving multiple cell types, cytokines and chemokines. Relevant biomarkers including but not limited to peripheral blood eosinophils, immunoglobulin E (IgE), lactate dehydrogenase, IL-13, interleukin 22 (IL-22), chemokine (C-C motif) ligand 17 (CCL17)/thymus- and activation-regulated chemokine (TARC), and chemokine (C-C motif) ligand 18 (CCL18)/pulmonary and activation-regulated chemokine (PARC) will be evaluated for potential diagnostic or prognostic importance.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
• To evaluate the clinical efficacy of 3 dosage regimens of CC-93538 ([redacted] mg once weekly [QW], [redacted] mg every other week [Q2W], and [redacted] mg Q2W), compared with placebo on the change in the core clinical outcome measure, Eczema Area and Severity Index (EASI), in subjects with moderate to severe atopic dermatitis (AD)
Secondary Objectives
• To evaluate the effect of 3 CC-93538 dosage regimens, compared with placebo on additional clinical outcome measures and patient reported outcomes in subjects with moderate to severe AD • To evaluate the safety and tolerability, including characterization of the immunogenicity profile, of 3 dosage regimens of CC-93538, compared with placebo in subjects with moderate to severe AD • To assess the serum trough concentration of CC-93538 in subjects with moderate to severe AD
Exploratory Objectives
• To characterize the population pharmacokinetics (PK) of CC-93538 and to evaluate the exposure-response and pharmacodynamic relationships between CC-93538 exposure and efficacy, safety, and biomarker measures • To explore the onset of action associated with core clinical outcome measures in subjects with moderate to severe AD • To assess improvements from baseline in patient-reported outcome measures relevant to subjects with moderate to severe AD • To explore the effect of 3 dosage regimens of CC-93538 on AD-related inflammatory biomarkers, including, but not limited to peripheral blood eosinophils, immunoglobulin E (IgE), lactate dehydrogenase, interleukin 13 (IL-13), interleukin-22 (IL-22), chemokine (C-C motif) ligand 17 (CCL17)/thymus- and activation-regulated chemokine (TARC), and chemokine (C-C motif) ligand 18 (CCL18)/pulmonary and activation-regulated chemokine (PARC) • To assess the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologic status on subjects receiving CC-93538 and AD and to support health authority requests

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Change in Eczema Area and Severity Index (EASI%)	Percent change in EASI from Baseline at Week 16	Week 16
Key Secondary	Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) 0 or 1	Proportion of subjects with an vIGA-AD score of 0 (clear) or 1 (almost clear) and a reduction ≥ 2 points from Baseline at Week 16	Week 16
	EASI-75	Proportion of subjects with at least a 75% improvement from Baseline in Eczema Area and Severity Index (EASI-75) at Week 16	Week 16
Secondary	Change in Pruritus Numerical Rating Scale (NRS)	Percent change from Baseline in Pruritus NRS at Week 16	Week 16
	Pruritus NRS Response Threshold	Proportion of subjects with Pruritus NRS change of ≥ 4 points from Baseline at Week 16	Week 16
	Onset of Change in Pruritus NRS	Time to achieve at least 4 points of improvement in the severity of pruritus NRS scale in the first 16 weeks of treatment	All planned time points through Week 16
	EASI-90	Proportion of subjects with at least a 90% improvement from Baseline in Eczema Area and Severity Index (EASI-90) at Week 16	Week 16
	SCORing Atopic Dermatitis (SCORAD) Index	Mean change in SCORAD Scores from Baseline at Week 16	Week 16
	AD Body Surface Area (BSA) involvement	Percent change in BSA involved with AD from baseline at Week 16	Week 16
	Safety and Tolerability	Safety and tolerability evaluated by the incidence, severity, and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, as well as an evaluation of the presence of serum antibodies to CC-93538.	All planned time points through Final Follow Up Visit
	Pharmacokinetics (PK)	Serum trough concentration of CC-93538	All planned time points through Final Follow Up Visit

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory	Onset of Action for Key Efficacy Parameters	Proportion of subjects with at least a 50% improvement from Baseline in Eczema Area and Severity Index (EASI-50) in the first 4 weeks of treatment	All planned time points through Week 4
		Proportion of subjects to achieve EASI-75 in the first 4 weeks of treatment	All planned time points through Week 4
		Proportion of subjects with an vIGA-AD score of 0 (clear) or 1 (almost clear) in the first 4 weeks of treatment	All planned time points through Week 4
	vIGA-AD 0 or 1 and EASI-75	Proportion of subjects achieving both a vIGA-AD score of 0 (clear) or 1 (almost clear) and an EASI-75 at Week 16	Week 16
	PROMIS® Sleep Disturbance Short Form 8a	Mean change in sleep disturbance total score from Baseline to Week 16	Week 16
	Patient Oriented Eczema Measure (POEM) Score	Mean change in POEM scores from Baseline to Week 16	Week 16
	Dermatology Quality of Life Index (DLQI) Score	Mean change in DLQI score from Baseline to Week 16	Week 16
	Hospital Anxiety and Depression Scale (HADS)	Mean change in anxiety and depression total scores from Baseline to Week 16	Week 16
	Population PK	CC-93538 population pharmacokinetic parameters and covariates	All planned time points through Final Follow Up Visit
	Exposure-responses and pharmacodynamics relationship	Exposure-response and pharmacodynamics relationships between CC-93538 exposure and efficacy, safety measures (eg, AEs, labs, etc) and biomarkers	All planned time points through Final Follow Up Visit

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory (Continued)	Biomarkers	CC-93538 treatment response as a function of baseline and change from Baseline in whole blood, serum, and tissue biomarkers (eg, peripheral blood eosinophils, immunoglobulin E [IgE], etc)	Week 16
	Biomarkers	Exploratory Measurements of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology (anti-SARS-CoV-2 total or IgG), from serum samples	Day 1 and Week 16

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, Phase 2 study to evaluate the efficacy and safety of CC-93538 in adult subjects with moderate to severe AD. Subjects participating in the study must also be candidates for systemic therapy, defined as having an intolerance or inadequate response to treatment with topical medications for at least 4 weeks, or who have required at least 1 systemic therapy to control their disease.

After completion of an up to 4-week screening period, approximately 200 eligible subjects (50 subjects per arm) will be randomized (1:1:1:1) to receive either CC-93538 ([redacted] mg QW, [redacted] mg Q2W, or [redacted] mg Q2W) or placebo for 16 weeks. Treatment assignment will be stratified by geographic region (Japan versus rest of world); within rest of world region only, randomization will also be stratified by disease severity based on the baseline vIGA-AD score (3 [moderate] or 4 [severe]). Randomization will occur on Day 1 (Baseline) through the use of Interactive Response Technology (IRT) system.

The overall benefit/risk profile of the CC-93538[redacted] mg SC QW dose will be initially explored in this study. [redacted] to further evaluate the safety and efficacy profile of CC-93538 [redacted], additional safety assessments, such as increased onsite visit frequency, ongoing blinded safety reviews of the study data, oversight from an internal Safety Management Team (SMT), and oversight from an external independent Data Monitoring Committee (DMC), further described in Section 6.6) will be conducted during the study to ensure that the safety of the subjects is adequately monitored.

Clinical laboratory tests, vital signs, physical examinations (including height and weight), pregnancy tests, clinical symptom assessments, patient-reported outcomes, serum CC-93538 concentrations, serum antibodies to CC-93538 (to assess immunogenicity), concomitant medications, and AE assessments will be performed according to the Table of Events as presented in Section 5. Relevant biomarkers including but not limited to peripheral blood eosinophils, IgE, lactate dehydrogenase, IL-13, IL-22, CCL17 (TARC), and CCL18 (PARC) will be measured pre- and post-treatment, as outlined in the table of events.

Although concurrent treatment with background therapy to alleviate AD symptoms is prohibited during the Treatment and Follow Up periods of the study, the use of rescue medication, described in Section 8.4, may be employed for subjects who experience intolerable AD symptoms after randomization.

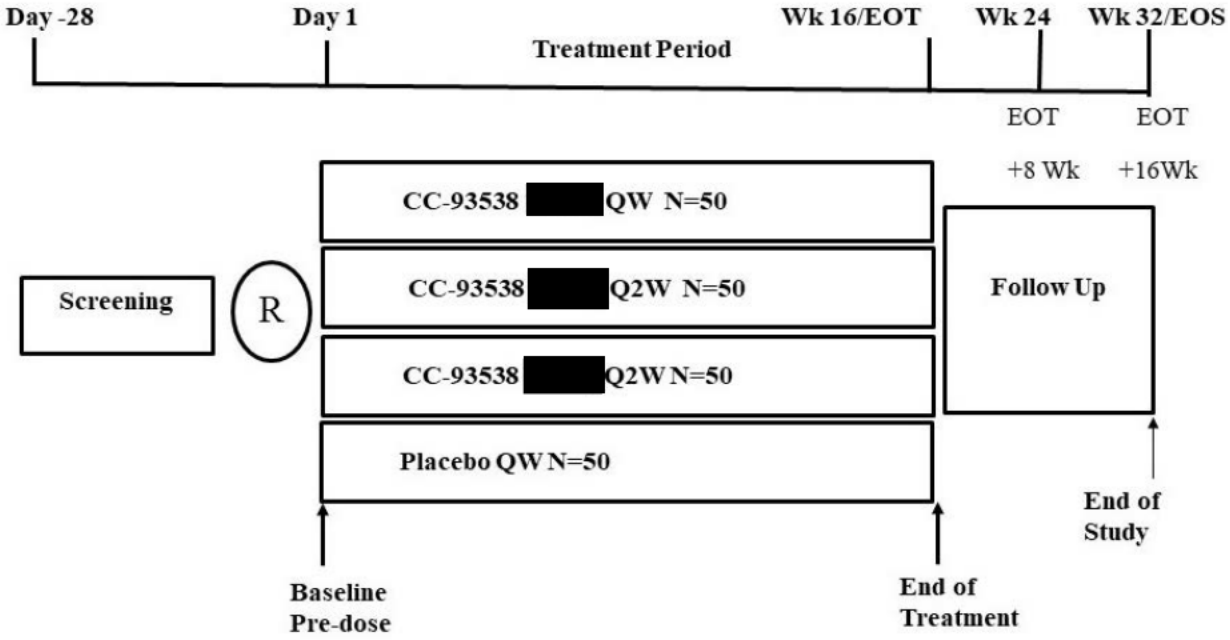
The maximum duration of subject participation in this study is approximately 36 weeks. Subjects will participate up to 4 weeks in the Screening Period. Subjects will participate in a Screening Period that lasts up to 4 weeks. Over the treatment period, subjects will receive a total of 16 doses IP, administered QW, starting at Day 1/ Week 0 and ending at Week 15. At Week 16, subjects will return for the End of Treatment Visit for safety and efficacy assessments. Following the Week 16 End of Treatment Visit, subjects will enter a 16 Week Follow Up Period, and will return for 2 additional visits to assess safety, clinical status, PK/PD, and serum antibodies to CC-93538.

The Initial Follow Up Visit will be conducted 8 weeks after the End of Treatment Visit (Week 24) and the Final Follow Up/End of Study Visit will be conducted 16 weeks after the End of Treatment Visit (Week 32).

The blind should be maintained for persons responsible for the ongoing conduct of the study until after the primary analysis database lock, that is projected to be initiated after all subjects have completed Week 16/End of Treatment Visit assessments. Blinded persons may include but are not limited to: Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, Clinical Research Associates.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Overall Study Design



3.2. Study Duration for Subjects

The maximum duration of subject participation in this study is approximately 36 weeks. Subjects will participate up to 4 weeks in the Screening Period. Upon randomization, subjects will enter the Treatment Phase of the study, and will receive a total of 16 doses of IP starting at Day 1 (Baseline) and ending at Week 15.

At Week 16, subjects will return for the End of Treatment Visit for safety and efficacy assessments. Following the Week 16 End of Treatment Visit, subjects will enter a 16 Week Follow Up Period, and will return for 2 additional visits to assess safety, clinical status, PK/PD, and serum antibodies to CC-93538. The Initial Follow Up Visit will be conducted 8 weeks after

the End of Treatment Visit (Week 24) and the Final Follow Up/End of Study Visit will be conducted 16 weeks after the End of Treatment Visit (Week 32).

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 200 adult subjects (aged 18 to 75 years) with moderate to severe AD will be randomized worldwide.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject must be ≥ 18 years and ≤ 75 years of age and have a body weight of ≥ 40 kg (88.2 lb) at the time of signing the informed consent form (ICF). Subjects in Japan must also be of legal age of consent (≥ 20 years of age) at the time of signing the ICF.
2. Subject has chronic AD as defined by Hanifin and Rajka (Appendix B) that has been present for ≥ 1 year prior to the baseline visit (Day 1).
3. Subject has moderate to severe, active, and symptomatic AD defined by meeting all of the following criteria on the day of the baseline visit (Day 1):
   a. Body Surface Area (BSA) ≥ 10%, and
   b. EASI score ≥ 16, and
   c. vIGA-AD ≥ 3, and
   d. Pruritus NRS severity score ≥ 4.
4. Subject must have a documented history of inadequate response to treatment with topical medications for at least 4 weeks, unless topical treatments are otherwise medically inadvisable (eg, because of important side effects, safety risks, and/or previous intolerance), or has required systemic therapy for control of disease.

   Inadequate response is defined as either or both of:

   a. failure to achieve and/or maintain a disease activity state comparable to IGA 0 [clear] to 2 [mild], despite treatment with a daily regimen of TCS of medium to higher potency (± TCI as appropriate), applied for at least 4 weeks (28 days) or for the maximum duration recommended by the product prescribing information, whichever was shorter, OR
   b. necessity of systemic therapy to control disease.
5. Subject must be willing to apply a stable dose of topical emollient (eg, over-the-counter moisturizer, non-medicated emollient, etc.) twice daily for ≥ 7 days prior to the Baseline visit and continue application throughout the study. Refer to Section 8.3 for additional requirements related to application of topical emollient throughout the study.
6. Subject must commit to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.
7. Subjects currently receiving concomitant medications for any reason other than AD, such as inhaled corticosteroids, leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) for asthma, must be on a stable regimen, which is defined as not starting a new drug, changing, or stopping dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and through the treatment duration of the study.

8. Female subjects of childbearing potential must agree to practice a highly effective method of contraception. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months) and must:

   a. Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study and through the Final Follow-up Visit. This applies even if the subject practices true abstinence* from heterosexual contact.
   b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, highly effective contraception without interruption throughout the study and for 5 months after the last dose of IP.

   Acceptable methods of birth control in this study are the following:

   a. combined hormonal (estrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
      Note: Intravaginal and transdermal combined hormonal contraception are not approved by Japan Health Authority and would therefore not be acceptable methods contraception for subjects enrolled in this region.
   b. progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable.
      Note: progestogen-only hormonal contraception is not approved by Japan Health Authority and would therefore not be acceptable methods contraception for subjects enrolled in this region.
   c. placement of an intrauterine device (IUD)
   d. placement of an intrauterine hormone-releasing system (IUS)
   e. bilateral tubal occlusion
   f. vasectomized partner
   g. sexual abstinence.

9. Subject is willing to receive weekly SC injections throughout the study.
10. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
11. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

* True abstinence is acceptable when this is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception.

4.3. Exclusion Criteria

1. The presence of any of the following will exclude a subject from enrollment: Evidence of an active and/or concurrent inflammatory skin condition (eg, seborrheic dermatitis, psoriasis, acute allergic contact dermatitis, etc.) that would interfere with the Investigator or subject-driven evaluations of AD.
2. Evidence of acute AD flare between the Screening and Baseline/ Randomization (eg, doubling of the EASI score between Screening and Baseline).
3. Use of topical treatments that could affect the assessment of AD (eg, corticosteroids, calcineurin inhibitors, tars, antibiotic creams, topical antihistamines) within 7 days of the Day 1 visit.
4. Received phototherapy narrowband UVB (NB-UVB) or broad band phototherapy within 4 weeks prior to the Baseline visit.
5. Evidence of immunosuppression, subject is receiving, or has received systemic immunosuppressive or immunomodulating drugs (eg, azathioprine, cyclosporine, systemic corticosteroids, interferon gamma (IFN-γ), Janus kinase inhibitors, methotrexate, mycophenolate-mofetil, etc.) within 4 weeks prior to the Baseline visit.
6. Treatment with immunomodulatory biologics as follows:
    a. Dupilumab within 3 months of Baseline visit.
    b. Cell-depleting biologics, including to rituximab, within 6 months prior to the Baseline visit.
    c. Other immunomodulatory biologics within 5 half-lives (if known) or 16 weeks prior to Baseline visit, whichever is longer.
7. Concurrent treatment with another IP, including through participation in an interventional trial for COVID-19. Prospective subjects may not participate in a concurrent IP study or have received an IP within 5 drug half-lives prior to signing the ICF for this study. Further, for subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Clinical Trial Physician.
8. Received a live attenuated vaccine within 1 month prior to the first Screening Visit or anticipates the need to be vaccinated with a live attenuated vaccine during the study. Administration of any live attenuated vaccine will be prohibited during the study through the Final Follow-up Visit.
9. Previously received CC-93538 treatment (formerly known as RPC4046 and ABT-308).
10. Liver function impairment or persisting elevations of aspartate aminotransferase (AST/ serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT/ serum glutamic pyruvic transaminase [SGPT]) that are 2 or more times the upper limit of normal (ULN), or total bilirubin 1.5 times the ULN. Subjects with elevations that are not clinically significant in total bilirubin associated with Gilbert's syndrome may participate.

11. Active chronic or acute skin infection that requires treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1.
12. Active parasitic/helminthic infection or a suspected parasitic/helminthic infection. Subjects with suspected infections may participate if clinical and/or laboratory assessments rule out active infection prior to randomization.
13. Ongoing infection (including but not limited to, hepatitis B or C, human immunodeficiency virus [HIV], or tuberculosis as defined by standard medical guidelines and as outlined in Section 6.1 for which testing to rule out is required during screening).
14. A previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 4 weeks prior to screening. Symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment. Refer to Section 6.1.3 for additional guidance related to SARS-CoV-2 testing during screening.
15. Is pregnant or lactating.
16. A history of idiopathic anaphylaxis or a major immunologic reaction (such as anaphylactic reaction, anaphylactoid reaction, or serum sickness) to an immunoglobulin G (IgG) containing agent. A known hypersensitivity to any ingredient in the investigational product (IP) is also exclusionary.
17. History of cancer or lymphoproliferative disease, other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or adequately treated cervical carcinoma in situ, within 5 years of screening.
18. History of alcohol or drug abuse within 5 years prior to initiation of screening.
19. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
20. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
21. Any other condition that confounds the ability to interpret data from the study.

5. TABLE OF EVENTS

Table 3: Screening Visit Procedures

List of Screening Visit Study Procedures	Visit Timing (Day -28 to Day 0)	Additional Notes (if applicable)
Informed consent (ICF)	X	Includes consent for the optional skin biopsy procedures.
Inclusion/Exclusion criteria	X	To be assessed at initially during screening and confirmed at Day 1. Screening laboratory tests will be used to determine eligibility for randomization with the exception of pregnancy tests, which will need to be confirmed by the Day 1 test results. The baseline validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD), Eczema Area and Severity Index (EASI), Body Surface Area (BSA), and the patient reported Pruritus Number Rating Scale (NRS) performed on Day 1 will be used to assess subject eligibility; the stratification data point for vIGA-AD score will be provided for randomization.
Demographics/baseline characteristics	X	Baseline characteristics and prior therapy assessments include the collection of details specifically related to atopic dermatitis (AD), including disease diagnosis and duration, the use of topical treatments, systemic treatments and other treatments for AD.
Medical history	X	
Prior therapy	X	
Concomitant therapy	X	All additional treatments (including prescription and over the counter [OTC] medications, herbal and dietary supplements, dietary modifications, and procedures) used by subjects within the 4 weeks (28 days) prior to the first Screening Visit or at any time during the study. Refer to Section 8 for additional guidance. During screening subjects should be instructed to apply a stable dose of topical emollient (over-the-counter moisturizer) twice daily for ≥ 7 days prior to the Baseline visit.
Adverse Events (AEs)/Serious Adverse Events (SAEs)	X	All AEs/SAEs will be recorded by the Investigator from the time the subject signs informed consent. Refer to Section 10 for additional guidance on AE/SAE collection.
Hematology and chemistry	X	Refer to Section 6.1 and Section 6.1.1 for additional guidance on the collection of safety laboratory samples.
Coagulation panel	X	
Urinalysis	X	

Table 3: Screening Visit Procedures (Continued)

List of Screening Visit Study Procedures	Visit Timing (Day -28 to Day 0)	Additional Notes (if applicable)
Testing for hepatitis B and C and Human immunodeficiency virus	X	Testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and Human immunodeficiency virus (HIV) will be performed at screening only, and will be analysed by the central laboratory. Refer to Section 6.1 for additional details.
Testing for tuberculosis (TB)	X	Testing for TB will be performed at screening only. Active TB must be ruled out according to local medical practices. TB must be assessed with a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (IGRA) (eg, T-SPOT). Refer to Section 6.1 for additional guidance.
Pregnancy test females of childbearing potential (FCBP) only	X	A serum pregnancy test will be required at screening Follicle-Stimulating Hormone (FSH) lab test should be performed to confirm that the status for subjects who assumed to be of non-childbearing potential. In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. For FCBP subjects: Birth control must be effective by the time the FCBP subject is randomized into the study (eg, hormonal contraception should be initiated at least 28 days before randomization). If necessary, the randomization/Day 1 Visit may be delayed up to a maximum of 28 days to achieve the minimum treatment duration. If the Day 1 Visit is delayed, the Medical Monitor should be contacted to confirm if any screening assessments (eg, safety labs, etc.) need to be repeated prior to randomization
Physical exam (complete)	X	A complete physical examination includes an evaluation of heart, lung, head and neck, abdomen, neurological assessment, and extremities.
Height and Weight	X	
Vital Signs	X	Vital signs: Heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature will be assessed. Blood pressure and pulse will be assessed in a sitting position and once the subject is at rest. An automated validated device may be used, if available.
Electrocardiogram (ECG)	X	Single 12-lead ECG will be conducted only at the Screening Visit when the subject is at rest and may be repeated to confirm any abnormal findings.

Table 3: Screening Visit Procedures (Continued)

List of Screening Visit Study Procedures	Visit Timing (Day -28 to Day 0)	Additional Notes (if applicable)
Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)	X	The vIGA-AD must be conducted before the EASI assessment. Further information on this assessment is available in Section 6.4.1 and Appendix C
Eczema Area and Severity Index (EASI)	X	Further information on this assessment is available in Section 6.4.2 and Appendix D
Body Surface Area % (BSA)	X	Further information on this assessment is available in Section 6.4.3 and Appendix E
Pruritus Numeric Rating Scale (NRS)	X	The electronic patient-reported outcome (ePRO) instrument on a handheld device will be distributed to subjects at the Screening Visit. After completion of a training module, the Pruritus NRS will be completed by the subject daily for at least the last week (7 days) during the Screening Period (prior to Day 1).

Table 4: Treatment Period Procedures

Study Procedure	Treatment Period[a]																EOT /ET
Visit Label (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Visit Week (W) Day (d) (Visit Window in Days)	**W0 d1 ±3d**	**W1 d8 ±3d**	**W2 d15 ±3d**	**W3 d22 ±3d**	**W4 d29 ±3d**	**W5 d36 ±3d**	**W6 d43 ±3d**	**W7 d50 ±3d**	**W8 d57 ±3d**	**W9 d64 ±3d**	**W10 d71 ±3d**	**W11 d78 ±3d**	**W12 d85 ±3d**	**W13 d92 ±3d**	**W14 d99 ±3d**	**W15 d106 ±3d**	**W16 d113 ±3d**
Inclusion/ Exclusion Criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry (pre-dose)	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Fasting Lipid Panel (pre-dose)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Urinalysis (pre-dose)	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X
SARS-CoV-2 Serology[b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Pregnancy test (FCBP only)[c]	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Physical exam complete	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Physical exam brief	-	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	-
Weight	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Vital signs	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Serum antibodies CC-93538 pre-dose[d]	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Serum CC-93538 PK sample (pre-dose)	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Whole blood and serum biomarker samples (pre-dose)	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Skin Biopsy (Optional)[e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Pharmacogenetic sample [f]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4: Treatment Period Procedures (Continued)

Study Procedure	Treatment Period[a]																EOT /ET
Visit Label (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Visit Week (W) Day (d) (Visit Window in Days)	**W0 d1 ±3d**	**W1 d8 ±3d**	**W2 d15 ±3d**	**W3 d22 ±3d**	**W4 d29 ±3d**	**W5 d36 ±3d**	**W6 d43 ±3d**	**W7 d50 ±3d**	**W8 d57 ±3d**	**W9 d64 ±3d**	**W10 d71 ±3d**	**W11 d78 ±3d**	**W12 d85 ±3d**	**W13 d92 ±3d**	**W14 d99 ±3d**	**W15 d106 ±3d**	**W16 d113 ±3d**
validated Investigator Global Assessment of Atopic Dermatitis (vIGA-AD)[g]	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Eczema Area and Severity Index (EASI)	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Body Surface Area (BSA)	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X
SCORing Atopic Dermatitis (SCORAD)	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Pruritus NRS[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Promise Sleep Disturbance Short Form 8a	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Patient Oriented Eczema Measure (POEM)	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Dermatology Life Quality Index (DLQI)	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X
Hospital Anxiety and Depression Scales (HADS)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Randomization via IRT	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IP administration[i, j, k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibody; AE = adverse event; d = day, EASI = Eczema Area and Severity Index; ePRO = electronic patient reported outcome; EOT = End of Treatment, ET = Early Termination, FCBP = female of child bearing potential, FU=Follow Up; IP = investigational product; IRT = Interactive Response Technology; NRS = numerical rating scale; POEM = Patient Oriented Eczema Measure; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; vIGA-AD = validated Investigator Global Assessment of Atopic Dermatitis, V = visit; Wk = week

[a] During the treatment period Day 1 through Visit 16/Week 15: On study visit days, showering or bathing is permitted prior to attending the study visit, but subjects must not moisturize or apply emollient. Non-medicated emollient is allowed after the visit.

[b] Serum will be collected at Day 1(Baseline), at the EOT/ET Visit, as well as approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, for possible measurements of anti-SARS-CoV-2 total or IgG per national and local requirements.

[c] For females of childbearing potential (FCBP), Urine (or serum) pregnancy test at Day 1, and urine pregnancy tests every 4 weeks thereafter are required. At each study visit, the Investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.
[d] Further analysis on samples that are positive for ADA may be performed, including assessment of neutralizing antibodies when warranted.
[e] An optional skin biopsy procedure will be performed to measure tissue biomarkers including target expression levels and inflammatory biomarkers in subjects who consented.
[f] The pharmacogenetic sample will be collected from subjects, provided that necessary governmental and local approvals have been obtained. If needed, the pharmacogenetic sample can be collected at any subsequent timepoint during the study.
[g] The vIGA-AD must be conducted before the EASI assessment.
[h] Pruritus NRS will be collected daily in a subject ePRO during the screening period. Scores will be captured daily from Day 1 (Baseline) through Week 4, followed by subsequent administration only on study visit/study drug administration days. Score recorded at Day 1(Baseline) (pre-dose) should be used to assess eligibility criteria. The electronic patient-reported outcome handheld device should be returned at the EOT/ET Visit.
[i] Once weekly IP administration (CC-93538 or placebo: subcutaneous [SC] doses on Day 1 followed by SC doses weekly from Week 1 through Week 15 [ie, a total of 16 weekly SC doses inclusive of the Day 1 dose]). The first 3 weekly SC doses will be administered in the clinic. Subjects will remain in the clinic for at least 30 minutes following dosing for observation for the first 3 visits.
[j] Starting at Week 3, subjects may have the option to return to the clinic every other week for IP administration, and have their alternate week injections administered at home by a visiting home health nurse. Subjects who utilize the home health nurse option will be required to return to the site every 2 weeks at a minimum (eg, Week 4 [Visit 5/Day 29], Week 6 [Visit 7/Day 43], Week 8 [Visit 9/Day 57], Week 10 [Visit 11/Day 71], Week 12 [Visit 13/Day85], Week 14 [Visit 15/Day 99], and Week 16 [Visit 17/Day 113]) during the treatment phase of study for scheduled laboratory collections, and additional safety and efficacy assessments. In addition, on the weeks that the IP is not administered in-clinic, the subject will be contacted by site personnel (within 24 hours) to assess for any changes in concomitant medication use and assess for adverse events.
[k] Subjects for whom home health nurse services are not available in their region, or who choose not to utilize the visit home health nurse service option, will be required return to the clinic weekly for their injections.

Table 5: Follow Up Period Procedures

Study Procedure	**Follow-Up (FU) Period**		
Visit Label	**Initial Follow Up Visit 18 (Week 24)**	**Final Follow Up/ End of Study (EOS) Visit 19 (Week 32)**	**Additional Notes (if applicable)**
Visit Timing (Visit Window)	**End of Treatment (EOT) Visit +8 Weeks (±7 day)**	**EOT Visit Last Dose +16 Weeks (±7 day)**	**All visits conducted during the Follow Up Period are onsite visits.**
Concomitant therapy	X	X	Refer to Section 8 for additional guidance.
Adverse Events (AEs)/Serious Adverse Events (SAEs)	X	X	Refer to Section 10 for additional guidance on AE/SAE collection.
Hematology and chemistry	X	X	Refer to Section 6.1 and Section 6.1.1 for additional guidance on the collection of safety laboratory samples.
Urinalysis	X	X	
Urine (or serum) pregnancy test (female of child-bearing potential only)	X	X	At each study visit, the Investigator will counsel female of child-bearing potential (FCBP) subjects on pregnancy precautions for the duration of the study
Physical exam (complete)	X	X	A complete physical examination includes an evaluation of heart, lung, head and neck, abdomen, neurological assessment, and extremities.
Vital signs	X	X	Vital signs: Heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature will be assessed at each visit. Blood pressure and pulse will be assessed in a sitting position and once the subject is at rest. An automated validated device may be used, if available.
Serum antibodies CC-93538	X	X	Further analysis on samples that are positive for anti-drug-antibodies (ADA) may be performed, including assessment of neutralizing antibodies when warranted.
Serum CC-93538 pharmacokinetic (PK) sample	X	X	
Whole blood and serum biomarker samples	X	X	

Table 5: Follow Up Period Procedures (Continued)

Study Procedure	Follow-Up (FU) Period		
Visit Label	Initial Follow Up Visit 18 (Week 24)	Final Follow Up/ End of Study (EOS) Visit 19 (Week 32)	Additional Notes (if applicable)
Visit Timing (Visit Window)	EOT Visit +8 Weeks (±7 day)	EOT Visit Last Dose +16 Weeks (±7 day)	All visits conducted during the Follow Up Period are onsite visits.
Skin Biopsy (Optional)		X	An optional skin biopsy procedure will be performed to measure tissue biomarkers including target expression levels and inflammatory biomarkers in subjects who consented
validated Investigator Global Assessment of Atopic Dermatitis (vIGA-AD)	X	X	The vIGA-AD must be conducted before the EASI assessment. Further information on this assessment is available in Section 6.4.1 and Appendix C
Eczema Area and Severity Index (EASI)	X	X	Further information on this assessment is available in Section 6.4.2 and Appendix D

6. PROCEDURES

Assessments and procedures for the Screening Period (Table 3), Treatment Period (Table 4), and the Follow-up Period (Table 5) are included in Section 5 the Table of Events. Study assessments and procedures are also described in Section 6. The day of administration of the first dose of IP is defined as Day 1 (Baseline/pre-dose).

It is recommended that the study visits are scheduled in the morning. Whenever possible, the assessment order sequence, as outlined in the Table of Events Section 5, should remain constant and should be conducted at approximately the same time of day throughout the study.

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days (4 weeks) prior to receiving the first dose of IP unless noted otherwise below. Waivers to the protocol will not be granted during the conduct of this study, under any circumstances.

Screening procedures, as specified in the Table of Events detailed in Section 5, Table 3, will be performed for all subjects to determine study eligibility. All screening procedures must be completed within 4 weeks prior to receiving the first dose of IP.

The electronic patient-reported outcome (ePRO) instrument on a handheld device will be distributed to subjects at the Screening Visit. After completion of a training module, the Pruritus NRS will be completed by the subject daily for at least the last week (7 days) during the Screening Period (prior to Day 1); however, value to assess inclusion criteria will be assessed on Day 1 (Baseline/pre-dose).

Safety laboratory analyses and all assessments will be performed. Screening laboratory values must demonstrate subject eligibility; however, analytes may be repeated (and analysed by the central laboratory) within the screening window, if necessary.

Written, signed, and dated informed consent from the subject prior to the performance of any study related procedures must be obtained by the Principal Investigator or designee (refer to Section 12.3 for further details regarding obtaining subjects informed consent). A copy of the signed informed consent must be given to the subject for his/her records.

The following evaluations will be performed at screening as specified in the Table of Events, after informed consent/assent has been obtained:

- Assessment of inclusion/exclusion criteria
- Demographics and baseline characteristics
- Medical history including atopy status (documentation of AD history, other atopic conditions, and past pharmacotherapy for AD, and other atopic conditions) and as well as details of any prior therapy or procedures to treat AD or other atopic conditions.

- Prior therapy and concomitant therapy (including all procedures occurring ≤ 28 days before screening).
- Adverse event assessment begins when the subject signs the informed consent/assent form. Throughout the course of the study, every effort must be made to remain alert to possible AEs or serious AEs (SAEs). Once subjects consent, AEs/SAEs will be recorded at each study visit. Refer to Section 10 for definitions of AEs/SAEs, monitoring, and reporting
- Hematology, chemistry, coagulation panel, and urinalysis (central laboratory). The following safety laboratory tests will be performed to assess the safety profile of CC-93538:
  - Hematology: red blood cell (RBC) count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin (hgb), hematocrit (hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)
  - Blood chemistry: indices included at all required chemistry timepoints are sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose (random, at timepoints not requiring fasting), albumin, alkaline phosphatase, creatinine, creatine phosphokinase (CPK), ALT/SGPT, AST/SGOT, gamma glutamyltransferase (GGT), amylase, total bilirubin, direct bilirubin and C reactive protein (CRP); in addition, fasting lipid panel (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) and fasting glucose (instead of random glucose) will be performed only at Day 1 and Week 16/EOT/ET.
  - Coagulation: Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- Testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV (central laboratory) will be performed at screening only.
  - HBV: Hepatitis B surface antigen (HBsAg) screening test and hepatitis B core antibody (HBcAb) test will be performed. Subjects who test positive for HBsAg will be excluded from the study. For subjects who test positive only for HBcAb, an HBV deoxyribonucleic acid (DNA) test must be performed. If the HBV DNA test is positive, the subject will be excluded from the study. If the HBV DNA test is negative (without antiviral therapy) and ALT and AST are ≤ ULN, the subject will be eligible for this study.
  - HCV: HCV antibody (anti-HCV IgG) test will be performed. Subjects testing positive for HCV antibody and have a positive confirmatory test (HCV ribonucleic acid [RNA]) will be excluded from the study. Subjects with evidence of cleared HCV infection (eg, HCV antibody positive subjects who are negative

for HCV RNA) and who have not received anti-HCV therapy for at least 12 weeks will be eligible for participation.

  - HIV: An HIV antibody test will be performed. Subjects testing positive for HIV (enzyme-linked immunosorbent assay [ELISA] test result, confirmed by western blot) will be excluded from the study.

- Testing for tuberculosis (TB) will be performed at screening only. Active TB must be ruled out according to local medical practices. TB must be assessed with a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (IGRA) (eg, T-SPOT). Subjects with latent TB must have documentation of completed prophylactic treatment by local standard of care. Subjects with an indeterminate test result using any IGRA test, must be discussed for eligibility on a case by case basis by the Sponsor's Medical Monitor or designee. Subjects with latent TB who were only partially treated or who are currently receiving prophylactic treatment will not be eligible for randomization.
- Serum pregnancy test (only for FCBP). A test for the β-subunit of serum human chorionic gonadotropin (β-hCG) must be performed at screening in females of childbearing potential. Urine (or serum) β-hCG will be performed at Day 1 and at the timepoints outlined in the Table of Events (Table 4). In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. At screening and at each subsequent study visit, the Investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.
- Physical examination: A complete physical examination (including evaluation of heart, lung, head and neck, abdomen, neurological assessment, and extremities) will be performed.
- Height and weight.
- Vital signs: Heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature will be assessed. Blood pressure and pulse will be assessed in a sitting position and once the subject is at rest. An automated validated device may be used, if available.
- Electrocardiogram (ECG): Single 12-lead ECG will be conducted only at the Screening Visit when the subject is at rest and may be repeated to confirm any abnormal findings.
- AD disease activity assessments:
  - vIGA-AD
  - EASI
  - BSA
  - Pruritus NRS

6.1.1. Additional Information Regarding Safety Laboratory Assessments

Analysis of samples will be conducted by a central laboratory. Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a Study Laboratory Manual. The results of the analysis will be made available to each site by the central laboratory.

Additional and repeat laboratory safety testing may be performed locally at the discretion of the Investigator. As local laboratory data will not be collected in the electronic case report form (eCRF), if feasible, a sample should also be sent to the central laboratory. In addition, when safety laboratory samples are being collected to further assess AEs, it is recommended that serum samples to assess ADA and PK also be collected and sent to the central laboratory, when feasible. Laboratory samples required to confirm study eligibility (eg, liver function test, serology panel, etc) are required to be performed by the central laboratory if a retest is required during Screening. Retesting of specific laboratory parameters to confirm eligibility is allowed once during screening. If upon retest the subject still does not meet eligibility criteria, the subject should be screen failed.

Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each abnormal finding in the subject's source documents. The laboratory reports/records will be filed with the subject's source documents. Reporting of laboratory AEs is described in Section 10.3.

6.1.2. Screening Failures and Rescreening of Potential Subjects

A screen failure is defined as a subject who has given informed consent/assent and failed to meet the inclusion and/or exclusion criteria. Subjects who initially fail to meet the inclusion/exclusion criteria may be re-screened as per the assessment of the Investigator. Subjects who are re-screened will be required to be re-consented and have all required Screening Visit procedures performed. Subjects may be re-screened only 1 additional time for the study without prior consultation with the Medical Monitor.

6.1.3. Rescreening of subjects who develop COVID-19 during the Screening Period

Molecular testing for asymptomatic COVID-19 infection is not required in this study. However, where local requirements or institutional practice are more restrictive, asymptomatic COVID-19 screening may be performed locally, to ensure compliance with current local guidance. In addition, some subjects may develop suspected or confirmed symptomatic COVID-19 infection, or it is discovered that subjects have asymptomatic COVID-19 infection during the Screening Period. In such cases, subjects may be considered eligible for the study after meeting all Inclusion/Exclusion Criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Symptoms (eg, cough and shortness of breath) have resolved, and

- In the opinion of the Investigator, there are no COVID-19 sequelae that may place the subject at a higher risk of receiving investigational treatment, and
- Negative follow-up molecular test for COVID-19 based on institutional, local and/or regional guidelines and/or requirements

6.2. Treatment Period

On Day 1, prior to randomization in the, the baseline assessments (including laboratory assessments, and the optional skin biopsy), as shown in the Table of Events Section 5, Table 4, will be completed prior to the administration of IP. The Investigator will review all available information to confirm subject eligibility.

- Screening laboratory tests will be used to determine eligibility for randomization with the exception of pregnancy tests, which will need to be confirmed by the Day 1 test results.
- A urine (or serum) pregnancy test must be performed for all females of childbearing potential on Day 1 and the results reviewed prior to randomization. A negative pregnancy test result must be obtained prior to randomization. If the urine pregnancy test result is positive but this is believed to be a false positive, the site must perform a serum pregnancy test at the local laboratory to confirm pregnancy status.
- Baseline laboratory tests will be performed on Day 1 for comparison with follow-up tests. However, the results of these tests will not be available prior to randomization on Day 1.
- The baseline vIGA-AD, EASI, BSA, and the subject reported Pruritus NRS performed on 1 Day will be used to assess subject eligibility; the stratification data point for vIGA-AD score will be provided for randomization.

After eligibility has been confirmed and baseline assessments have been completed, eligible subjects will be randomized to treatment on Day 1. Subsequent visits, assessments and procedures will be performed as per the Table of Events Section 5.

- Assessment of inclusion/exclusion criteria to confirm eligibility (Day 1 only)
- Concomitant therapy
- Assessment of AEs/SAEs. In addition, starting at Day 1, device (ie, pre-filled syringe) failures or malfunctions should be captured, and device related AEs should also be collected.
- Hematology, chemistry, fasting lipid panel, and urinalysis
- Urine (or serum) pregnancy test (only for FCBP)
- Physical examination (A complete physical examination (including evaluation of heart, lung, head and neck, abdomen, neurological assessment, and extremities) or an abbreviated (interim/brief) physical examination (including areas with previously noted abnormalities and/or that are associated with any new complaints from the subject) will be performed according to the Table of Events Section 5, Table 4

- Weight
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- Whole blood and serum biomarkers assessment
- SARS-CoV-2 serology assessment
- Pharmacogenetic assessment, if applicable per government and local regulations, will be collected one time at Day 1 (note, the sample may be obtained at any subsequent visit).
- Optional Skin Biopsy
- AD disease activity and efficacy assessments:
  - vIGA-AD
  - EASI
  - BSA
  - SCORing Atopic Dermatitis (SCORAD) Index
  - Pruritus NRS
  - PROMIS Sleep Disturbance SF
  - Patient Oriented Eczema Measure (POEM)
  - Dermatology Life Quality Index (DLQI)
  - Hospital Anxiety and Depression Scale (HADS)
- IP administration

Refer to Section 6.5 for a detailed description of the efficacy assessments and outcome measures conducted throughout the study.

6.2.1. End of Treatment or Early Termination

For subjects who complete treatment phase of the study (Week 16) or discontinue the study prematurely for any reason (ie, subjects that do not complete Week 16) an EOT/ET visit will be conducted. For subjects who discontinue the study prematurely, every attempt should be made to complete the assessments detailed in the ET Visit conducted as close as possible to the time of study discontinuation. If study discontinuation occurs at the regularly scheduled visit, the ET Visit and all corresponding ET Visit procedures should be conducted. In addition, these subjects should return for the Follow-up Visits.

The evaluations that will be performed at the EOT/ET Visit are specified in Table of Events in Section 5.

6.3. Follow-up Period

6.3.1. Safety Follow-up (Initial [Week 24] and Final [Week 32])

All subjects will be followed for 16 weeks after the EOT/ET visit for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1. Subjects will return for an Initial (Week 24) and a Final (Week 32) Follow-up Visit at 8 and 16 weeks, respectively after completion of the EOT/ET Visit. For subjects who prematurely discontinue from the study, the 16 Week Follow Up Period should be based off of the date of last study visit conducted during the Treatment Phase of the study (eg, the ET visit) and therefore, may be conducted earlier then Week 24 and Week 32.

The evaluations that will be performed at the Follow Up Visits are specified in Table of Events Section 5, Table 5.

6.4. Efficacy Assessments

The following efficacy assessments are completed by the Investigator include the validated Investigator Global Assessment for Atopic Dermatitis, Eczema Area and Severity Index, , Body Surface Area (BSA) % , and the SCORing Atopic Dermatitis Index.Clinical efficacy evaluations of atopic dermatitis will be performed by an experienced and qualified medical professional, with experience in the conduct of AD clinical trials.

All efficacy evaluators must receive and document protocol specific and applicable efficacy assessment scales training prior to performing the evaluations. To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject throughout the study whenever possible; a back-up experienced, and qualified, protocol-trained evaluator will only be allowed on rare occurrences, when the designated evaluator is unable to perform the evaluation. Every effort should be made to ensure that the same assessor conducts the assessments at all study visits for a given subject.

6.4.1. Validated Investigator Global Assessment

The vIGA-AD is a validated 5-point assessment intended to assess the global severities of key acute clinical signs of AD, including erythema, induration/papulation, oozing/crusting (lichenification excluded). (Simpson, 2020) The rating of cleared (0), almost cleared (1), mild (2), moderate (3) and severe (4), will be assessed at scheduled visit specified in Section 5. The vIGA-AD must be conducted before the EASI assessment. The IGA is a static evaluation conducted without regard to the score obtained at a previous visit. Further details on the vIGA-AD assessment are reference in Appendix C.

6.4.2. Eczema Area and Severity Index

The EASI is a composite scoring system assessed by the Investigator based on the proportion of each of the 4 body regions (head and neck, upper limbs, lower limbs, and trunk) affected with AD and the intensity of each of 4 main signs of AD (eg, erythema, induration/papulation, excoriation, and lichenification) and is based on a 4-point scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Assessment of the 4 main clinical signs is performed separately for 4 body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). The total EASI score ranges from 0 to 72, with higher scores indicative of more severe disease. Further details on the EASI assessment are referenced in Appendix D.

6.4.3. Body Surface Area

Body Surface Area involvement will be calculated from the sum of the number of handprints of skin afflicted with atopic dermatitis in a body region. The number of handprints of skin afflicted with atopic dermatitis in a body region can be used to determine the extent (%) to which a body region is involved with AD. When measuring, the handprint unit refers to the size of each individual subject's hand with fingers in a closed position. BSA will be calculated by the Investigator or qualified designee using the 1% handprint rule, in which the area represented by the palm with all 5 digits adducted together is approximately 1% of the subject's BSA Further details related to the BSA assessment are referenced in Appendix E.

6.4.4. SCORing Atopic Dermatitis Index

The SCORAD is a validated scoring index for atopic dermatitis, which combines extent (0 to 100), severity (0 to 18), and subjective symptoms (0 to 20) based on pruritus and sleep loss, each scored (0 to 10). The subject will assess the subjective symptoms (itch and sleepless) part of the assessment. Further details related to the SCORAD index are referenced in Appendix F

6.5. Subject Reported Efficacy Assessments and Outcome Measures

Subject reported efficacy assessments and patient reported outcome measure relevant to AD include the following assessments:

- Pruritus Numeric Rating Scale
- PROMIS Sleep Disturbance Short Form 8a
- Patient Oriented Eczema Measure
- Dermatology Quality of Life Index
- Hospital Anxiety and Depression Scale

6.5.1. Pruritus Numeric Rating Scale

Pruritus will be assessed by the subject using the Pruritus NRS, which was developed and validated as a single item, patient reported outcome (PRO) of itch severity. Clinical response is indicated by a ≥ 2 to 4-point change from baseline in Peak Pruritus NRS score (Yosipovitch, 2019) The intensity of pruritus will be assessed based on last 24 hours using a validated 11-point NRS, ranging from 0 ("no pruritus") to 10 ("the worst pruritus imaginable"). The subject will complete an electronic diary recording the intensity of their pruritus on daily basis, through Week 4, and weekly (eg, on study visit/study drug administration days) thereafter through the Week 16 visit.

6.5.2. PROMIS Sleep Disturbance Short Form

The PROMIS Sleep Disturbance Short Form 8a is an 8-question subject questionnaire, designed to capture the subject's perceptions of sleep quality, sleep depth, and restoration associated with sleep over the past week. The questionnaire is scored by: [sum of items x 8) ÷ number items answered]. The higher the total score, the more severe the symptom. Total scores less than 24 suggest no to slight sleep disturbance, 24 to 28 suggest mild disturbance, 29 to 38 moderate disturbance, and greater than 38 severe sleep disturbance

The subject will complete the questionnaire onsite at study visits.

6.5.3. Patient Oriented Eczema Measure

The Patient Oriented Eczema Measure (POEM) is a validated tool used for monitoring atopic eczema severity. It is a 7-item questionnaire completed by the subject to assess the severity of eczema over the last week. The 7 questions each carry equal weight, and the responses are scored from 0 to 4 for a total score range of scored 0 to 28: To date, 2 published studies have broadly concurred that the minimally important change (MIC) of the POEM is 3 points (Howells, 2018).

The subject will complete the questionnaire onsite at study visits.

6.5.4. Dermatology Quality of Life Index

The DLQI will be completed by the subject at study visits. It is self-administered, easy-to-use, dermatology-specific quality of life (QOL) questionnaire that consists of 10 questions related to a subjects' perception of the impact of skin diseases on different aspects of their QOL over the last week. Questions are scored from 0 to 3, giving a possible total score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life).

6.5.5. Hospital Anxiety and Depression Scale (HADS)

The HADS is questionnaire completed by the subject that assesses anxiety and depression in a non-psychiatric population. The HADS has 2 subscales (depression and anxiety), both with 7 questions. Responses are based on the relative frequency of symptoms over the past week, using a four-point scale ranging from 0 (not at all) to 3 (very often indeed). The HADS is completed by the subject at study visits.

6.6. Safety Assessments

The safety parameters outlined in Section 5 that will be assessed in this study are the similar to those used in previously or currently conducted clinical studies of CC-93538. Careful safety monitoring of clinical and laboratory findings by both the sponsor's medical monitors and by the Investigators has been implemented in this protocol. As this will be the first clinical study to further explore the safety and efficacy profile of CC-93538 at higher cumulative exposures, additional risk minimization measures, such as the frequency of onsite visits, ongoing blinded safety reviews of the study data, oversight from an internal Safety Management Team (SMT), and oversight from an external independent Data Monitoring Committee (DMC), will be implemented throughout this Phase 2 study to ensure that the safety of the subjects is adequately

monitored. An overview of the additional safety oversight measures for the study are summarized below.

6.6.1. Onsite Visit Frequency

All subjects will return to the site weekly for the first 3 weeks for routine safety monitoring, IP administration, and a 30-minute post IP administration observation period. Subjects will either return to the clinic weekly throughout the 16-week treatment period, or starting at Week 3, subjects may have the option to return to the clinic every other week for IP administration, and have their alternate week injections administered at home by a visiting home health nurse.

Subjects who utilize the home health nurse option will be required to return to the site every 2 weeks at a minimum (eg, Week 4 [Visit 5/Day 29], Week 6 [Visit 7/Day 43], Week 8 [Visit 9/Day 57, Week 10 [Visit 11/Day 71], Week 12 [Visit 13/Day 85, Week 14 [Visit 15/Day 99], and Week 16 [Visit 17/Day 113]) to ensure additional safety assessments, such as the collection safety laboratory samples, and onsite assessments by Investigator and site personnel can be performed. Subjects who utilize the home health services option for any visits will still be contacted by site personnel (within 24 hours) to assess for any changes in concomitant medication use, and assess for AEs, to ensure there is continuity in the safety oversight being performed by the Investigator and site personnel.

6.6.2. Blinded Safety Data Reviews

From the start of the study (defined as first subject randomized) blinded safety reviews will be conducted by the internal study team/blinded data review team members on an ongoing basis. In addition, safety data will also be assessed by the SMT on a regular basis, and specific members of the SMT may also participate in the ongoing study data review related activities. The expected frequency of these planned reviews is outlined below:

- A preliminary interim blinded safety review involving the internal study team and the SMT will also be conducted after the first 8 subjects have received at least 4 weeks of treatment with IP. A similar review will be initiated after the first 8 Japanese subjects have received at least 4 weeks of treatment. The purpose of these preliminary interim reviews will be to review data in a blinded, aggregate fashion to assess for any potential clinically significant safety findings early in the study conduct.
- From the start of the study (as defined as first subject randomized) ongoing blinded safety reviews will be conducted by the internal study team/data review team members on approximately a monthly basis. More frequent review may be conducted on an ad-hoc basis if needed.

6.6.3. Internal Safety Management Team

In addition to ongoing safety monitoring conducted by Investigators and study personnel, cumulative and interval blinded AEs, adverse events of special interest (AESI), SAEs, discontinuations due to AEs, and abnormal laboratory findings will be reviewed internally by the Sponsor Safety Management Team (SMT). The SMT is comprised of lead representatives from multiple Sponsor functions engaged in the CC-93538 development program. The scope, conduct, processes, and accountabilities are specified by the Sponsor's Standard Operating Procedure (SOP).

Subject or study level safety assessments, and any subsequent study conduct related recommendations and/or actions provided by the SMT will be made from blinded data only. The DMC will be informed of relevant subject or study level decisions made by the SMT.

6.6.4. Data Monitoring Committee Safety Oversight

A DMC, that is independent of the study team, and SMT, has been established to provide an additional level of safety oversight. The DMC will function in advisory capacity, making recommendations the to study team and SMT based on their independent assessment of the safety data. Members of the internal study team/data review team or SMT may also consult with the DMC on an ad-hoc basis throughout the duration of the study to discuss relevant safety findings (eg, SAE, AESI, findings related to subject discontinuation, etc) that may arise during study the conduct of the study. Additional details related to DMC structure and oversight are available in Section 9.9.3.

6.7. Anti-drug Antibody Assessments

Serum samples to assess blood levels of antibodies to CC-93538 will be obtained pre-dose at study visits during the Treatment Period, at the EOT/ET visit, and the Follow-up Visits at the timepoints outlined in the Table of Events Section 5.

Details of the procedures to be followed for sample collection, processing, storage, shipment, and testing will be documented in a separate Study Laboratory Manual.

The development of serum antibodies to CC-93538 will be monitored to assess the impact of immunogenicity on safety, PK, and efficacy of CC-93538. The impact of immunogenicity will be evaluated by considering the results of PK, pharmacodynamic, and immunogenicity data taken together. Samples will be stored for additional analysis if necessary.

Further analysis on samples that are positive for ADA may be performed, including assessment of neutralizing antibodies when warranted. Samples will be stored for up to 5 years after study completion.

6.8. Subject Reported Outcomes

Patient reported outcome measure that will be assessed during the study are summarized above in Section 6.5.

6.9. Pharmacokinetics

Serum samples to assess CC-93538 concentrations will be obtained pre-dose at study visits at study visits during the Treatment Period, at the EOT/ET visit, and at the Follow-up Visits at the timepoints outlined in the Table of Events in Section 5.

Details of the procedures to be followed for sample collection, processing, storage, shipment, and testing will be documented in a separate Study Laboratory Manual.

6.10. Biomarkers, Pharmacodynamics, Pharmacogenomics

6.10.1. Whole Blood and Serum Biomarker Assessments

Blood samples will be obtained pre-dose at study visits during the treatment period, at the EOT/ET visit, and the Follow-up Visits at the timepoints outlined in the Table of Events (Section 5) to evaluate levels of various biomarkers in whole blood and serum, including but not limited to peripheral blood eosinophils, IgE, lactate dehydrogenase, IL-13, IL-22, CCL17 (TARC), and CCL18 (PARC), and possible assessments of SARS-CoV-2 serologic status, at the timepoints define in the Table of Event (Table 4, Table 5). Serum will be collected for measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) per national and local regulations. Of note, serum will be collected for SARS-CoV-2 serology at Day 1 (baseline), EOT/ET Visit, as well as approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, if applicable.

A pharmacogenomics sample will be collected only at one timepoint and is scheduled at Day 1 (see Section 5) for biomarker assessment including but not limited to IL-13 single nucleotide polymorphism (SNP) characterization. The pharmacogenetic sample will be collected from subjects, provided that necessary governmental and local approvals have been obtained. If needed, the pharmacogenetic sample can be collected at any subsequent timepoint during the study.

These samples will be shipped to a central laboratory for analysis. Details of the procedures to be followed for sample collection, processing, storage, and shipment will be documented in a separate Study Laboratory Manual.

6.10.2. Tissue Biomarker Assessments

Skin punch biopsies will be optional but will be critical to a full understanding of response to these therapies in AD patients. Looking to future studies, having as many skin samples as possible will also allow for greater understanding of which tissue measures may have viable blood/serum surrogates and what can only be assessed accurately from biopsies. Skin punch biopsies from the site of the same AD lesion will be taken at baseline, at the EOT/ET, and at the Final Follow Up Visit. For comparison, a biopsy of adjacent nonlesional skin will be taken at baseline, in order to provide a reference point. Samples will either be frozen, placed in formalin, or sent into an equivalent process as appropriate for the experimental end use of the material (eg, separate processing for RNA extraction). Details for the biopsy procedures will be provided in the Study Laboratory Manual.

6.11. Additional and Optional Research

Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.11.1. Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.11.2. Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

The active ingredient of CC-93538 is a recombinant humanized IgG1 monoclonal antibody directed against human IL-13. Investigational products (CC-93538 and placebo solutions for injection) are to be stored at [redacted] °C. The IP should not be frozen. The labeling will be in accordance with GCP and any other local regulatory requirements. During the study, IP will be dispensed in pre-filled syringes (PFS) provided by the Sponsor.

CC-93538 solution for injection (or placebo) will be provided as a sterile liquid in PFS at a concentration of [redacted] mg/mL (or placebo), a [redacted] mL fill will be utilized in the study, and IP will be packaged in cartons [redacted] PFS per carton).

Additional instructions related to IP handling, preparation, dispensation, and administration will be provided in a separate Study Pharmacy Manual.

7.2. Treatment Administration and Schedule

[redacted] injections at a volume of [redacted] mL each will be administered SC QW using a PFS of CC-93538 [redacted] mg/mL (active IP) or matching placebo. In order to maintain the blind, all subjects, regardless of their treatment assignment, will receive [redacted] injections of either active IP, placebo, or a combination of both. Subjects will be randomized 1:1:1:1 to one of the following treatment arms:

- CC-93538 [redacted] mg SC QW for 16 weeks, administered via [redacted] injections of active IP each week.
- CC-93538 [redacted] mg SC Q2W for 16 weeks. Starting at the baseline visit, [redacted] injections of active IP will be administered. On the alternate weeks, [redacted] injections of placebo will be administered to maintain the blind.
- CC-93538 [redacted] mg SC Q2W for 16 weeks. Starting at the baseline visit, [redacted] injection of active IP and [redacted] injection of matching placebo will be administered. On the alternate weeks, [redacted] injections of placebo will be administered weekly to maintain the blind.
- Matching placebo SC QW for 16 weeks, administered via [redacted] injections of placebo each week.

The first 3 doses of IP are required to be administered in the clinic. For the first 3 dosing visits, subjects will be required to remain in the clinic for at least 30 minutes for further observation. Per Investigator discretion, the number of injections administered in the clinic, and the post injection observation time period may be extended, as needed, to comply with local requirements.

Thereafter, dosing with two SC injections of IP will continue weekly through the Week 15 visit. Starting at Week 3 (Visit 4/Day 22), subjects have the option to return to the clinic every other week for IP administration, and have their alternate weekly injection administered at home by a licensed home health care provider. Subjects who utilize the home health care service will be required to return to the site every 2 weeks at a minimum (eg, Week 4 [Visit 5/Day 29], Week 6 [Visit 7/Day 43], Week 8 [Visit 9/Day 57], Week 10 [Visit 11/Day 71], Week 12 [Visit 13/Day

85], Week 14 [Visit 15/Day 99], and Week 16 [Visit 17/Day 113]) during the treatment phase of study for scheduled laboratory collections, and additional safety and efficacy assessments. In addition, on the weeks that the IP is not administered in-clinic, the subject will be contacted by site personnel (within 24 hours) to assess for any changes in concomitant medication use and assess for AEs.

Subjects for whom home health care provider services are not available in their region, or who choose not to utilize the service, will be required return to the clinic weekly to receive all of their IP injections.

The [redacted] SC doses should be administered in [redacted], in the abdomen or other appropriate alternate location including the thigh or back of the upper arm (rotating the injection site each time), avoiding any blood vessels, thickened or tender skin, scars, fibrous tissue, stretch marks, bruises, redness, nevi, or other skin imperfections.

7.2.1. Administration by a Visiting Home Health Care Provider

Starting at Week 3, subjects may have the option to return to the clinic every other week for IP administration, and have their alternate week injections administered at home by a visiting home health nurse. Subjects who utilize the home health nurse option will be required to return to the site every 2 weeks at a minimum (eg, Week 4 [Visit 5/Day 29]. Week 6 [Visit 7/Day 43], Week 8 [Visit 9/Day 57], Week 10 [Visit 11/Day 71], Week 12 [Visit 13/Day 85], Week 14 [Visit 15/Day 99], and Week 16 [Visit 17/Day 113]) during the treatment phase of study for scheduled laboratory assessments, and additional safety and efficacy assessments. The home health care providers will be trained and will be able to monitor for injection site reactions at the time of administration. Within 24 hours of the home health care provider visit, the subject will be contacted by the site personnel to assess for any changes in AEs and/or concomitant medications. Subjects for whom home health nurse services are not available in their region, or who choose not to utilize the visit home health nurse service option, will be required return to the clinic weekly for their injections.

7.2.2. Missed Dose(s)

If subjects are unable to take a dose on the usually scheduled day:

- They may take the dose within ±3 days of the normal dosing day and then continue dosing on their regular day the next week
- If the dose cannot be taken within ±3 days of the normal dosing day, they should wait to take their next dose on their regular dosing day the following week

Any missed doses will be captured within the study records. If 3 or more consecutive doses are missed, the subject will be required to permanently discontinue IP.

7.2.3. Overdose

An overdose is any dose of IP given to a subject or taken by a subject that exceeds the dose described in the protocol. There is no information regarding overdose with CC-93538. Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor. See Section 10.1. Any doses of IP administered more frequently than the minimum of 3 calendar

days in between dose administrations allowed by visit window, further described in Section 7.2.2, should be reported as an overdose.

7.2.4. Dose Adjustments

There is no provision for dose adjustments in this study. Subjects who cannot tolerate their assigned dose of IP, as determined by the Investigator, will be permanently discontinued from IP.

7.2.5. Guidelines for Temporary Interruption of Dosing

Dosing for subject should be interrupted (temporary discontinuation of IP) if any of the following events occur:

- The subject experiences any AE, intercurrent medical condition, or major surgery that could present an unreasonable risk to the subject due to study treatment continuation, as determined by the Investigator.
- The subject experiences a single or multiple severe laboratory abnormalities. Laboratory tests should be repeated for confirmation within 48 to 72 hours from when the abnormality was first observed, when pragmatically possible.
- The subject experiences an infection requiring parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal medications.
- For an infection requiring oral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal medications for longer than 2 weeks, interruption of IP is not required; however, the Investigator should determine if an interruption of dosing is in the best interest of the subject.
- For local infections and recurrent infections, the Investigator should determine the appropriate action related to the interruption of IP. Depending on the severity of the infection, the Investigator should contact the Medical Monitor to determine if additional actions, such as discontinuation of IP would be in the best interest of the subject.
- For subjects who develop suspected or confirmed symptomatic COVID-19 infection, or it is discovered that subjects have asymptomatic COVID-19 infection during the Treatment Period. IP should be temporary interrupted until the following conditions are met:

  For symptomatic subjects:

  – At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
  – At least 24 hours have passed since last fever without the use of fever-reducing medications, and
  – Symptoms (eg, cough and shortness of breath) have resolved, and
  – In the opinion of the Investigator, there are no COVID-19 sequelae that may place the subject at a higher risk of receiving investigational treatment, and,

– Negative follow-up molecular test for COVID-19 based on institutional, local or regional guidelines and/or requirements

For asymptomatic subjects:

– At least 7 days have passed since positive test result (based on date of collection, not date of test result availability), and

– Negative follow-up molecular test for COVID-19 based on institutional, local or regional guidelines and/or requirements

The decision to interrupt dosing of IP remains the responsibility of the treating physician. However, prior to interruption of dosing, the Investigator may contact the Medical Monitor. Once the laboratory abnormality stabilizes or the condition resolves, IP dosing may be resumed at the discretion of the, preferably at the next scheduled visit. The Medical Monitor may also be consulted to Investigator discuss the timing and appropriateness for the reintroduction of IP. If 3 or more consecutive doses are missed, the subject must be permanently discontinued from IP, as defined in Section 7.2.6.

7.2.6. Criteria for Discontinuation of Dosing

Dosing will be required to be permanently discontinued (treatment discontinuation) for a subject if the subject experiences any of the events listed below following initiation of IP.

- SAE which is suspected of being related to IP, and study treatment continuation could present an unreasonable risk to the subject as determined by the Investigator, or Sponsor.
- [redacted]
- Experiences a severe or serious (per Investigator assessment) opportunistic infection (suggestive of subject being immunocompromised)
- Receives a malignancy diagnosis, excluding carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin if it can be successfully treated by local resection
- Experiences an anaphylactic reaction or other severe systemic reaction (eg, hypersensitivity, allergic, or autoimmune) suspected of being related to IP by the Investigator or the Sponsor

- Experiences 2 separate occurrences of severe injection site reactions (ISR) that last longer than 24 hours.
  - A severe ISR is defined as an ISR that manifests with symptoms causing severe discomfort/pain; symptoms requiring medical/surgical attention/intervention; interference with activities of daily life (ADLs) including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest); and/or when drug therapy is required
- Becomes pregnant
- Uses prohibited systemic immunosuppressive or immunomodulating drugs
- Uses systemic rescue therapy
- Misses 3 or more consecutive doses

These subjects will be encouraged to remain in the study and complete all required study assessments (which the exception of dosing with IP) remaining in the treatment period and follow up period of the study. In order to prevent missing data, the site staff will ensure attempts are made to reach subjects by phone or email that do not maintain contact with the Investigator. Any subject discontinuing the study prematurely will be asked to complete the ET Visit and the Initial and the Final Follow-up Visits.

Additional events that are considered sufficient reasons for discontinuing a subject from the IP are summarized in Section 11.1.

7.3. Method of Treatment Assignment

Subjects enrolled in the study will be centrally randomized on Day 1 after all screening and baseline assessments have been completed and the Investigator has verified that the subject is eligible per the inclusion (Section 4.2) and exclusion criteria (Section 4.3).

Subjects will be randomized (1:1:1:1) to receive either CC-93538 ([redacted] mg QW, [redacted] mg Q2W, or [redacted] mg Q2W) or placebo for 16 weeks. Treatment assignment will be stratified by geographic region (Japan versus rest of world). Within the rest of world region only, randomization will also be stratified by disease severity based on the Day 1 baseline validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score (3 [moderate] or 4 [severe]). Randomization will occur on Day 1 (Baseline) through the use of Interactive Response Technology (IRT) system, also referred to as an Interactive Web Response System (IWRS) system.

Treatment groups are described in Section 7.2. The treatment each subject will receive will not be disclosed to the Investigator, study center personnel, subject, Sponsor or their representatives. The treatment codes will be held according to the IWRS. Further instructions will be provided in a separate IWRS manual.

The study blind should be maintained for persons responsible for the ongoing conduct of the study (after all subjects have completed the Week 16 assessments for endpoint analysis). Blinded persons may include but are not limited to: Clinical Research Physician (also referred to as Clinical Trial Physician), Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, and Clinical Research Associates (CRAs). For details

of the emergency procedure for unblinding of individual subjects, see Section 11.4.

7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

[redacted] a label cover on the active and placebo syringes (to be applied during packaging/labeling) will be used to maintain the blind.

7.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

All supplies of IP and placebo will be accounted for in accordance with GCP. There will be an individual IP accountability record for each subject and the Investigator should maintain accurate records relating to IP supplies received during the study. These records should include the amount of and dates clinical drug supplies were received, dispensed and administered to the subject by the investigative site or by a home healthcare service, or returned by the designated investigative site staff or by a home healthcare service and returned to the Sponsor. If errors or damages in the clinical drug supply shipments occur, the Investigator should contact the IP supplier and the Study Monitor immediately. Copies of the IP accountability records will be provided by each Investigator for inclusion in the Trial Master File after database lock. The Study Monitor will periodically check the supplies of IP held by the Investigator or pharmacist to verify accountability of all IP used.

The Investigator will provide IP only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, the Study Monitor will ensure that all unused IP and all medication containers, as applicable, can be destroyed on-site as long as proper documentation is supplied. If destruction on-site is not possible then any unused medication and containers, as applicable, will be returned to the Sponsor or designee. The Study Monitor will perform final accountability, package, seal and prepare for shipment. The clinical research organization (CRO) will verify that a final report of drug accountability is prepared and maintained in the Investigator Trial Master File.

7.6. Investigational Product Compliance

The Investigator must ensure that the IP will be used only in accordance with the protocol and that subjects are correctly instructed on how to take their IP and that each subject is fully compliant with their assigned dosage regimen. Investigational product non-compliance is defined as taking less than 80% or more than 120% of IP doses during the entire study. Records

of IP used and intervals between visits will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. The IP should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All treatments (including prescription and over the counter [OTC] medications, herbal and dietary supplements, dietary modifications, and procedures) used by subjects within the 4 weeks (28 days) prior to the first Screening Visit or at any time during the study are regarded as prior or concomitant treatments and must be documented on the appropriate section of the eCRF. In addition, a history of previous treatments for AD will be documented.

All concomitant treatments, including blood and blood products, used from 28 days prior to the first Screening Visit until the Final Safety Follow-up Visit, or Final Study Visit must be reported on the eCRF.

8.1. Permitted Concomitant Medications and Procedures

The following concomitant medications are permitted during the study:

- Oral antihistamines are permitted; however, the dose and regimen should remain stable from at least 2 weeks prior to the Day 1 (Baseline) Week 16, EOT/ ET visit). Subjects should also refrain from dosing within 24 hours prior to a study visit.
- Subjects may use inhaled corticosteroids, leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) for indications other than AD, such as asthma, if on stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens should remain stable throughout the treatment duration of the study. If one of these medications was recently discontinued, it must have been discontinued at least 4 weeks prior to the first Screening Visit.
- Medically necessary dose adjustments (eg to treat unanticipated exacerbations, etc) will be permitted; however, changes should consistent with local treatment guidelines. In addition, the Medical Monitor should be consulted to discuss the potential impact of the medication changes.
- Ophthalmic corticosteroids are allowed for subjects receiving a stable dose to treat allergic conjunctivitis.

Unless prohibited, subjects may be administered any other medications necessary for the treatment of concurrent medical conditions or AEs, as deemed necessary by the Investigator. Following Day 1, addition of concomitant medications or any change in the dosage should be limited to those considered medically necessary.

8.2. Prohibited Concomitant Medications and Procedures

The introduction of medications or therapies for other medical conditions known to affect AD (eg, systemic corticosteroids, mycophenolate-mofetil, interferon gamma (IFN-y), Janus kinase inhibitors, biologic therapies, TCS (except when given for rescue therapy), TCI, cyclosporine, azathioprine, methotrexate, phototherapy, etc) are not permitted during the study.

Additional details related to the concomitant medications and procedures that are prohibited throughout the duration of the study are initially identified in the exclusion criteria (Section 4.3) are summarized below.

- Topical treatments that could affect the assessment AD (eg, corticosteroids, calcineurin inhibitors, tars, antibiotic creams, topical antihistamines) within 7 days of the Day 1 visit, and throughout the duration of study.
- Treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to Day 1; however, during the study, use will be allowed to treat infection AEs.
- Phototherapy narrowband UVB (NB-UVB) or broad band phototherapy within 4 weeks prior to the baseline visit, and throughout the duration of the study.
- Systemic immunosuppressive or immunomodulating drugs (eg, azathioprine, cyclosporine, systemic corticosteroids, IFN-γ, Janus kinase inhibitors, methotrexate, mycophenolate-mofetil, etc.) within 4 weeks prior to the Baseline visit, and throughout the duration of the study.
- Treatment with immunomodulatory biologics as follows, and throughout the duration of the study:
  - Dupilumab within 3 months of Baseline visit.
  - Cell-depleting biologics, including to rituximab, within 6 months prior to the Baseline visit.
  - Other immunomodulatory biologics within 5 half-lives (if known) or 16 weeks prior to Baseline visit, whichever is longer
- With the exception of oral antihistamines, any additional medications and/or treatments that could affect AD are also prohibited throughout the study.
- Due to the potential to affect AD with ultraviolet light exposure, subjects must also avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.
- Concurrent treatment with another IP, including through participation in an interventional trial for COVID-19 are prohibited throughout the duration of the study. Prospective subjects may not participate in a concurrent IP study or have received an IP within 5 drug half-lives prior to signing the ICF/assent for this study. Further, for subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Clinical Trial Physician.
- Live attenuated vaccines are prohibited within one month prior to the first Screening Visit, and throughout the duration of the study.

8.3. Required Concomitant Medications and Procedures

Non-medicated topical emollient should be applied twice daily for ≥ 7 days prior to the Baseline/Day 1 visit and application (at the same twice daily frequency) should continue throughout the study. On study visit days, subjects must not moisturize or apply emollient before the visit. The last application emollient should be applied the night before the planned

study visit. Non-medicated emollient is allowed after the visit is completed, and the same type of emollient should be used throughout the duration of the study.

8.4. Rescue Medication

In the event a subject develops intolerable AD symptoms that requires rescue therapy, exceptions related to prohibited medications, such as TCS use, will be permitted. The use of rescue therapy should be discouraged throughout the treatment phase of trial, and reserved for only severe symptoms associated with AD flares. In such cases, subjects may continue study participation, while continuing concomitant rescue therapy use; however, discontinuation of IP may be required depending on the type of rescue medication that is administered.

- Subjects requiring rescue therapy should consider the addition of TCS prior to considering systemic treatment. Any subject who requires TCS rescue therapy treatment are encouraged to continue the TCS for as brief a period as possible (eg less than 7 days), while continuing with treatment with IP, and maintaining the study visit schedule.
- Any subject requiring systemic rescue therapy to treat their AD during the treatment phase of the study will be discontinued from IP and will be encouraged to continue participation in the study without IP administration. Subjects who decline further participation in the study should proceed with the Early Termination Visit and follow up visit assessments. Subjects requiring systemic rescue therapy during the follow up period of the study should continue the study visits as planned. All instances of rescue therapy administration that occur during the course of study participation will be captured accordingly within the source documentation in the eCRF.

The impact of rescue therapy will also be evaluated by defining these endpoints as missing for subjects who initiate rescue therapy prior to Week 16 and analyzed according to methods described in Section 9.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 2, multicenter, global, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of CC-93538 in adult subjects with moderate to severe AD. Subjects will be randomized to receive study medication for 16 weeks and the randomization will be stratified by geographic region (Japan versus rest of world) and, within RoW region only, randomization will also be stratified by disease severity based on baseline vIGA-AD score (3 [moderate] or 4 [severe]). An independent DMC will be used to review the safety data regularly during the course of the study.

Analysis details not explained in the statistical section of the protocol will be provided in the Statistical Analysis Plan (SAP).

9.2. Study Population Definitions

The following analysis populations will be used in the statistical analysis:

Modified intent to treat (mITT) Population

All randomized participants who received at least 1 dose of IP.

The mITT population will be used as the primary population for all efficacy parameters. Subjects who prematurely withdraw from the trial for any reason and for whom an assessment is not performed for any reason will still be included in the mITT population. Subjects will be included in the treatment group to which they are randomized. Subjects who were randomized with a misreported stratum will be classified according to their original (misreported) stratum.

Safety Population

The Safety population will consist of all subjects who received at least one dose of IP. This population will be used for all summaries of safety data. Subjects randomized to placebo who receive any dose of CC-93538 will be summarized in the CC-93538 group. Subjects randomized to CC-93538 who receive only placebo will be summarized in the placebo group; otherwise, they will be summarized in the CC-93538 group.

Pharmacokinetic Population

All subjects who received at least one dose of active drug and have at least one measurable concentration data.

Biomarkers

All participants that received any study treatment and have any available biomarker measurement.

9.3. Sample Size and Power Considerations

Approximately 200 subjects will be randomized in this Phase 2 dose ranging study. Randomization will be equal among the 4 dose groups of placebo, [redacted] mg Q2W, [redacted] mg Q2W, and [redacted] mg QW (approximately 50 subjects per group).

Assuming a 10% dropout rate, a sample size of 45 subjects per group will provide approximately 90% power to detect a treatment difference relative to placebo (difference in means) of 35% with respect to the primary endpoint of percentage change from baseline in EASI scores at Week 16. In these power calculations superiority over placebo for a particular dose group is met if the lower bound of the (2-sided) 95% confidence interval (z-score) for the treatment difference exceeds zero (adjusted for multiplicity).

The sample size calculations are based on the following considerations for comparing mean percentage changes from baseline in EASI scores at Week 16 versus placebo. In particular, the recent Phase 2b study of dupilumab reported an observed mean for placebo of 18.1% and corresponding treatment differences of 50.1% (standard error [SE = 6.7%]) and 55.7% (SE = 6.7%), for the doses of 300 mg Q2W, and 300 mg QW, respectively (Thaçi, 2016). This study evaluating CC-93538 is designed to detect a (true) treatment difference relative to placebo of 35%. We assume a (true) mean of 20% for placebo, and means for the active dose groups corresponding to treatment differences of 25% [redacted] mg Q2W), 30% [redacted] mg Q2W), and 35% ([redacted] mg QW), with a common standard deviation (SD) of 50%. We note that the common SD assumption of 50% for the percentage change from baseline in EASI scores at Week 16 was also assumed in the dupilumab Phase 2b study design (Thaçi, 2016). Under these assumptions, it is estimated that with a sample size of 45 subjects per group the study provides approximately 90% power to detect superiority relative to placebo for at least 1 dose at the overall type-1 error of $\alpha = 0.05$ (two-sided) using a hierarchical testing approach (in the order of [redacted] mg QW versus placebo, [redacted] mg Q2W versus placebo, and [redacted] mg Q2W versus placebo).

In addition, the study will provide more than 90% power to detect superiority relative to placebo for at least one dose with respect to the key secondary endpoint of vIGA-AD response (0-clear, 1-almost clear) at Week 16 assuming true proportions of 2% (placebo), 15% [redacted] mg Q2W), 25% ([redacted] mg Q2W), and 25% [redacted] mg QW). We note that the Phase 2 dupilumab study reported proportions of 30% and 33% for the doses of 300 mg Q2W, and 300 mg QW, respectively (Thaçi, 2016). The hierarchical testing approach used for the primary endpoint was utilized to maintain the overall type-1 error of $\alpha = 0.05$ (two-sided) with respect to the IGA response endpoint. However, multiplicity adjustments are not implemented across endpoints jointly (eg, for both the primary and key secondary endpoints simultaneously).

9.4. Background and Demographic Characteristics

Summaries for the demographics, baseline characteristics, medical history, prior medications, and protocol deviations will be presented for the mITT population by treatment groups. Concomitant medications will be presented for the Safety population by treatment groups. Individual listings will also be provided, including concomitant medical procedures for the Safety population.

9.5. Subject Disposition

The disposition of subjects will be summarized with numbers and percentages by treatment group for all enrolled subjects. Summaries will include the number and percentage of subjects in the following categories:

- Randomized, dosed (at least one dose of study treatment), permanently discontinued from IP, discontinued from the study, discontinued from IP and remained in study follow up, and completed study
- Primary reasons for discontinuation from the study

9.6. Efficacy Analysis

9.6.1. Efficacy Analysis of the Primary Endpoint

9.6.1.1. Percentage Change from Baseline in EASI Scores at Week 16

The primary efficacy endpoint of percentage change from baseline in EASI scores at Week 16 will be analyzed using an analysis of covariance (ANCOVA) model, based on the modified intent to treat (mITT) population, with treatment group indicators as the main effects adjusting for baseline EASI scores, and the stratification factors of vIGA-AD score (3 [moderate] or 4 [severe]) and region (Japan versus RoW) as covariates. For each of the active treatment arms, the adjusted mean percentage changes from baseline and corresponding differences versus placebo in EASI scores at Week 16 will be estimated (based on Least-Squares Means) along with 95% Wald confidence intervals (CIs) and p-values.

Missing EASI scores at Week 16 (eg, due to study dropout or other reasons for lack of assessment) will be handled using a multiple imputation (MI) approach (SAS Institute, 2015) under a missing at random (MAR) assumption. In the sequel we refer to this as the MI approach.

To adjust for multiplicity, a standard hierarchical approach will be utilized by conducting comparisons, each at the 2-sided 0.05 alpha-level (based on the aforementioned adjusted p-values), in the order of [redacted] mg QW versus placebo, [redacted] mg Q2W versus placebo, and [redacted] mg Q2W versus placebo.

Sensitivity analyses will be conducted to support the primary analysis by utilizing an alternative missing data approach as well as by assessing the impact of rescue therapy. The first sensitivity analysis will replace the MI approach for missing EASI scores at Week 16 with imputation by LOCF (last observation carried forward). The second and third sensitivity analyses will evaluate the impact of rescue therapy by defining EASI scores after rescue therapy (prior to Week 16) initiation as missing. The second sensitivity analysis will apply the MI approach with the addition (further degree) of missingness due to rescue. The third sensitivity analysis will combine the first and second sensitivity analyses by replacing the MI approach in the second sensitivity analysis with LOCF.

9.6.1.2. Subgroup Analysis of Primary Endpoint

To assess whether the treatment effect is consistent across various groups, subgroup analyses will be performed for the primary endpoint at Week 16. Treatment differences and 2-sided 95% CIs will be provided for each subgroup listed below. Forest plots for the treatment differences by subgroup will also be provided.

1. Non-elderly adults [< 65 years] versus elderly adults [≥ 65 years])
2. vIGA-AD baseline score (4 versus 3)

3. Sex (female versus male)
4. Region (Japan versus Rest of world)
5. Race (white versus non-white)
6. Prior experience with systemic immunosuppressive drugs

If there are not enough subjects (eg, < 8% mITT population, based on observed cases) in each subgroup and treatment category, the corresponding subgroup analyses will not be performed; instead, summary statistics will be provided. Details will be described in the SAP

Additional planned subgroup analyses may be considered and further defined in the SAP.

9.6.2. Efficacy Analysis of Secondary Endpoints

9.6.2.1. Analysis Methods

For the first key secondary endpoint of proportion of subjects with both a vIGA-AD score of 0 (clear) or 1 (almost clear) and a reduction of 2 or more points in vIGA-AD score from Baseline at Week 16 will be analyzed based on the mITT population using a stratified Cochran-Mantel-CMH test at a two-sided 5% significance level. The randomization stratification levels are: (1) Japan region, (2) RoW region and vIGA-AD score 3, and (3) RoW region and vIGA-AD score 4. Estimates of the differences in proportions between each treatment group versus placebo, and associated 95% confidence intervals will be provided along with p-values. Missing endpoint values (eg, due to study dropout or other reasons for lack of assessment) will be imputed as non-responders. A sensitivity analysis will be conducted based on defining subjects who initiate rescue therapy (prior to Week 16) as missing and treated as non-responders.

The second key secondary endpoint of proportion of subjects with at least a 75% improvement from baseline in Eczema Area and Severity Index (EASI-75) at Week 16 will be analyzed in the same manner as above.

The hierarchical testing approach used for the primary endpoint will be utilized to adjust for multiplicity with respect to the 3 active doses for each of these key secondary endpoints. However, multiplicity adjustments are not implemented across the primary and 2 key secondary endpoints simultaneously.

The following endpoints will be analyzed in the same manner as the key secondary endpoints, excepting that p-values will not be provided:

- The secondary endpoint of proportion of subjects with Pruritus NRS change of ≥ 4 from Baseline at Week 16
- The secondary endpoint of proportion of subjects with a 90% improvement from Baseline in EASI (EASI-90) at Week 16

The following endpoints will be analyzed in the same manner as the primary endpoint, excepting that p-values will not be provided:

- The secondary endpoint of percentage change from baseline in Pruritus NRS at Week 16
- The secondary endpoint of percent change in SCORAD Scores from Baseline at Week 16

- The secondary endpoint of mean percent change in Body Surface Area (BSA) involved with AD from Baseline at Week 16

For the secondary endpoint of time to achieve at least 4 points of improvement in the severity of pruritus NRS scale in the first 16 weeks of treatment, the distribution of times to the first event of 4-point improvement will be compared based on Kaplan-Meier (K-M) and log-rank approaches. Comparisons versus placebo, for each dose group separately, will be based on a stratified log-rank test with associated p-value provided. The stratification levels are: (1) Japan region, (2) RoW region and IGA score 3, and (3) RoW region and vIGA-AD score 4. The K-M estimates for the cumulative proportions of subjects achieving a 4-point improvement, by specific timepoints, will be provided by dose group as well as differences with placebo and associated 95% confidence intervals. These will be reported at various timepoints (eg, Day 1 to 28, followed by weekly assessments). Censoring rules will be described in the SAP.

9.7. Safety Analysis

All analyses of safety data will be conducted using the Safety population by treatment for the entire study duration of 32 weeks. The assessment of safety will include AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs leading to discontinuation from the study; changes from baseline in laboratory values and vital signs; and incidence and type of laboratory, vital signs, and physical examination abnormalities. Individual data listings will also be provided.

Adverse events will be monitored during the trial, and the data will be summarized by worst severity grade. Adverse events, with focus on treatment-emergent AEs, will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, and preferred term. Investigational product-related AEs, AEs leading to death or to discontinuation from treatment, events assessed as moderate or severe, IP-related events, and SAEs, and events of interest.

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the Standard International System of Units (SI) provided by the central lab. Each subject's hematology, blood chemistry, and urinalysis values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory.

Summary statistics of actual values and changes from baseline in vital signs will be provided by visit.

9.8. Interim Analysis

No formal interim analysis is planned for this study.

9.9. Other Topics

9.9.1. Analysis of Exploratory Endpoints

Exploratory analyses will be conducted on the exploratory efficacy endpoints listed in Section 2. Exploratory efficacy endpoints will be summarized using descriptive statistics by treatment group. For continuous endpoints, number of subjects (n), mean, SD, SE, median, minimum, and maximum will be provided. Binary endpoints will be summarized by number and percentages.

9.9.2. Pharmacokinetics, Pharmacodynamics and Exposure-Response

Serum trough concentrations (C_{trough}) of CC-93538 will be summarized with descriptive statistics by treatment and visit. Additional analysis may be conducted as appropriate (eg, by ADA status).

Population PK analysis will be performed using nonlinear mixed-effects modeling to characterize the population PK of CC-93538 and to identify key covariate effects (eg, immunogenicity, intrinsic and extrinsic factors). Data from other studies may be included if appropriate. Exposure-response and pharmacodynamic relationships will be conducted for efficacy, safety, and biomarker endpoints. Details on the studies and methodology will be outlined in a separate PK Analysis Plan, and results will be issued separately from the clinical study report as a stand-alone report.

9.9.3. Data Monitoring Committee

Additional safety monitoring will be performed by an external, independent Data Monitoring Committee (DMC). A DMC will be convened that will include physicians with experience in treating subjects with type 2 inflammatory diseases, as well as a statistician, all of whom are not otherwise involved in the study conduct and for whom there is no identified conflict of interest.

During the study, the DMC will review selected data (to be specified in the DMC charter) on a regular basis for the assessment of benefit-risk and determination of study continuation. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, for the DMC members for each scheduled meeting. Operational details for the DMC, including a blinding plan to assure that all personnel involved in the conduct of the study remain blinded to the results of data reviews, will also be described in the DMC charter. The DMC will function in advisory capacity, making recommendations based on their independent assessment of the safety data. Unblinded safety data may be reviewed on a periodic or ad-hoc basis by the DMC, as needed, to further enhance the ongoing assessment of the risk/benefit of the IP.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2.3 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF. The overdose itself should not be reported as an AE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-93538 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 16 weeks after the last dose of IP, or the last Follow Up visit, whichever is longer, as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. All AEs (serious/non-serious) will be recorded on the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For each AE, the Investigator must assess the severity/intensity of the event.

The following grading scale should be used to evaluate severity/intensity:

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of each AE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 5 months of the subject's last dose of IP are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.5. Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 16 weeks after the last dose of IP, or the last Follow Up Visit, whichever is longer) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is recorded within the CRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the CRF as well.

10.6. Adverse Events of Special Interest

Although the risk for serious infections is expected to be low in this Phase 2 study, adverse events of special interest (AESI) have been identified to provide further safety monitoring guidance to the Investigators. AESIs fall into a number of categories based on the safety observations from dupilumab, lebrikizumab, other CC-93538 clinical studies and the potential pharmacologic effects of IL-4 receptor antagonist and anti-IL-13 antibodies. Investigators should identify AEs that meet the following criteria for AESIs. All AESIs must be reported within 24 hours of the Investigator's knowledge of the event. These include the following:

10.7. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-93538 based on the Investigator Brochure.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in accordance with 21 CFR 312.32. For reporting to the FDA, events that are not suspected to be causally related to CC-93538 by the sponsor will not be considered adverse reactions.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information (in Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Other important safety information and periodic reports according to the local regulations.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC. (See Section 13.3 for record retention information.)

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for permanently discontinuing a subject from the IP:

- Adverse event
- Physician decision
- Lack of efficacy
- Protocol deviation
- Withdrawal by subject
- Death
- Lost to follow-up
- Non-compliance with IP
- Other (to be specified on the eCRF)

Subjects who are permanently discontinued from IP will be encouraged to continue participation in the study without IP administration in order to complete all remaining required study assessments including efficacy evaluations. Subjects who decline further participation in the study should complete the early termination visit, and follow up visit assessments. Subjects who discontinue early from IP and/or study participation will not be replaced.

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Physician decision
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents. Because follow-up of subjects who discontinue from the study prematurely is of particular importance, every attempt should be made to collect all or specific final data on a discontinued subject.

11.3. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

11.4. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblended dose information.

12. REGULATORY CONSIDERATIONS

12.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council on Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

12.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

12.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

12.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

12.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

12.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

12.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

13. DATA HANDLING AND RECORDKEEPING

13.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

13.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

13.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

14. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

14.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

14.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs, and/or Bristol Meyer Squibb SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

14.3. Investigational Medicinal Product Quality Issues

Issues that call into question investigational medicinal product (IMP) safety, purity, potency, quality and identity (e.g., evidence of suspected tampering of product) must be reported as soon as possible to your study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IMP, non-investigational medicinal product (NIMP) or auxiliary medicinal product (AxMP), suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IMP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated and a response will be provided back to the investigational site.

15. PUBLICATIONS

As described in Section 12.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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APPENDIX A. TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AD	Atopic dermatitis
ADL	Activity of daily life
ADAs	Anti-drug antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AxMP	Auxiliary medicinal product
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BSA	Body surface area
CCL17	Chemokine (C-C motif) ligand 17
CCL18	Chemokine (C-C motif) ligand 18
CI	Confidence interval
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
COVID	Corona virus disease
CRF	Case report form
CRO	Contract research organization
CPK	Creatine phosphokinase
CRP	C reactive protein
CRS	Clinical research scientist
C_{trough}	Serum trough concentration
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI-50	Improvement of at least 50% in Eczema Area and Severity Index

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EASI-75	Improvement of at least 75% in Eczema Area and Severity Index
EASI-90	Improvement of at least 90% in Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EoE	Eosinophilic esophagitis
EOT	End of treatment
E/R	Exposure/response
ET	Early Termination
Fc	Fragment, crystallizable
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council on Harmonisation
IFN-y	Interferon gamma
IgE	Immunoglobulin E
IgG1κ	Immunoglobulin G1 Kappa
IGRA	Interferon gamma release assay
IL	Interleukin
IL-4	Interleukin-4

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IL-4R	Interleukin-4 receptor
IL-5	Interleuikin-5
IL-13	Interleukin-13
IL-13Rα1	IL-13 receptor alpha 1
IL-13Rα2	IL-13 receptor alpha 2
IL-22	Interleukin-22
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
IV	Intravenous
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
K-M	Kaplan-Meier
LOCF	Last observation carried forward
mAb	Monoclonal antibody
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MI	Multiple imputation
MOA	Mechanism of action
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse effect level
NRS	Numeric Rating Scale

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PARC	Pulmonary and activation-regulated chemokine
PD	Pharmacodynamics
PFS	Pre-filled syringe
PK	Pharmacokinetics
POEM	Patient Oriented Eczema Measure
PT	Prothrombin time
QOL	Quality of life
QW	Once weekly
Q2W	Every other week
RBC	Red blood cell count
RNA	Ribonucleic acid
RoW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis Index
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	Standard International System of Units
SMT	Safety Management Team
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TARC	Thymus- and activation-regulated chemokine
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TCI	Topical calcineurin inhibitor

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
TCS	Topical corticosteroid
Th2	Type 2 T helper
t_{max}	Time to the observed maximum concentration
ULN	Upper limit of normal
US	United States
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
WBC	White blood cell count

APPENDIX B. HANIFIN/RAJKA DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

Diagnosis of atopic dermatitis requires the presence of at least 3 basic features plus 3 or more minor features as listed below:

Basic Features: Must have three or more basic features:

- ☐ Pruritus
- ☐ Typical morphology and distribution
- ☐ Flexural lichenification or linearity in adults
- ☐ Chronic or chronically-relapsing dermatitis
- ☐ Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Features: Plus, three or more minor features

- ☐ Xerosis
- ☐ Ichthyosis, palmar hyperlinearity, or keratosis pilaris
- ☐ Immediate (type 1) skin-test reactivity
- ☐ Elevated serum IgE
- ☐ Early age of onset
- ☐ Tendency toward cutaneous infections (especially Staph. aureus and Herpes simplex)/impaired cell-mediated immunity
- ☐ Tendency toward non-specific hand or foot dermatitis
- ☐ Nipple eczema
- ☐ Cheilitis
- ☐ Recurrent conjunctivitis
- ☐ Dennie-Morgan infraorbital fold
- ☐ Keratoconus
- ☐ Anterior subcapsular cataracts
- ☐ Orbital darkening
- ☐ Facial pallor/facial erythema
- ☐ Pityriasis alba
- ☐ Anterior neck folds
- ☐ Itch when sweating
- ☐ Intolerance to wool and lipid solvents
- ☐ Perifollicular accentuation
- ☐ Food intolerance
- ☐ Course influenced by environmental or emotional factors
- ☐ White dermographism/delayed blanch

Reference: (Hanifin, 1980)

APPENDIX C. VALIDATED INVESTIGATOR GLOBAL ASSESSMENT SCALE FOR ATOPIC DERMATITIS (V-IGA™)

Instructions: The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0-Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1-Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2-Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3-Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4-Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.
Reference (Simpson, 2020)	

1. In indeterminate cases, please use extent to differentiate between scores. For example: Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3- Moderate".
2. Excoriations should not be considered when assessing disease severity.

APPENDIX D. ECZEMA AREA AND SEVERITY INDEX (EASI)

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

1. **Select a body region**

   Four body regions are considered separately:

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

2. **Assess the extent of eczema in that body region**

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

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

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

   - Erythema
   - Edema/papulation
   - Excoriation
   - Lichenification

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

0	None	Take an average of the severity across the involved region. Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1) Palpation may be useful in assessing edema/papulation as well as lichenification
1	Mild	
2	Moderate	
3	Severe	

APPENDIX D. ECZEMA AREA AND SEVERITY INDEX (EASI) (CONTINUED)

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

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

EASI guidance v3 January 2017 (www.homeforeczema.org)

APPENDIX E. BODY SURFACE AREA

Determine BSA using the subject handprint = 1% rule.

The handprint unit refers to the size of each individual subject's hand with fingers adducted (eg in a closed position) measured from the wrist to the proximal interphalangeal (PIP) and thumb.

Estimate the number of handprint it takes to cover the affected AD area. Add up the number of handprints to give a total estimate of the area covered in AD.

Below are estimates when entire areas of the body are covered:

Table 7: Handprint Assessment of BSA

Body Region	Total Number of Handprints Estimated per Body Region	Total Estimated BSA% per Body Region
Head and Neck	10	10%
Upper Limbs	20	20%
Trunk (including axillae and groin/genitals)	30	30%
Lower Limbs (including buttocks)	40	40%

Additional guidance:

- When many small lesions are present, lesions may be counted in combination to achieve the handprint 1% measure.
- Areas of a lesion that have cleared should not be counted
- Final BSA% calculation should be cross checked against across other efficacy parameters (eg, % involvement assessed via during EASI) to ensure consistency

APPENDIX F. SCORING ATOPIC DERMATITIS INDEX

The SCORAD Index formula is: A/5 + 7B/2 + C.

A=Extent (maximum score of 100%)

To determine extent of AD, rule of 9 is used to calculate body surface area affected by AD as a percentage of the whole-body surface area. Body surface area as percentage of total body surface area for each body region is as follows:

- Head and neck 9%;
- Upper limbs 9% each;
- Lower limbs 18% each;
- Anterior trunk 18%;
- Back 18%;
- 1% for genitals.

The score for each body region is added up to determine the BSA affected by AD.

B=Severity (maximum score of 18)

A representative area of AD is selected. In this area, the severity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

- Erythema (reddening);
- Edema (swelling)/papulation;
- Oozing/crusting;
- Excoriation (scratch marks);
- Skin thickening (lichenification);
- Xerosis (dryness) (this is assessed in an area where there is no inflammation).

The severity scores are added together.

C= Subjective Symptoms (maximum score of 20)

Subjective symptoms (ie, itch and sleep loss) are each scored by the subject using a visual analog scale (VAS) where "0" is no itch (or no sleep loss) and "10" is the worst imaginable itch (or sleep loss).

The value for each should reflect the average on a 10-point scale for the last 3 days/nights. These scores are added together.

SCORAD Total Score: The SCORAD for an individual is calculated by the formula: A/5 + 7B/2 + C (can range from 0 to 103).

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