A Phase 2 Randomized, Double-blinded, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI3506 in Adult Subjects with Moderate-to-severe Atopic Dermatitis

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PROTOCOL SYNOPSIS

TITLE

A Phase 2 Randomized, Double-blinded, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI3506 in Adult Subjects with Moderate-to-severe Atopic Dermatitis

HYPOTHESES

Primary Hypothesis:

Atopic dermatitis (AD) disease severity will be decreased in adult subjects with moderate-to-severe AD administered MEDI3506 compared with placebo.

Secondary Hypotheses:

In adult subjects with moderate-to-severe AD:

- AD disease severity and symptoms, as measured by additional endpoints, will be decreased in subjects administered MEDI3506 compared with placebo.
- MEDI3506 will be safe and well tolerated compared with placebo.
- The pharmacokinetic (PK) profile will support further clinical development of MEDI3506.
- The immunogenicity profile will support further clinical development of MEDI3506.

OBJECTIVES AND ENDPOINTS

Type	Objective	Endpoint
Primary		
Efficacy	To assess the effects of MEDI3506 compared with placebo on AD disease severity, in adult subjects with moderate-to-severe AD.	Percent change from baseline to Week 16 in EASI score.
Secondary		
Efficacy	To further assess the effects of MEDI3506 compared with placebo on AD disease severity and symptoms, in adult subjects with moderate-to-severe AD.	• EASI: ° Percentage of subjects achieving a 90% reduction from baseline in EASI score (EASI 90) at Week 16. ° Percentage of subjects achieving a 75% reduction from baseline in EASI score (EASI 75) at Week 16. ° Percentage of subjects achieving a 50% reduction from baseline in EASI score (EASI 50) at Week 16.

		• Percentage of subjects achieving an IGA of 0 (clear) or 1 (almost clear) with at least a 2 grade reduction from baseline score at Week 16. • Peak pruritus NRS: Percentage of subjects achieving a reduction of ≥ 3 from baseline to Week 16 in weekly mean of daily peak pruritus NRS. • Peak pruritus NRS: Change from baseline to Week 16 in weekly mean of daily peak pruritus NRS. • Skin pain NRS: Change from baseline to Week 16 in weekly mean of daily peak skin pain NRS. • SCORAD: Percent change from baseline to Week 16. • PGI-S at Week 16. • Change from baseline to Week 16 in: ° % BSA affected by AD. ° 5-D itch. ° POEM. ° DLQI.
Safety	To assess the safety and tolerability of MEDI3506 compared with placebo, in adult subjects with moderate-to-severe AD.	During the treatment and follow-up periods: • TEAEs and TESAEs. • Vital signs. • Safety laboratory analysis. • ECGs. The following parameters will be recorded for each ECG: ° Date and time of ECG. ° Heart rate (beats/min). ° QT (ms). ° Overall evaluation (normal/abnormal). • Left ventricular ejection fraction as measured by echocardiogram.
PK	To evaluate the PK of MEDI3506 in adult subjects with moderate-to-severe AD.	Serum MEDI3506 concentration profiles during the treatment and follow-up periods.
Immunogenicity	To evaluate the immunogenicity of MEDI3506 in adult subjects with moderate-to-severe AD.	Incidence of ADA during treatment and follow-up periods.
Exploratory		
Efficacy	To assess the effects of MEDI3506 compared with placebo on AD disease severity and symptoms over time to Week 24, in adult subjects with moderate-to-severe AD.	• EASI: ° Percentage of subjects achieving a 90% reduction from baseline in EASI score (EASI 90) at Weeks 2, 4, 8, 12, 20, and 24.

		° Percentage of subjects achieving a 75% reduction from baseline in EASI score (EASI 75) at Weeks 2, 4, 8, 12, 20, and 24. ° Percentage of subjects achieving a 50% reduction from baseline in EASI score (EASI 50) at Weeks 2, 4, 8, 12, 20, and 24. ° Percent change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in EASI score. • IGA: Percentage of subjects achieving an IGA of 0 (clear) or 1 (almost clear) with at least a 2 grade reduction from baseline score at Weeks 2, 4, 8 ,12, 20, and 24. • Peak pruritus NRS: Reduction of ≥ 3 from baseline to Weeks 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak pruritus NRS. • Peak pruritus NRS: Reduction of ≥ 4 from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in weekly mean of daily peak pruritus NRS. • Peak pruritus NRS: Change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in the weekly mean of daily peak pruritus NRS. • Skin pain NRS: Change from baseline to Week 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak skin pain NRS. • SCORAD: Percent change from baseline to Weeks 2, 4, 8, 12, 20, and 24. • PGI-S at Weeks 2, 4, 8, 12, 20, and 24. • Change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in: ° % BSA affected by AD. ° 5-D itch. ° POEM. ° DLQI.

Biomarkers	To evaluate the effect of MEDI3506 on blood biomarkers that may either predict or reflect an efficacy response in adult subjects with moderate-to-severe AD.	• Change from baseline to Week 16 in serum concentrations of: ° sST2. ° CCI [redacted] • Change from baseline to Week 16 in whole blood PBMC subsets • Change from baseline to Weeks 1, 2, 4, 8, 12, 16, 20, and 24 in serum biomarker levels, including but not limited to: ° Eosinophils. ° IL-5. ° IL-13. ° CCL17. • Change from baseline to Weeks 1, 2, 4, 16, 20 and 24 in serum IL-33 bound to MEDI3506. • Change from baseline to Weeks 2, 8, 16, and 24 in serum IgE levels. • Change from baseline to Week 16 in proinflammatory gene signatures in whole blood. • Change from baseline to Weeks 4, 16, and 24 in plasma EDN levels.
Biomarkers	To evaluate the effect of MEDI3506 on skin biomarkers that may either predict or reflect an efficacy response in adult subjects with moderate-to-severe AD.	• Colonization of pathogenic bacteria (ie, *Staphylococcus aureus*) in lesional and non-lesional skin, from baseline to Week 16. • From baseline to Week 16 in lesional and non-lesional skin: ° Proinflammatory gene signatures in tape strips and biopsies. ° Gross inflammation evaluation.
Efficacy	To assess the effect of MEDI3506 compared with placebo on the need for rescue therapy, in adult subjects with moderate-to-severe AD.	• Proportion of subjects requiring rescue therapy during the treatment and follow-up periods. • Time to first use of rescue therapy throughout the treatment and follow-up periods. • Incidence of skin infection TEAEs requiring systemic treatment during the treatment and follow-up periods.
Efficacy	To evaluate the effect of MEDI3506 compared with placebo on nasal symptom control, in a subset of adult subjects with moderate-to-severe AD and comorbid chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses.	Change from baseline to Week 16 and 24 in SNOT-22.

Efficacy	To evaluate the effect of MEDI3506 on asthma symptom control compared with placebo, in a subset of adult subjects with moderate-to-severe AD and comorbid asthma.	Change from baseline to Week 16 and 24 in ACQ-6.
CCI	CCI	CCI

ACQ = Asthma Control Questionnaire; AD = atopic dermatitis; ADA = anti-drug antibody(ies); BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction from baseline in Eczema Area and Severity Index score; EASI 75 = 75% reduction from baseline in Eczema Area and Severity Index score; EASI 90 = 90% reduction from baseline in Eczema Area and Severity Index score; ECG = electrocardiogram; EDN = eosinophil derived neurotoxin; Ig = immunoglobulin; IGA = Investigator's Global Assessment; IL = interleukin; NRS = Numerical Rating Scale; PBMC = peripheral blood mononuclear cell; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; SNOT-22 = Sino-nasal Outcome Test; sST2 = soluble ST2; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

STUDY DESIGN

This is a Phase 2 randomized, double-blinded, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI3506 in adult subjects with moderate-to-severe AD. Approximately 152 subjects will receive CCI MEDI3506 subcutaneous (SC); or placebo CCI SC, or placebo CCI SC; in a 3:1:1:1:2 ratio overall CCI. The randomization ratio will change during the study. The randomization will be stratified based on total immunoglobulin (Ig)E (< 150 kU/L or ≥ 150 kU/L) at screening. The study will be conducted at approximately 40 to 50 study sites in Australia, Europe, and North America.

Subjects will be enrolled in this study for approximately 7 months (28 weeks), comprising a screening and topical corticosteroid (TCS)/topical calcineurin inhibitor (TCI) wash out period of up to 4 weeks, a 16-week treatment period, and an 8-week follow-up period:

1 Screening and TCS/TCI wash out period: Following the signing of informed consent, subjects will be assessed for study eligibility at screening Visit 1 and, if eligible, invited to attend screening Visit 2, which must occur 7 or more days prior to randomization. Subjects who meet the eligibility (inclusion/exclusion) criteria will discontinue use of TCSs and TCIs at Visit 2. Subjects will be required to apply moisturizers twice daily for at least 7 days before randomization at Visit 3 (Day 1) with a minimum of 85% compliance.

2 Treatment period: To be randomized at Visit 3 (Day 1), subjects must meet all the eligibility criteria before receiving investigational product by SC injection CCI Subjects will be required to apply moisturizers twice daily throughout the treatment period, and will not be permitted to use TCSs and TCIs, except if medically necessary. CCI and the primary endpoint assessment will occur at Visit 10 (Week 16).

The first 72 subjects randomized will attend Visit 4a, whereas the remaining subjects will attend Visit 4b instead.

Following provision of informed consent, skin punch biopsies at Visit 3 (Day 1) and Visit 10 (Week 16) will be collected from a subset of subjects (ie, approximately 45 subjects in total). Subjects with comorbid chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) will complete the Sino-nasal Outcome Test-22 questionnaire. Similarly, subjects with comorbid asthma will complete the Asthma Control Questionnaire-6 questionnaire.

3 Follow-up period: Safety, sustained efficacy, and the need for rescue therapy will be assessed in the follow-up period. Subjects will be required to apply moisturizers twice daily through to the end of the follow-up period at Visit 12 (Week 24), and will not be permitted to use TCSs and TCIs, except if medically necessary.

The primary analysis will occur once all subjects have either completed the Visit 10 (Week 16) assessments or have withdrawn from the study. The final analysis will occur when all subjects have completed the follow up period at Visit 12 (Week 24) or have withdrawn from the study.

TARGET SUBJECT POPULATION

Subjects aged 18 to 65 years inclusive with chronic, moderate-to-severe AD; with documented recent history of inadequate response to topical medications for AD, intolerance to treatment with topical medications for AD, or for whom topical medications are otherwise medically inadvisable.

TREATMENT GROUPS AND REGIMENS

At Visit 3 (Day 1), eligible subjects will be randomized to receive SC investigational product CCI as follows:

- MEDI3506 CCI 58 subjects),
- MEDI3506 CCI (18 subjects),
- MEDI3506 CCI (18 subjects),
- Placebo CCI (6 subjects), or
- Placebo CCI (52 subjects).

STATISTICAL METHODS

General Considerations:

The placebo CCI groups will be pooled for planned analyses, except where stated otherwise. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

The study populations that will be used in the reporting of the study include the intent-to-treat (ITT), As-treated, and PK populations. The ITT population will be used to summarize demographic and baseline characteristics, concomitant medications, and efficacy endpoints. The As-treated population will be used to summarize safety endpoints (adverse events [AEs], laboratory tests, electrocardiograms [ECGs], left ventricular ejection fraction, and vital signs), and will be used for other endpoints unless otherwise stated. The PK population will be used to summarize PK endpoints.

Sample Size:

A sample size of 144 subjects in an overall 3:1:1:3 ratio of MEDI3506 CCI :MEDI3506 CCI :MEDI3506 CCI : pooled placebo, will provide at least 90% power to detect a statistically significant difference in the percent change from baseline to Week 16 in Eczema Area and Severity Index (EASI) score between the highest dose of MEDI3506 and pooled placebo in a responder subgroup, assuming a 35% point difference between placebo and MEDI3506 at the highest dose, based on a SD of 40% points, a two-sided 10% alpha level, and 50% of subjects in the responder subgroup. Based on identical assumptions, the sample size provides > 99% power to detect a statistically significant dose response in percent change from baseline to Week 16 in EASI score in all-comers.

The calculations for dose response assume that percent change from baseline to Week 16 in EASI score will increase monotonically with the administration of higher MEDI3506 doses. The power was calculated using a multiple comparison procedure with modelling techniques (MCP-Mod) with 4 candidate models for the dose response (linear, maximum effect attributable to the drug [E_{max}], and 2 Hill-E_{max} models). Randomization will be stratified by total immunoglobulin E (IgE) (< 150 kU/L or ≥ 150 kU/L) at screening.

To allow for the possibility that ≤ 5% of the subjects per treatment group may be ineligible for the ITT population, the total sample size will comprise approximately 152 subjects (58 for MEDI3506 CCI , 18 for MEDI3506 CCI , 18 for MEDI3506 CCI , and 58 for pooled placebo) randomized approximately to 3:1:1:3 ratio overall to the treatment groups.

Statistical Analyses:

Primary Efficacy Analysis

The primary efficacy endpoint is the percent change from baseline to Week 16 in EASI score. To assess the dose response at Week 16, percent change from baseline to Week 16 in EASI score will be analyzed using the mixed-effects model for repeated measures (MMRM) including data from visits up to Week 16. The model will include treatment group, randomization stratum (total IgE level < 150 kU/L or ≥ 150 kU/L), visit, and treatment group by visit interaction as categorical factors, with baseline EASI as a covariate and the baseline*visit interaction term. Visit will be a repeated factor within a subject and unstructured variance-covariance matrix will be used to describe the correlations between observations on a subject between visits. The coefficient of the treatment effects at Week 16 obtained from the MMRM will then be incorporated into an MCP-Mod, with 4 candidate models (linear, E_{max} and 2 Hill-E_{max} models) to determine the dose response profile. The estimand of primary interest is the difference in mean percent change from baseline to Week 16 in EASI score between MEDI3506 and placebo in the ITT population. Data that are collected after withdrawal from the study or the use of rescue therapy will be treated as missing and excluded from the analysis.

Secondary Efficacy Analyses:

A key secondary efficacy endpoint is the percentage of subjects achieving an IGA response of 0 (clear) or 1 (almost clear) and at least a 2 grade reduction from baseline at Week 16. IGA response at Week 16 will be analyzed for the ITT population using logistic regression including treatment group, randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L), and baseline IGA as categorical factors. The coefficient of the treatment effects at Week 16 obtained from the logistic regression will then be used in an MCP-Mod analysis with 4 candidate models for the dose response (linear, E_{max}, and 2 Hill-E_{max} models). As part of the MCP-Mod model, the testing of the 4 candidate dose response models will be adjusted for multiplicity using a family-wise error rate of 0.10. If more than 1 candidate model shows a statistically significant dose response, the final model will be selected based on the Akaike Information Criteria obtained from each model.

A subject is defined as achieving a 50% reduction from baseline in Eczema Area and Severity Index score (EASI 50), a 75% reduction from baseline in Eczema Area and Severity Index score (EASI 75), or 90% reduction from baseline in Eczema Area and Severity Index score (EASI 90) response if they have at least a 50%, 75%, or 90% reduction from baseline in EASI score, respectively. EASI 50, EASI 75, and EASI 90 response at Week 16 will be analyzed using a logistic regression model including treatment group and randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L) as categorical factors, and baseline EASI score as a covariate for each endpoint. In addition, the percentage of subjects achieving an EASI 75 response at Week 16 will be analyzed for the ITT population using logistic regression followed by a dose response model similar to that described above for IGA response at Week 16.

Change from baseline to Week 16 in % body surface area affected by AD as assessed by EASI, 5-D itch, Patient-Oriented Eczema Measure, Dermatology Life Quality Index; and percent change from baseline to Week 16 in SCORing Atopic Dermatitis; will be summarized descriptively and analyzed for the ITT population using a MMRM, including data from visits up to Week 16. Details of the model for each endpoint are similar to those described above for the primary efficacy endpoint.

Daily peak pruritus Numerical Rating Scale (NRS) assessments will be summarized as weekly means. The weekly mean score will be set to missing if > 3 assessments are missed in that 7-day period. The percentage of subjects achieving a ≥ 3 point reduction from baseline to Week 16 in weekly mean of daily peak pruritus NRS will be analyzed using a logistic regression model including treatment group and randomization stratum (total serum IgE < 150 kU/L or ≥ 150 kU/L), and baseline weekly mean of daily peak pruritus score as a covariate. Furthermore, change from baseline to Week 16 in the weekly mean of daily peak pruritus NRS will be analyzed using a MMRM, using a model similar to those described above for the primary efficacy endpoint.

Daily peak skin pain NRS assessments will be summarized as weekly means. The weekly mean score will be set to missing if > 3 assessments are missed in that 7-day period. Change from baseline to Week 16 in weekly mean peak skin pain NRS will be analyzed using a MMRM in a similar way as described above for the primary efficacy endpoint.

Patient Global Impression of Severity will be summarized with descriptive statistics including number of subjects, mean, SD, median, minimum, and maximum at each visit. In addition, the number and percentage of subjects in each category will be summarized by visit.

Safety:

AEs will be coded using the Medical Dictionary for Regulatory Activities by system organ class and preferred term. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented.
Frequencies of abnormal laboratory measurements will be presented for each laboratory parameter. Also, laboratory parameters will be assessed by presenting tables containing information related to laboratory shifts from baseline relative to the normal range, as well as descriptively over time.
Vital signs, ECG parameters and left ventricular ejection fraction as measured by echocardiogram will be summarized descriptively.

Analysis of Immunogenicity and PK:

The incidence rate of positive antibodies to MEDI3506 and anti-drug antibody (ADA) titer will be reported by treatment group. Depending on the incidence of ADA, further analysis of ADAs effects may include assessment of the relationships between ADA titer and:

- MEDI3506 exposure.
- Biomarker endpoints.
- Occurrence of AEs.

MEDI3506 serum concentrations will be tabulated and analyzed using descriptive statistics. Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported in the Clinical Study Report.

Primary and Final Analyses:

No formal interim analyses are planned for this study. The primary analysis will occur once all subjects have either completed the Visit 10 (Week 16) assessments or have withdrawn from the study and will include all available data. The final analysis will occur when all subjects have completed the follow-up period at Visit 12 (Week 24) or have withdrawn from the study.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACQ	Asthma Control Questionnaire
AD	atopic dermatitis
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANCOVA	Analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate transaminase
AUCB	area under the concentration-time curve
BSA	body surface area
CI	confidence interval
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady-state
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CYP450	Cytochrome P450
DBP	diastolic blood pressure
DLQI	Dermatology Life Quality Index
DSMB	Data and Safety Monitoring Board
EASI	Eczema Area and Severity Index
EASI 50	50% reduction from baseline in Eczema Area and Severity Index score
EASI 75	75% reduction from baseline in Eczema Area and Severity Index score
EASI 90	90% reduction from baseline in Eczema Area and Severity Index score
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
E_{max}	maximum effect attributable to the drug
FDA	Food and Drug Administration

Abbreviation or Specialized Term	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbA1c	hemoglobin A1c
HbsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HL	Hy's Law
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGA	Investigator's Global Assessment
IGRA	interferon gamma release assay
IL	interleukin
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	interactive voice/web response system
IV	intravenous
LSLV	last subject last visit
mAb	monoclonal antibody
MCP-Mod	multiple comparison procedure with modelling techniques
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed-effects model for repeated measures
NOAEL	no observed adverse effect level
NRS	Numerical Rating Scale
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
PBMC	Peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PEI	Paul Ehrlich Institute
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure

Abbreviation or Specialized Term	Definition
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SID	subject identification
SNOT	Sino-nasal Outcome Test
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
Q2W	every 2 weeks
Q4W	every 4 weeks
QW	every week
T2	Type 2
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal

1 INTRODUCTION

1.1 Disease Background

Atopic dermatitis (AD) is a chronic inflammatory skin disease commonly referred to as eczema. In severe AD, there is widespread skin involvement. Affected skin may be red, itchy, swollen, cracked, weeping with crusting, and/or scaling. Pruritus is frequently intractable and with breakdown of barrier function there is an increased risk of bacterial, viral, and/or fungal skin infections. There may also be scarring in the form of lichenification, excoriation, papulation, or induration, due to chronic disease, the effects of treatment, or infective complications.

Up to 25% of children (DaVeiga, 2012) and 5% of adults (Barbarot et al, 2018) are affected by AD. Of the adults, 20% to 37% have moderate disease with 10% to 34% reported with severe disease (Kim et al, 2016; Pawankar, 2013). Patients with moderate-to-severe AD have a poor quality of life through a combination of symptoms, emotional stress from poor self-image, the burden of applying topical treatments regularly, sleep disturbance, and reductions in work productivity (Kiebert et al, 2002). Treatment recommendations for AD include liberal use of emollients, dry skin care protocols, topical corticosteroids (TCSs), and topical calcineurin inhibitors (TCIs).

For many patients with moderate-to-severe AD, TCS therapy has inadequate efficacy. In addition, long-term TCS use is associated with side effects such as thinning and discoloration of the skin, increased risk of skin infection, contact dermatitis, decreased bone density, and slowing of growth in children (Ring et al, 2012). A high proportion of patients have a partial or no clinical response to TCI therapy. Moreover, long-term safety of TCIs has not been established, and continuous, long-term use should be avoided (Elidel, 2017; Protopic, 2012). Off-label use of systemic immunomodulatory agents including cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil is reserved for patients with poor AD control despite optimized use of first line topical therapies and phototherapy (Sidbury et al, 2014). Dupilumab (Dupixent®), an anti-interleukin (IL) 4Rα monoclonal antibody (mAb), is approved as an add-on therapy for adults and adolescents with moderate-to-severe AD whose disease is not adequately controlled with topical therapies. However, dupilumab also has limited efficacy in many patients. Consequently, there is an unmet need for new therapeutic agents for AD that improve outcomes in patients with moderate-to-severe disease.

1.2 MEDI3506 Background

MEDI3506 is briefly described below. Refer to the current Investigator's Brochure (IB) for details.

MEDI3506 is a human immunoglobulin (Ig) G1 mAb that binds to human IL-33. MEDI3506 neutralizes the pro-inflammatory actions of IL-33 by preventing binding of IL-33 to its

receptor ST2, which is expressed by a variety of inflammatory cells linked to AD pathophysiology. Nonclinical data support a role for anti-IL-33 therapy in AD. Blocking of IL-33 signaling through ST2 has a therapeutic effect in murine models of AD (Imai et al, 2013; Peng et al, 2018). Clinical data also support a role for anti-IL-33 therapy in AD. An uncontrolled (ie, no placebo group), Phase 2a clinical study of a single intravenous (IV) dose of etokimab (ANB020; anti-IL-33 neutralizing antibody) showed efficacy of etokimab in adults with moderate-to-severe AD, indicating the potential of anti-IL-33 therapy for treating AD (Ogg, 2018). As both MEDI3506 and etokimab have a similar mechanism of action, the Phase 2a etokimab clinical study data provide support for investigating the therapeutic potential of MEDI3506 in AD. However, a Phase 2b, randomized, double-blinded, placebo-controlled clinical study of multiple doses of etokimab in adults with moderate-to-severe AD has, according to a preliminary report, not met its primary endpoint of statistically significant improvement in the Eczema Area and Severity Index (EASI) compared with placebo at Week 16 (AnaptysBio, 2019).

1.3 Summary of Nonclinical Experience

CCI [redacted]

Nonclinical pharmacology studies demonstrated that MEDI3506 binds CCI [redacted] specifically and with high affinity. In addition, studies performed in vitro and in vivo have demonstrated the mechanism of action of MEDI3506. CCI [redacted]

The potential toxicity of MEDI3506 was evaluated in 2 repeat-dose studies. CCI [redacted]

CCI [redacted]

CCI

CCI

Please refer to the IB for further details.

1.4 Summary of Clinical Experience

One Phase 1 clinical study of MEDI3506 (Study D9180C00001) has been completed to date.

Study D9180C00001 was a Phase 1, first time in human, randomized, blinded (investigator and subject blinded; sponsor unblinded), placebo-controlled clinical study to evaluate the safety, tolerability, PK, and immunogenicity of single and repeated doses of MEDI3506. The study had 3 parts. Part I involved single ascending dose administration of MEDI3506 either SC or IV to healthy adult subjects with a history of mild atopy, Part II involved multiple ascending dose administration of MEDI3506 SC to adult subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) I to II chronic obstructive pulmonary disease (COPD), and Part III involved single dose administration of MEDI3506 IV to healthy adult Japanese subjects.

In healthy subjects with a history of mild atopy in Part I of the study, a similar proportion of subjects experienced at least 1 treatment-emergent adverse event (TEAE; ie, adverse events [AEs] occurring after the first dose of investigational product [MEDI3506 or placebo]) in the MEDI3506 and placebo groups. All reported TEAEs were Grade 1 or 2 (mild or moderate) in severity. There were no TEAEs leading to discontinuation of investigational product, treatment-emergent serious adverse events (TESAEs), or deaths.

In subjects with GOLD I to II COPD in Part II of the study, a similar proportion of subjects experienced at least 1 TEAE in the MEDI3506 and placebo groups. A majority of reported

TEAEs were Grade 1 or 2 in severity. One subject experienced a TEAE leading to discontinuation of investigational product, and 2 subjects experienced 2 TESAEs (1 TESAE in each subject). There was 1 death due to non-small cell lung cancer. The TEAE leading to discontinuation of investigational product, TESAEs, and death were considered not related to investigational product by the investigator.

In healthy Japanese subjects in Part III of the study, a similar proportion of subjects experienced at least 1 TEAE in the 300 mg IV MEDI3506 and placebo groups. All reported TEAEs were Grade 1 in severity. There were no TEAEs leading to discontinuation of investigational product, TESAEs, or deaths.

The MEDI3506 serum concentration versus time profiles from healthy subjects with a history of mild atopy showed linear and time-invariance first order absorption and first order elimination for single doses of 1 to 300 mg SC. There was no evidence of an antigen sink. For multiple every 2 weeks (Q2W) SC doses in subjects with GOLD I to II COPD, slight accumulation was observed, based on the trough concentration, following the first and third dose. The multiple and single dose half-lives were consistent.

Nine out of 88 subjects were anti-drug antibody (ADA)-positive at any time point. Treatment-emergent ADA were detected in 4 out of 66 subjects in the MEDI3506 groups. No subjects in the placebo groups (N = 22) had treatment-emergent ADA. TEAEs were similar in frequency and severity for ADA-positive and ADA-negative subjects. No impact of ADA on MEDI3506 PK was observed, except in 1 subject where the onset of treatment-emergent ADA coincided with a decrease in MEDI3506 serum concentration.

Please refer to the IB for further details.

1.5 Rationale for Conducting the Study

IL-33 is a cytokine constitutively expressed at endothelial and epithelial barrier surfaces and is released following injury. On release, IL-33 induces Type 2 (T2) inflammation, stimulating production of IL-5 and IL-13 cytokines and promoting eosinophil recruitment.

T2 inflammation is a characteristic feature of AD. Studies have found increased concentrations of IL-33 mRNA, and ST2 mRNA and protein, in the skin lesions of patients with AD and in the skin of mice induced to develop AD (Dickel et al, 2010; Savinko et al, 2012). In addition, IL-33 impacts skin barrier integrity by downregulating the expression of filaggrin, a structural protein that plays a key role in AD skin barrier function (Salimi et al, 2013; Seltmann et al, 2015). Genetic studies also support a role for IL-33 in the pathogenesis of AD. Single nucleotide polymorphisms in the IL-33 gene that result in loss of protein function have been linked to protection from allergic disorders (Smith et al, 2017). Genetic polymorphisms within the ST2 gene region are associated with AD (Shimizu et al, 2005).

Safety, PK, and immunogenicity results from the Phase 1 clinical study support further investigation of MEDI3506 (Study D9180C00001; Section 1.4). Phase 2a clinical data from patients with AD administered etokimab (Section 1.2), an anti-IL-33 mAb, support investigation of MEDI3506 in AD.

1.6 Benefit-Risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

One Phase 1 clinical study of MEDI3506 (Study D9180C00001) has been completed to date. Safety data from this study has not identified medically important risks associated with single SC doses of 1 to 300 mg, and a single IV dose of 300 mg, MEDI3506 in healthy subjects with a history of mild atopy (N = 42). In addition, no medically important risks are associated with multiple SC doses of 30 to 300 mg MEDI3506 in subjects with GOLD I to II COPD (N = 18), and a single IV dose of 300 mg MEDI3506 in healthy Japanese subjects (N = 6). Data analysis does not suggest any increase in frequency of TEAEs with increased dose, with the exception of injection-site reactions. Except for the TESAEs described (Section 1.4), all TEAEs were Grade 1 or 2 in severity. No new safety findings related to MEDI3506 have been identified.

The purpose of this Phase 2, proof-of-concept clinical study is to evaluate the efficacy and safety of MEDI3506 in subjects with AD. For subjects randomized to MEDI3506, there is a potential benefit in terms of improvement of their AD disease status. However, as the efficacy of MEDI3506 in subjects with AD is yet to be determined, subjects might not receive any individual benefit from participating in this study.

To date, there are no identified risks associated with MEDI3506. Potential risks for MEDI3506 include, as follows:

- Gastrointestinal adverse reactions. This is based on the observation of what was considered an incidental finding of ulcerative colitis in the 26-week toxicity study in cynomolgus monkeys (Section 1.3). The gastrointestinal effects of IL-33 blockade in humans are currently unclear. IL-33 is expressed in the gastrointestinal tract, where it has multiple downstream effects (Hodzic et al, 2017). Expression of IL-33 is elevated in patients with active ulcerative colitis.
- Serious infections (including opportunistic infections and viral reactivations). This is based on the mechanism of action of MEDI3506, in particular, the role of IL-33 as an "epithelial alarmin (Martin and Martin, 2016)."
- CCI [redacted]

CCI [redacted]

- Injection-site reactions. This is based on the SC route of administration and the nature of MEDI3506 as an exogenous protein substance.
- Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions). As mAbs are foreign proteins they have the potential to provoke hypersensitivity reactions.
- Reproductive toxicity. Consistent with ICH guidance on the timing of nonclinical studies, MEDI3506 has not been evaluated in embryo-fetal development toxicity studies.

The study design aims to minimize potential risks to subjects through the inclusion/exclusion criteria and safety monitoring. This includes exclusion of subjects who are more likely to experience the potential risks, stipulating contraceptive requirements for subjects, routine clinical monitoring of subjects including monitoring for injection-site reactions, and routine blinded review of the safety data including potential anaphylactic symptoms by the medical monitor and the sponsor study team. In addition, sites should be equipped to manage anaphylaxis and serious allergic reactions until the subject can be transferred to a suitable facility.

A more detailed description of each potential risk and mitigation strategy can be found in the IB.

1.6.1 Coronavirus Disease 2019 (COVID-19)

Since the first subject was enrolled in this study, coronavirus disease 2019 (COVID-19) has emerged as a worldwide pandemic disease with significant public health implications. As stated above, serious infections are a potential risk of MEDI3506; however, AstraZeneca is not aware of any current evidence of a direct link between IL-33, or its suppression, and COVID-19. Moreover, it is hypothesized that IL-33 suppression might be beneficial in the hyperinflammatory phase of severe COVID-19 illness (Allinne et al, 2019; Lin et al, 2016; Zhang et al, 2017). This hypothesis will be tested in patients hospitalized with COVID-19 pneumonia as part of the ACCORD-2 study (EudraCT Number: 2020-001736-95). Nevertheless, the principles of GCP should continue to be adhered to, including protection of subject well-being.

AstraZeneca accepts that a careful benefit-risk analysis should be performed in each region before initiating a clinical trial that impacts on clinical resources needed for the COVID-19 pandemic. Specifically, this study would not be initiated in regions where local and/or national authorities have issued stay-in-place or lock-down orders, which would inhibit its conduct. Hence, AstraZeneca will commence this study when national guidance indicates that it is acceptable to perform such a study.

The study population is not considered to be particularly vulnerable to COVID-19, as study subjects are generally younger and without significant cardiac comorbidity. The incidence of asthma in the study population is expected to be higher than in the general population but mild in most cases.

Investigators should consider whether potential subjects who are considered to have particular significant risk factors for COVID-19 should be included during the pandemic, per Exclusion Criterion 10. Subjects older than 65 years are additionally excluded as they are at greater risk, per Inclusion Criterion 2.

Subjects who are suspected (or known) to have COVID-19 should not be included, per Exclusion Criterion 10. Subjects who, during the course of the study, are suspected of having contracted COVID-19 should not be brought into contact with other subjects. If it is not possible for a subject to attend a study visit, then the patient should be contacted by telephone for the assessment of AEs, changes in concomitant medications, and other assessments that may be performed entirely verbally. Polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus causing COVID-19) is not mandated for this study, as a subject with a negative result may become infected at any time after the sample was taken. Testing for COVID-19 may and should be performed, if required, by local / national guidelines.

It is recognized that depending on the location and facilities of a clinical site, study visit attendance may place subjects at risk of exposure to SARS-CoV-2. Furthermore, it is recognized that more general population level measures to reduce infection rates (eg, travel restrictions) may inhibit the ability of subjects to attend study visits. Necessary healthcare responses to the pandemic at sites (eg, additional infection control measures) may also inhibit the ability of a clinical site to effectively and properly conduct the study. Study visit attendance for dosing and for clinical assessments of treatment response are critical for the scientific value of the study.

Therefore, investigators should not enrol subjects unless they have reasonable confidence that throughout the duration of the study:

- Subjects will be able to attend study visits, whilst avoiding contact with concentrations of COVID-19 patients (eg, hospital entrances used by such patients) and
- The site will be able to effectively and safely conduct the study, considering relevant national and local factors.

The sponsor will conduct risk-based enrolment assessments on a country and site level, on a regular basis during the pandemic phase, and decisions will be documented.

All site staff should wear personal protective equipment in accordance with local or national guidelines.

The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM) which, in the event of missing data, uses all data that are available. The sponsor will monitor the number of discontinuations, withdrawals, missed visits, and other missing data.

Given the limited additional risks to the study population related to COVID-19, from study participation, beyond those they would experience in everyday life, the mitigations described above are considered sufficient to ensure a favorable benefit-risk balance.

1.6.1.1 Vaccination Against COVID-19

There are no clinical data available to assess the interaction (if any) of MEDI3506 with any COVID-19 vaccine.

The sponsor accepts that vaccination against COVID-19, when and where it is available and subjects are eligible according to applicable guidelines, is in the subject's best interest. Consequently, vaccination during the study is, in general, permitted and any delays in vaccination due to study participation should be minimized.

To help ensure the interpretability of safety data, receipt of COVID-19 vaccine (either first or subsequent dose) is prohibited within 30 days before randomization or within 7 days before or after any dose of investigational product (Section 4.7.3). Receipt of, at least, the first dose of COVID-19 vaccine more than 30 days before randomization, without significantly delaying enrollment, should be preferred but may not be possible, eg, not locally available at the time, subject not eligible at the time, express subject decision not to be vaccinated. Otherwise, vaccination may be performed at any time outside the prohibited 7-day window before or after any dose of investigational product. If the (approximate) date of a subsequent dose of COVID-19 vaccination is known, then enrollment of the subject should be timed so that the dose is not within 30 days prior to scheduled randomization. If this date is not known then enrollment into study should not be delayed. If an enrolled subject does (unexpectedly) receive COVID-19 vaccine within 30 days prior to scheduled randomization, the site should contact the AstraZeneca Study Physician for advice on how the situation should be managed.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

AD disease severity will be decreased in adult subjects with moderate-to-severe AD administered MEDI3506 compared with placebo.

1.7.2 Secondary Hypotheses

In adult subjects with moderate-to-severe AD:

- AD disease severity and symptoms, as measured by additional endpoints, will be decreased in subjects administered MEDI3506 compared with placebo.
- MEDI3506 will be safe and well tolerated compared with placebo.
- The PK profile will support further clinical development of MEDI3506.
- The immunogenicity profile will support further clinical development of MEDI3506.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To assess the effects of MEDI3506 compared with placebo on AD disease severity, in adult subjects with moderate-to-severe AD.	Percent change from baseline to Week 16 in EASI score.

AD = atopic dermatitis; EASI = Eczema Area and Severity Index.

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Efficacy	To further assess the effects of MEDI3506 compared with placebo on AD disease severity and symptoms, in adult subjects with moderate-to-severe AD.	• EASI: ° Percentage of subjects achieving a 90% reduction from baseline in EASI score (EASI 90) at Week 16. ° Percentage of subjects achieving a 75% reduction from baseline in EASI score (EASI 75) at Week 16. ° Percentage of subjects achieving a 50% reduction from baseline in EASI score (EASI 50) at Week 16. • Percentage of subjects achieving an IGA of 0 (clear) or 1 (almost clear) with at least a 2 grade reduction from baseline score at Week 16. • Peak pruritus NRS: Percentage of subjects achieving a reduction of ≥ 3 from baseline to Week 16 in weekly mean of daily peak pruritus NRS. • Peak pruritus NRS: Change from baseline to Week 16 in weekly mean of daily peak pruritus NRS.

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
		• Skin pain NRS: Change from baseline to Week 16 in weekly mean of daily peak skin pain NRS. • SCORAD: Percent change from baseline to Week 16. • PGI-S at Week 16. • Change from baseline to Week 16 in: ° % BSA affected by AD. ° 5-D itch. ° POEM. ° DLQI.
Safety	To assess the safety and tolerability of MEDI3506 compared with placebo, in adult subjects with moderate-to-severe AD.	During the treatment and follow-up periods: • TEAEs and TESAEs. • Vital signs. • Safety laboratory analysis. • ECGs. The following parameters will be recorded for each ECG: ° Date and time of ECG. ° Heart rate (beats/min). ° QT (ms). ° Overall evaluation (normal/abnormal). • Left ventricular ejection fraction as measured by echocardiogram.
PK	To evaluate the PK of MEDI3506 in adult subjects with moderate-to-severe AD.	Serum MEDI3506 concentration profiles during the treatment and follow-up periods.
Immunogenicity	To evaluate the immunogenicity of MEDI3506 in adult subjects with moderate-to-severe AD.	Incidence of ADA during the treatment and follow-up periods.

AD = atopic dermatitis; ADA = anti-drug antibody(ies); BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction from baseline in Eczema Area and Severity Index score; EASI 75 = 75% reduction from baseline in Eczema Area and Severity Index score; EASI 90 = 90% reduction from baseline in Eczema Area and Severity Index score;
ECG = electrocardiogram; IGA = Investigator's Global Assessment; NRS = Numerical Rating Scale;
PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; TEAE = treatment-emergent adverse event;
TESAE = treatment-emergent serious adverse event.

2.3 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	To assess the effects of MEDI3506 compared with placebo on AD disease severity and symptoms over time to Week 24, in adult subjects with moderate-to-severe AD.	• EASI: ° Percentage of subjects achieving a 90% reduction from baseline in EASI score (EASI 90) at Weeks 2, 4, 8, 12, 20, and 24. ° Percentage of subjects achieving a 75% reduction from baseline in EASI score (EASI 75) at Weeks 2, 4, 8, 12, 20, and 24. ° Percentage of subjects achieving a 50% reduction from baseline in EASI score (EASI 50) at Weeks 2, 4, 8, 12, 20, and 24. ° Percent change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in EASI score. • IGA: Percentage of subjects achieving an IGA of 0 (clear) or 1 (almost clear) with at least a 2 grade reduction from baseline score at Weeks 2, 4, 8 ,12, 20, and 24. • Peak pruritus NRS: Reduction of ≥ 3 from baseline to Weeks 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak pruritus NRS. • Peak pruritus NRS: Reduction of ≥ 4 from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in weekly mean of daily peak pruritus NRS. • Peak pruritus NRS: Change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in the weekly mean of daily peak pruritus NRS. • Skin pain NRS: Change from baseline to Week 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak skin pain NRS. • SCORAD: Percent change from baseline to Weeks 2, 4, 8, 12, 20, and 24. • PGI-S at Weeks 2, 4, 8, 12, 20, and 24. • Change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in: ° % BSA affected by AD. ° 5-D itch. ° POEM. ° DLQI.

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
Biomarkers	To evaluate the effect of MEDI3506 on blood biomarkers that may either predict or reflect an efficacy response in adult subjects with moderate-to-severe AD.	• Change from baseline to Week 16 in serum concentrations of: ◦ sST2. ◦ CCI [redacted] • Change from baseline to Week 16 in whole blood PBMC subsets • Change from baseline to Weeks 1, 2, 4, 8, 12, 16, 20, and 24 in serum biomarker levels, including but not limited to: ◦ Eosinophils. ◦ IL-5. ◦ IL-13. ◦ CCL17. • Change from baseline to Weeks 1, 2, 4, 16, 20 and 24 in serum IL-33 bound to MEDI3506 • Change from baseline to Weeks 2, 8, 16, and 24 in serum IgE levels. • Change from baseline to Week 16 in proinflammatory gene signatures in whole blood. • Change from baseline to Weeks 4, 16, and 24 in plasma EDN levels.
Biomarkers	To evaluate the effect of MEDI3506 on skin biomarkers that may either predict or reflect an efficacy response in adult subjects with moderate-to-severe AD.	• Colonization of pathogenic bacteria (ie, *Staphylococcus aureus*) in lesional and non-lesional skin, from baseline to Week 16. • From baseline to Week 16 in lesional and non-lesional skin: ◦ Proinflammatory gene signatures in tape strips and biopsies. ◦ Gross inflammation evaluation.
Efficacy	To assess the effect of MEDI3506 compared with placebo on the need for rescue therapy, in adult subjects with moderate-to-severe AD.	• Proportion of subjects requiring rescue therapy during the treatment and follow-up periods. • Time to first use of rescue therapy throughout the treatment and follow-up periods. • Incidence of skin infection TEAEs requiring systemic treatment during the treatment and follow-up periods.

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	To evaluate the effect of MEDI3506 compared with placebo on nasal symptom control, in a subset of adult subjects with moderate-to-severe AD who have comorbid chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses.	Change from baseline to Week 16 and 24 in SNOT-22.
Efficacy	To evaluate the effect of MEDI3506 on asthma symptom control compared with placebo, in a subset of adult subjects with moderate-to-severe AD who have comorbid asthma.	Change from baseline to Week 16 and 24 in ACQ-6.
[redacted]	CCI [redacted]	[redacted]

ACQ = Asthma Control Questionnaire; AD = atopic dermatitis; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction from baseline in Eczema Area and Severity Index score; EASI 75 = 75% reduction from baseline in Eczema Area and Severity Index score; EASI 90 = 90% reduction from baseline in Eczema Area and Severity Index score; EDN = eosinophil derived neurotoxin; Ig = immunoglobulin; IGA = Investigator's Global Assessment; IL = interleukin; NRS = Numerical Rating Scale; PBMC = peripheral blood mononuclear cell; PGI-S = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; SNOT-22 = Sino-nasal Outcome Test; sST2 = soluble ST2; TEAE = treatment-emergent adverse event.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a Phase 2 randomized, double-blinded, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI3506 in adult subjects with moderate-to-severe AD (Figure 1). Approximately 152 subjects will receive CCI [redacted] MEDI3506 SC; or placebo CCI [redacted] SC, or placebo CCI [redacted] SC; in a 3:1:1:1:2 ratio overall CCI [redacted] The randomization ratio will change during the study

(Section 4.6.1). The randomization will be stratified based on total IgE (< 150 kU/L or ≥ 150 kU/L) at screening. The study will be conducted at approximately 40 to 50 study sites in Australia, Europe, and North America.

Subjects will be enrolled in this study for approximately 7 months (28 weeks), comprising a screening and TCS/TCI wash out period of up to 4 weeks, a 16-week treatment period, and an 8-week follow-up period (Figure 1):

1 Screening and TCS/TCI wash out period: Following the signing of informed consent, subjects will be assessed for study eligibility (Sections 4.1.2 and 4.1.3) at screening Visit 1 and, if eligible, invited to attend screening Visit 2, which must occur 7 or more days prior to randomization. Subjects who meet the eligibility (inclusion/exclusion) criteria will discontinue use of TCSs and TCIs at Visit 2. Subjects will be required to apply moisturizers twice daily for at least 7 days before randomization at Visit 3 (Day 1) with a minimum of 85% compliance.

2 Treatment period: To be randomized at Visit 3 (Day 1), subjects must meet all the eligibility criteria (Sections 4.1.2 and 4.1.3) before receiving investigational product by SC injection [redacted]. Subjects will be required to apply moisturizers twice daily throughout the treatment period, and will not be permitted to use TCSs and TCIs, except if medically necessary (Section 4.7.4). [redacted] and the primary endpoint assessment will occur at Visit 10 (Week 16).

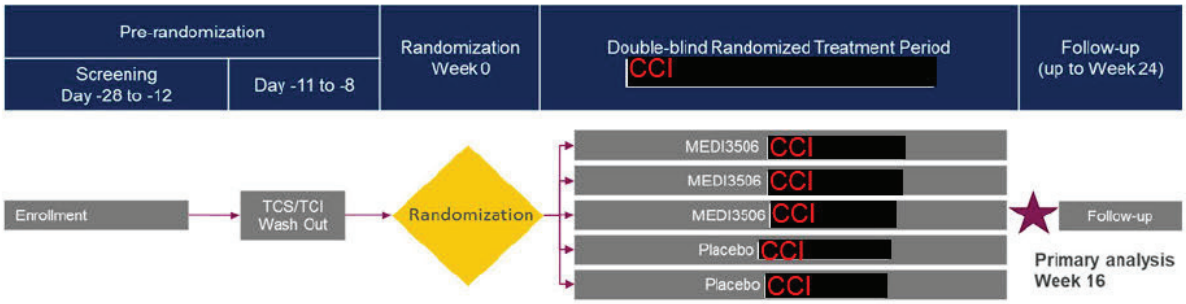
   The first 72 subjects randomized will attend Visit 4a, whereas the remaining subjects will attend Visit 4b instead (Table 7).

   Following provision of informed consent, skin punch biopsies at Visit 3 (Day 1) and Visit 10 (Week 16) will be collected from a subset of subjects (ie, approximately 45 subjects in total). Subjects with comorbid chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis) will complete the Sino-nasal Outcome Test (SNOT)-22 questionnaire. Similarly, subjects with comorbid asthma will complete the Asthma Control Questionnaire (ACQ)-6 questionnaire.

3 Follow-up period: Safety, sustained efficacy, and the need for rescue therapy will be assessed in the follow-up period. Subjects will be required to apply moisturizers twice daily through to the end of the follow-up period at Visit 12 (Week 24), and will not be permitted to use TCSs and TCIs, except if medically necessary (Section 4.7.4).

Definitions for withdrawal criteria (Section 4.1.5) and subject completion of the study (Section 6.3) are provided.

Figure 1 Study Flow Diagram



Q4W = every 4 weeks; SC = subcutaneous; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

The primary analysis will occur once all subjects have either completed the Visit 10 (Week 16) assessments or have withdrawn from the study. The final analysis will occur when all subjects have completed the follow-up period at Visit 12 (Week 24) or have withdrawn from the study.

3.1.2 Treatment Regimen

At Visit 3 (Day 1), eligible subjects will be randomized to receive SC investigational product CCI 12, as follows:

- MEDI3506 CCI (58 subjects),
- MEDI3506 CCI (18 subjects),
- MEDI3506 CCI (18 subjects),
- Placebo CCI (6 subjects), or
- Placebo CCI (52 subjects).

3.1.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be formed to evaluate safety data from concurrently conducted MEDI3506 Phase 2 clinical studies in other indications. Unblinded review of safety data will be required for indications where the potential risks of MEDI3506 are high due to the disease under study and the common comorbidities of particular subject populations. Safety data from this study will be provided to the DSMB for oversight of all safety data.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Rationale for Dose and Dose Regimen

The highest dose of MEDI3506 administered to subjects in this Phase 2 clinical study will be CCI by SC injection CCI. This dose is predicted to have a lower exposure, in terms of

maximum concentration at steady-state ($C_{max,ss}$; approximately 2.5-fold) and AUC (approximately 1.6-fold), compared with the highest dose administered (ie, single dose of [redacted] IV MEDI3506) in the Phase 1 clinical study (Study D9180C00001; Section 1.4). A dose of [redacted] W is predicted to have a higher $C_{max,ss}$, but the same AUC compared with the highest multiple dose administered (ie, [redacted] SC Q2W) in the same study (Table 4).

Table 4 Predicted Maximum Dose Human Exposure comparison based on Phase 1 Study

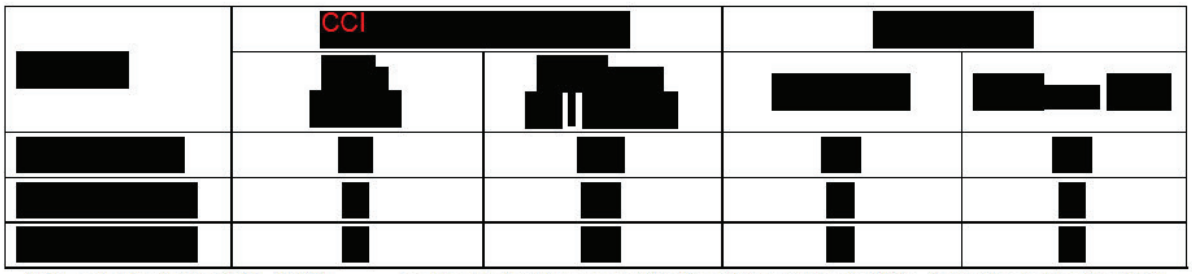
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

$AUC_{0\text{-}4\ weeks}$ = area under the concentration time curve for 0 to 4 weeks at steady state; $C_{max,ss}$ = maximum concentration at steady state; SC = subcutaneous; [redacted].

The nature and severity of disease in the study population are not expected to significantly impact the overall exposure nor clearance. The published PK data for a monoclonal antibody licensed for use in AD indicate that the disease status (ie, healthy subjects vs subjects with AD) had no significant impact on exposure or clearance (Kovalenko et al, 2016). Hence, we anticipate that MEDI3506 exhibits similar PK profiles for both healthy subjects and subjects with AD.

Exposures (ie, mean $C_{max,ss}$ of 1,276 µg/mL, and area under the concentration-time curve for 0 to 4 weeks at steady-state of 28,012 µg • day/mL) achieved at the 26-week NOAEL of 150 mg/kg in cynomolgus monkeys (Section 1.3) are approximately 34- and 45-fold higher than predicted at the proposed highest dose of [redacted] in this Phase 2 clinical study (Table 5).

Table 5 Predicted Human Exposures and Safety Margins for the Phase 2 Clinical Study in AD



AD = atopic dermatitis; $AUC_{0\text{-}4\ weeks}$ = area under the concentration time curve for 0 to 4 weeks at steady state; $C_{max,ss}$ = maximum concentration at steady state; GLP = Good Laboratory Practice; NOAEL = no observed adverse effect level; Q4W = every 4 weeks; QW = every week; SC = subcutaneous.
Predicted human exposures and safety margins were calculated based on the NOAEL of 150 mg/kg SC QW observed in the GLP 26-week, repeat-dose toxicity study in cynomolgus monkeys (Section 1.3). $AUC_{0\text{-}4\ weeks}$ is 28,012 µg • day/mL. $C_{max,ss}$ is 1,276 µg/mL.

The optimal serum concentration for MEDI3506 efficacy in AD is not known. A mouse challenge model suggests a target concentration of 20 µg/mL (refer to the IB for additional details). Preliminary analysis of the PK data from the Phase 1 clinical study of MEDI3506 predicts that CCI will achieve an average steady-state concentration of 22 µg/mL, similar to the target concentration established in the mouse model. In addition, this dose is predicted to achieve > 90% suppression of CCI in the skin based on the theoretical PK/pharmacodynamic (PD) model. If replicated in humans with AD, CCI CCI is anticipated to achieve near-maximum efficacy based on the mouse and PK/PD models. Lower doses of CCI will be used in this Phase 2 clinical study to define the exposure/dose response relationship of MEDI3506.

Administering CCI MEDI3506 will CCI SC injections per dose, whereas administering CCI MEDI3506 will CCI injections per dose. Two placebo groups will be included in this study so that there will be injection volume matched placebo groups for the MEDI3506 groups.

3.2.2 Rationale for Study Population

Biological therapy is presently offered only to adults with moderate-to-severe AD. It is therefore appropriate to select this population of patients for assessing the efficacy and safety of MEDI3506. To investigate the anti-inflammatory effects of MEDI506 in moderate-to-severe AD, withholding of topical and systemic anti-inflammatory medications (ie, TCSs or TCIs) is considered appropriate for patients with AD who have shown inadequate response to these therapies. A placebo comparator group is included for detecting an efficacy response.

Comorbidities of AD including chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses, or asthma, may exist in up to one-third of the target population. Subjects

with the aforementioned comorbidities will be included as subgroup populations for exploratory endpoints to investigate if these comorbidities might be improved by treatment with MEDI3506 (Silverberg and Simpson, 2013; Spergel, 2010).

3.2.3 Rationale for Endpoints

3.2.3.1 Primary Endpoint

The primary endpoint is percent change from baseline in EASI score. The EASI is a valid and reliable quantitative tool for assessing AD severity over time (Schmitt et al, 2013) (Section 4.3.1.1).

3.2.3.2 Secondary Endpoints

The secondary efficacy endpoints will provide information to support the interpretation of the primary endpoint.

Clinical scientific experts advise that an EASI score ≥ 16 at randomization and an Investigator's Global Assessment (IGA) score ≥ 3 reliably identify subjects with moderate-to-severe AD, so cut-off values for EASI and IGA were included as inclusion criteria (Section 4.1.2).

Standard safety, PK, and immunogenicity endpoints will be evaluated.

3.2.3.3 Exploratory Endpoints

Blood samples will be collected from subjects for the assessment of biomarkers that are relevant to disease pathology and/or the mechanism of action of MEDI3506.

Skin punch biopsies and skin tape strips will allow biomarker analyses directly from the target tissue.

Skin swabs will be collected from subjects to evaluate *Staphylococcus aureus (S aureus)* colonization. Levels of *S aureus* have been correlated with disease severity (Simpson et al, 2018).

Many patients with AD have comorbid chronic rhinosinusitis. SNOT-22, a measure of nasal symptoms, will be performed and evaluated in subjects with comorbid chronic rhinosinusitis. Changes in SNOT-22 will be used to assess the impact of MEDI3506 on chronic rhinosinusitis.

Many patients with AD have comorbid asthma. The ACQ-6, a measure of asthma control, will be performed and evaluated in subjects with comorbid asthma to assess the impact of MEDI3506 on asthma symptoms.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 152 subjects are planned to be randomized in this study in 5 treatment groups, as follows:

- MEDI3506 [redacted] (58 subjects).
- MEDI3506 [redacted] (18 subjects).
- MEDI3506 [redacted] (18 subjects).
- Placebo [redacted] (6 subjects).
- Placebo [redacted] (52 subjects).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

Criteria to be Assessed at Screening Visit 1:

If any criterion cannot be fully assessed at screening Visit 1 (eg, due to awaiting information from the subject's usual physician), the criterion must be fully assessed prior to randomization.

1 Written informed consent and any locally required authorization (eg, data privacy) prior to performing any protocol-related procedure, including screening.
2 Age 18 to 65 years inclusive at the time of consent.
3 Body mass index between 19.0 and 40.0 kg/m^2 inclusive at screening Visit 1.
4 Documented history of chronic AD as defined using Hanifin and Rajka's criteria (Hanifin and Rajka, 1980), for at least 1 year prior to screening Visit 1.
5 Meets at minimum 1 of the criteria, as follows:
   (a) A documented history, within the 6 months prior to screening Visit 1, of an IGA score of ≥ 3, despite treatment with daily, medium or high potency TCSs (Appendix G) in the presence or absence of TCIs, applied for ≥ 4 weeks or for the maximum duration recommended by the product prescribing information, whichever is shorter, or
   (b) A documented history, within the 6 months prior to screening Visit 1, of requiring intermittent or continuous systemic therapy,
   (c) Subject intolerance to treatment with topical medications for AD, or

(d) Topical medications are otherwise medically inadvisable (eg, due to important side effects or safety risks that outweigh the potential treatment benefits), as assessed by the investigator or by the physician who treats the subject's AD.

Note, acceptable evidence of documented history includes:

(i) Contemporaneous clinical notes that record ≥ 1 topical medication prescription and treatment outcome, from which an IGA score of ≥ 3 can be inferred.

(ii) Contemporaneous clinical notes that record ≥ 1 systemic medication prescription.

(iii) Investigator documentation based on communication with the physician who treats the subject's AD.

Note, meeting (a) and/or (b) is considered to indicate a history of inadequate response to topical medications for AD.

6 Able and willing to comply with the requirements of the protocol including ability to read, write, be fluent in the translated language of all subject facing questionnaires used at site, and use electronic devices.

Criteria to be Assessed at Screening Visit 1, and Visit 3 (Day 1) Prior to Randomization:

7 AD that affects ≥ 10% of the body surface area (BSA) at both Visit 1 and Visit 3 (Day 1), as assessed by EASI.

8 An EASI score of ≥ 12 at Visit 1 and ≥ 16 at Visit 3 (Day 1).

9 An IGA score of ≥ 3 at both Visit 1 and Visit 3 (Day 1).

10 Female subjects, regardless of childbearing potential, must have negative pregnancy tests both at screening Visit 1 (serum pregnancy test) and pre-dose of investigational product at Visit 3 (Day 1; urine pregnancy test).

11 Female subjects of childbearing potential who are sexually active with a male partner must agree to use a highly effective method of contraception from screening until the end of the follow-up period at Visit 12 (Week 24) of the study. See Appendix A for definitions of childbearing potential and highly effective methods of contraception.

- In countries where spermicide is available, it is strongly recommended for the male partner of a female subject of childbearing potential to also use male condom plus spermicide throughout this period.
- In countries where spermicide is not available, it is strongly recommended for the male partner of a female subject of childbearing potential to also use male condom throughout this period.

Note there are no contraception requirements for female subjects who are not of childbearing potential. However, all female subjects should refrain from egg cell donation and breastfeeding throughout the study.

Criteria to be Assessed at Visit 3 (Day 1) Prior to Randomization:

12 Female subjects of childbearing potential who are sexually active with a male partner must agree to use a highly effective method of contraception.

- In countries where spermicide is available, male subjects who are sexually active with a female partner of childbearing potential must agree to use a male condom with spermicide and another highly effective method of contraception during the treatment and follow-up periods from Visit 3 (Day 1) through to Visit 12 (Week 24) of the study.
- In countries where spermicide is not available, male subjects who are sexually active with a female partner of childbearing potential must agree to use a male condom and another highly effective method of contraception during the treatment and follow-up periods from Visit 3 (Day 1) through to Visit 12 (Week 24) of the study.

See Appendix A for definitions of childbearing potential and highly effective methods of contraception. Male subjects should also refrain from biologically fathering a child or donating sperm during the same period.

13 As confirmed from electronic diary (eDiary) entries, the subject has applied a stable dose of topical emollient (moisturizer) twice daily for ≥ 7 consecutive days immediately before baseline at Visit 3 (Day 1) with a minimum of 85% compliance.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

Criteria to be Assessed at Screening Visit 1 and Visit 2:

If any criterion cannot be fully assessed at screening Visit 1 and Visit 2 (eg, laboratory results not yet available), the criterion must be fully assessed prior to randomization.

1 Subjects with a recent history of or who have a positive test for infective hepatitis, HIV, or unexplained jaundice, or subjects who have been treated for hepatitis B, hepatitis C, or HIV. For the hepatitis B testing (hepatitis B surface antigen [HbsAg], hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]), any of the following would exclude the subject from the study:

(a) Subjects positive for HbsAg.

(b) Subjects positive for anti-HBc.

Subjects with a history of hepatitis B vaccination without a history of hepatitis B are permitted.

2 Evidence of active or latent tuberculosis (TB):

(a) Positive diagnostic TB test during screening Visit 1 defined as a positive interferon gamma release assay [IGRA] test).

(b) Subjects with an indeterminate IGRA should undergo a repeat test and if still indeterminate may be enrolled only after being treated for TB and having a subsequent negative test.

(c) Subjects with a positive IGRA but no clinical history or suspicion of TB and no significant risk factors for TB may undergo a retest and be enrolled if that result is negative.

3 N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) level greater than the upper limit of the laboratory reference range at screening Visit 1; if the result is greater than the upper limit but this is clinically unexpected, the test may be repeated once.

4 A left ventricular ejection fraction < 45% measured by echocardiogram during screening, between the time of signing informed consent and prior to randomization.

5 A family history of heart failure defined as either of the following:

(a) ≥ 2 first degree relatives with clinically significant heart failure, or

(b) ≥ 1 first degree relative with heart failure known to be heritable (eg, hypertrophic cardiomyopathy), unless inheritance is excluded by genetic testing.

Criteria to be Assessed at Screening Visit 1, Visit 2, and Visit 3 (Day 1) Prior to Randomization:

6 Concurrent enrollment in another clinical study involving an investigational product.

7 Participated in a clinical study for a medical device within 3 months, prior to screening at Visit 1.

8 Subject is a participating investigator, sub-investigator, study coordinator, or employee of the participating site, or is a first-degree relative of the aforementioned.

9 Subject has been committed to an institution by virtue of an order issued either by the courts or by a public authority.

10 Any active medical or psychiatric condition, or other reason, prior to randomization, that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results. This includes but is not limited to:

(a) Diabetes mellitus, except for subjects with type 2 diabetes mellitus of ≤ 2 years' duration who are well controlled (ie, hemoglobin A1c [HbA1c] < 8%) and are not using insulin.

(b) History of heart failure.

(c) Clinically significant or unstable ischemic heart disease, arrhythmia, or cardiomyopathy, including acute coronary syndrome within the last 6 months; or any history of myocardial infarction.

(d) Clinically significant aortic stenosis.

(e) Systemic hypertension, unless ≤ 2 years' duration and well controlled using a single medication.

(f) Pulmonary arterial hypertension.

(g) History of an underlying condition that predisposes the subject to infections (eg, history of splenectomy, known primary or secondary immune deficiency syndromes).

(h) History of ulcerative colitis, Crohn's disease, or microscopic colitis diagnosed by either a gastroenterologist or by histopathology.

(i) Obstructive sleep apnea.

(j) History of treatment with cardiotoxic medications (eg, as part of cancer therapy) including thiazolidinediones.

(k) Significant risk factors for COVID-19, such that study participation is not in the best interests of the subject in the opinion of the investigator.

(l) Known or clinically suspected COVID-19 infection within 3 months of randomization.

11 Any other clinically relevant abnormal findings from physical examination (including vital signs and electrocardiogram [ECG]) or from safety laboratory analysis (including hematology, coagulation, serum chemistry, or urinalysis) between informed consent and randomization, that in the opinion of the investigator or medical monitor might compromise the safety of the subject in the study or interfere with evaluation of the investigational product. Abnormal findings include, but are not limited to:

(a) Abnormal vital signs, after 10 minutes of supine rest (confirmed by 1 controlled measurement), defined as any of the following:

(i) Systolic blood pressure (SBP) < 80 mmHg or ≥ 130 mmHg.

(ii) Diastolic blood pressure (DBP) < 50 mmHg or ≥ 90 mmHg.

(iii) Pulse < 45 or > 100 beats per minute.

(b) Signs of pulmonary edema or volume overload.

(c) Any clinically significant rhythm, conduction, or morphology abnormalities in the 12-lead ECG including but not limited to QTc (Fridericia) (Vandenberk et al, 2016) > 450 ms.

(d) Alanine transaminase (ALT) or aspartate transaminase (AST) > 2 × upper limit of normal (ULN).

(e) Total bilirubin (TBL) > 1.5 × ULN (unless due to Gilbert's disease).

(f) Evidence of chronic liver disease.

12 A known history of severe reaction to any medication including biologic agents or human gamma globulin therapy.

13 Active dermatologic conditions that might confound the diagnosis of AD or would interfere with the assessment of the skin, for example scabies, seborrheic dermatitis, cutaneous lymphoma, or psoriasis.

14 Known **active** allergic or irritant contact dermatitis.

15 Known history of allergy or reaction to any component of the investigational product formulation, including hereditary fructose intolerance.

16 Pregnancy or intention to become pregnant during the course of the study, breastfeeding, or unwillingness to use a highly effective method of contraception throughout the study in female subjects of childbearing potential.

17 History of, or a reason to believe a subject has a history of, drug or alcohol abuse within the past 2 years prior to screening.

18 Major surgery within 8 weeks prior to screening at Visit 1, or planned inpatient surgery or hospitalization during the TCS/TCI wash out, treatment, or follow-up periods.

19 Donation of blood or blood products in excess of 500 mL within 3 months prior to screening Visit 1.

20 Current diagnosis of cancer.

21 History of cancer, except if treated with apparent success with curative therapy (response duration of > 5 years).

22 History of allogeneic bone marrow transplant.

23 History of herpes zoster within 3 months prior to randomization at Visit 3 (Day 1).

24 A helminth parasitic infection diagnosed within 6 months prior to randomization at Visit 3 (Day 1) that has not been treated, or has not responded to standard of care therapy.

25 Receiving any prohibited concomitant medications or therapies as specified in the protocol (Section 4.7.3), as follows:

(a) Identified any time from Visit 1 through to randomization Visit 3 (Day 1):

(i) Systemic (oral or injectable) corticosteroids within 4 weeks of Visit 1.

(ii) Live or attenuated vaccines within 4 weeks of Visit 1. (Note: Vaccines with adenoviral vectors that are unable to replicate, eg, ChAdOx1, are not considered live attenuated).

(iii) Ig or blood products within 4 weeks of Visit 1.

(iv) If subjects are on a stable dose of moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products commenced at least 4 weeks prior to Visit 1, this may continue otherwise initiation of such products during the study is prohibited.

(b) Identified at randomization Visit 3 (Day 1):

(i) TCSs or TCIs; or any other topical anti-inflammatory treatment for AD (eg. Crisaborole) within 7 days of randomization.

(ii) Any other immunosuppressive therapy within 3 months of randomization.

(iii) Any immunotherapy within 3 months of randomization, except for stable maintenance dose allergen-specific immunotherapy started, at least, 4 weeks prior to Visit 1 and expected to continue through to the end of the follow-up period.

(iv) Interferon gamma within 3 months of randomization.

(v) Investigational products within 4 months or 5 half-lives of randomization, whichever is longer.

(vi) Marketed biologics including dupilumab within 4 months or 5 half-lives of randomization, whichever is longer.

(vii) Use of tanning beds or phototherapy including NBUVB, UVB, UVA1, or PUVA within 4 weeks prior to randomization.

(viii) Use of > 2 bleach baths per week within 4 weeks prior to randomization.

(ix) Vaccination against COVID-19 (either first or subsequent dose) within 30 days prior to randomization.

Criteria to be Assessed at Visit 3 (Day 1) Prior to Randomization:

26 History of a clinically significant non-skin infection within 4 weeks prior to Visit 3 (Day 1; including unexplained diarrhea) or clinical suspicion of a non-skin infection at the time of dosing of investigational product. A clinically significant infection is defined as:

(a) A systemic infection, or

(b) An infection requiring treatment with a broad-spectrum antibiotic.

27 History of a skin infection that requires systemic antibiotics, antiviral medication, or antifungal medication for > 7 days within 4 weeks prior to Visit 3 (Day 1) or clinical suspicion of a skin-infection at time of dosing of investigational product.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is “enrolled”) once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (ie, an interactive voice/web response system [IXRS]) and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation. At Visit 3 (Day 1), once a subject has been fully assessed as meeting the eligibility criteria, the central IXRS system will be used to randomize the subject (Section 4.6.1).

A log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure. Rescreening of subjects who fail to

meet the eligibility criteria is generally only permitted once, when there is a reasonable expectation that the subject will become eligible for the study. Permission to rescreen > 1 time may be granted by the medical monitor in the presence of extenuating circumstances. Prior to rescreening, subjects must be reconsented and receive a new SID number.

If acceptable documentation of previous inadequate response cannot be obtained, a subject may, at the investigator's discretion, be prescribed a course of medium or high potency TCSs (Appendix G), in the presence or absence of TCIs, and be rescreened if the subject's response is documented as inadequate.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. AEs will be followed up; the eDiary should be returned by the subject. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1 Withdrawal of consent to further treatment with investigational product.
2 Lost to follow-up.
3 Any anaphylactic reaction to investigational product requiring epinephrine administration.
4 Any TESAE that is considered related to investigational product by the investigator.
5 Any TESAE that is in the Cardiac Disorders system organ class, regardless of whether or not the event is considered related to investigational product by the investigator.
6 Confirmed diagnosis of new onset of heart failure during the study, regardless of severity or whether or not the event is considered related to investigational product by the investigator. For a subject with suspected new onset of heart failure, the subject should not be administered investigational product unless and until the diagnosis is refuted.
7 Any other AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing of investigational product.
8 Pregnancy.
9 Following randomization, the subject meets ≥ 1 of the exclusion criteria (Section 4.1.3) or fails to meet all of the inclusion criteria (Section 4.1.2) for study participation.
10 Receipt of prohibited medications (as defined in Section 4.7.3) except for:
   (a) TCS and TCI as rescue therapy (as defined in Section 4.7.4).

(b) Where the principal investigator and the medical monitor agree that nature, duration, etc of the receipt of prohibited medication does not justify discontinuation and the subject may continue receiving investigational product.

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation, the subject is lost to follow-up, or the subject is enrolled in another clinical study.

4.1.7 Replacement of Subjects

Randomized subjects will not be replaced.

4.1.8 Withdrawal of Informed Consent for Biological Sample Retention and Analyses

AstraZeneca ensures that biological samples will be destroyed at the end of a specified period as described in the informed consent.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Collection of the non-optional biological samples is an integral part of the study; therefore, if a subject withdraws consent to the use of the samples the subject is withdrawn from further study participation.

The principal investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca. AstraZeneca will ensure the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action is documented and that the subject and AstraZeneca are informed about the sample disposal.

4.2 Schedule of Study Procedures

Disease severity assessments including EASI, IGA, and SCORing Atopic Dermatitis (SCORAD) should be performed by the same investigator for each subject, whenever possible.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.

4.2.1 Screening and TCS/TCI Wash Out Period

Table 6 shows all procedures to be conducted at the screening and TCS/TCI wash out visits.

Table 6 Schedule of Screening and TCS/TCI Wash Out Procedures

Study Period	**Screening**	**TCS/TCI Wash Out**
Visit Number	**Visit 1**	**Visit 2**
Procedure/Study Day	**Day -28 to -12** [a]	**Day -11 to -8** [a]
Study Week	**Week -4 to -2**	**Week -1**
Written informed consent/assignment of SID number	X	
Written informed consent for future use and/or DNA analysis (optional)	X	
Verify eligibility criteria	X	X
Efficacy assessments:		
EASI including % BSA affected by AD, and IGA	X	X
DLQI, 5-D itch, PGI-S, and POEM		X
SNOT-22 and ACQ-6 [b]		X
eDiary		Daily for ≥ 7 consecutive days immediately before baseline (Visit 3)
Preparation for future efficacy assessments:		
Select area of non-lesional skin for SCORAD assessments in treatment and follow-up periods	X	
Provision of and training on use of eDiary for daily recording of peak pruritus NRS, skin pain NRS, and moisturizer use	X	
Assess adherence to the completion of daily eDiary entries for peak pruritus NRS, skin pain NRS, and moisturizer use		X
Safety assessments:		
Assessment of AEs/SAEs	X	X
Concomitant medications	X	X
Physical examination (full)	X	
Weight and height	X	

Table 6 Schedule of Screening and TCS/TCI Wash Out Procedures

Study Period	Screening	TCS/TCI Wash Out
Visit Number	**Visit 1**	**Visit 2**
Procedure/Study Day	**Day -28 to -12** [a]	**Day -11 to -8** [a]
Study Week	**Week -4 to -2**	**Week -1**
Demography; medical and dermatology history	X	
12-lead ECG	X	
Vital signs	X	
Echocardiogram		X [e]
Urine collection for:		
Urinalysis	X	
Blood collection for:		
Serum chemistry	X	
Hematology	X	
HbA1c	X	
NT-proBNP [c]	X	
IgE (serum)	X	
EDN (plasma)	X	
Serum pregnancy test (all female subjects)	X	
FSH (if needed to confirm post-menopausal status in female subjects aged < 50 years)	X	
Hepatitis B (HbsAg, anti-HBs, anti-HBc) and C antibodies; HIV-1 and HIV-2 antibodies	X	
IGRA (TB test) [d]	X	
Coagulation	X	
Discontinue use of TCSs/TCIs		X
Application of stable dose of topical emollient (moisturizer)		Twice daily for ≥ 7 consecutive days immediately before baseline (Visit 3) [f]

Table 6 Schedule of Screening and TCS/TCI Wash Out Procedures

Study Period	Screening	TCS/TCI Wash Out
Visit Number	Visit 1	Visit 2
Procedure/Study Day	Day -28 to -12 [a]	Day -11 to -8 [a]
Study Week	Week -4 to -2	Week -1

AD = atopic dermatitis; ACQ = Asthma Control Questionnaire; AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EDN = eosinophil derived neurotoxin; eDiary = electronic diary; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HbsAg = hepatitis B surface antigen; Ig = immunoglobulin; IGA = Investigator's Global Assessment; IGRA = interferon gamma release assay; NRS = Numerical Rating Scale; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PGI-S = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; SAE = serious adverse event; SCORAD = SCORing Atopic Dermatitis; SID = subject identification; SNOT = Sino-nasal Outcome Test; TB = tuberculosis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

[a] Visit 2 must occur a minimum of 7 days prior to randomization. If inclusion criterion 13 is (or will) not be met at or on Visit 3 then (if considered appropriate by the investigator and may lead to the criterion being met) Visit 3 may be delayed so as occur up to 14 days after Visit 2 ie, retrospectively Visits 1 and 2 may be as early as Days -31 and -14 respectively.

[b] SNOT-22 and ACQ-6 will be administered to a subset of subjects as described in Sections 4.3.1.11 and 4.3.1.12, respectively.

[c] If the NT-proBNP result is greater than the upper limit but this is clinically unexpected the test may be repeated once.

[d] See exclusion criterion 2.

[e] Echocardiogram may be performed at any time after informed consent is signed. Echocardiogram results must be available prior to randomization at Visit 3 (Day 1).

[f] Minimum of 85% compliance.

4.2.2 Randomized Treatment Period

Table 7 shows all procedures to be conducted during the treatment period.

Table 7 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period								
Visit Number	**Visit 3 [a]**	**Visit 4a [b] TC**	**Visit 4b [b]**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy assessments:									
EASI including % BSA affected by AD, IGA, and SCORAD [a]	X [c]			X	X	X	X	X	X
DLQI, 5-D itch, PGI-S, and POEM	X				X	X	X	X	X
SNOT-22 and ACQ-6 [d]	X					X	X	X	X
eDiary	Daily throughout treatment period								
Assess adherence to the completion of daily eDiary entries for peak pruritus NRS, skin pain NRS, and moisturizer use	X	X	X	X	X	X	X	X	X
Safety assessments:									
Assessment of TEAEs/TESAEs	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination (abbreviated)	X [e]					X	X	X	X [e]
Weight	X								
12-lead ECG [f]	X			X		X	X	X	X
Vital signs [g]	X			X	X	X	X	X	X
Echocardiogram								X [h]	

Table 7 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period								
Visit Number	**Visit 3** [a]	**Visit 4a** [b] **TC**	**Visit 4b** [b]	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP and echocardiogram		As required, for subjects who might be experiencing heart failure, or as soon as possible after heart failure might have occurred							
Verify eligibility criteria	X								
Randomization	X [c]								
Urine collection for:									
Urinalysis	X				X	X	X	X	X
Pregnancy test (all female subjects)	X					X	X	X	X
Blood collection for:									
Serum chemistry [i]	X			X	X	X	X	X	X
Hematology [i]	X			X	X	X	X	X	X
NT-proBNP [i]							X	X	X
PK (serum) [i]	X		X	X	X	X	X	X	X
sST2 and CCI [redacted]	[redacted] CC								[redacted]
ADA (serum) [i]	X			X		X	X		X
IgE (serum) [i]	X				X		X		X
EDN (plasma) [i]	X					X			X
IL-33 (serum) [i]	X			X	X	X			X

Table 7 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period								
Visit Number	**Visit 3** [a]	**Visit 4a** [b] **TC**	**Visit 4b** [b]	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]								
Additional exploratory biomarkers (serum) [i]	X			X	X	X	X	X	X
CCI [redacted]									[redacted]
RNA PAXgene for quantifying proinflammatory gene signatures (whole blood) [i]	X								X
DNA analysis (optional) [j]	X								
PBMCs (CPT tube) [i]	X								X
Lesional and non-lesional skin swabs for *Staphylococcus aureus* [i]	X								X
Skin punch biopsies [k]	X								X
Adhesive skin tape patches	X								X
Application of stable dose of topical emollient (moisturizer)	Twice daily throughout treatment period								
CCI [redacted]	[redacted]					[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period								
Visit Number	Visit 3 [a]	Visit 4a [b] TC	Visit 4b [b]	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACQ = Asthma Control Questionnaire; AD = atopic dermatitis; ADA = anti-drug antibody(ies); BSA = body surface area; CPT = Cell Preparation Tubes; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eDiary = electronic diary; EDN = eosinophil derived neurotoxin; Ig = immunoglobulin; IGA = Investigator's Global Assessment; IL = interleukin; NRS = Numerical Rating Scale; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PBMC = peripheral blood mononuclear cell; PGI-S = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; PK = pharmacokinetic(s); SC = subcutaneous; SCORAD = SCORing Atopic Dermatitis; SNOT = Sino-nasal Outcome Test; sST2 = soluble ST2; TC = telephone contact; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a] Specifications for moisturizer use prior to visits when SCORAD will be assessed are described in Section 4.3.1.3.
[b] Visit 4a only applies to the first 72 subjects randomized, subsequent subjects will attend Visit 4b instead, as described in Section 3.1.1.
[c] Subjects must be assessed on IGA, EASI, and SCORAD rating scales prior to randomization to ensure the subjects still qualify for the study.
[d] SNOT-22 and ACQ-6 will be administered to a subset of subjects only as described in Sections 4.3.1.11 and 4.3.1.12, respectively.
[e] At the visits specified, the physical examination will include an alopecia areata assessment as described in Section 4.3.2.2.
[f] Detailed procedures including the frequency and timing of ECGs by visit are described in Section 4.3.2.4.
[g] Detailed procedures and the timing of vital signs are described in Section 4.3.2.3.
[h] Echocardiogram may be performed at any time at or between Visit 9 (Week 12) and Visit 10 (Week 16) inclusive.
[i] Prior to administration of investigational product on days when investigational product is administered.
[j] Blood samples will be collected on Day 1 or on any other day during the treatment period.
[k] Skin punch biopsies will be collected from a subset of subjects as described in Section 4.3.7.3.
[l] If a suspected anaphylactic reaction occurs during or within a 24-hour period after administration of investigational product, blood samples for serum tryptase will be collected as soon as possible after the event, at 60 ± 30 minutes after the event, at discharge, and between 2 and 4 weeks post-discharge. Immediate care of the subject and treatment of the reaction must take priority over collecting blood samples. Additional details on anaphylactic reactions are provided in Appendix C and Appendix D.

4.2.3 Follow-up Period

Table 8 shows all procedures to be conducted during the follow-up period.

Table 8 Schedule of Follow-up Procedures

Study Period	Follow-up		
Visit Number	Visit 11	Visit 12	Unscheduled/ Early Discontinuation Visit
[redacted]	CCI [redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
Efficacy assessments:			
EASI including % BSA affected by AD, IGA, and SCORAD [a]	X	X	X
DLQI, 5-D itch, PGI-S, and POEM	X	X	X
SNOT-22 and ACQ-6 [b]		X	X
eDiary	Daily throughout follow-up period		
Assess adherence to the completion of daily eDiary entries for peak pruritus NRS, skin pain NRS, and moisturizer use	X	X	X
Safety assessments:			
Assessment of TEAEs/TESAEs	X	X	X
Concomitant medications	X	X	X
Physical examination (abbreviated)		X	X
12-lead ECG		X	X
Vital signs		X	X
NT-proBNP and echocardiogram	As required, for subjects who might be experiencing heart failure, or as soon as possible after heart failure might have occurred		
Urine collection for:			
Urinalysis	X	X	X
Pregnancy test (all female subjects)	X	X	X
Blood collection for:			
Serum chemistry	X	X	X
Hematology	X	X	X
NT-proBNP		X	X
PK (serum)	X	X	X

Table 8 Schedule of Follow-up Procedures

Study Period	Follow-up		
Visit Number	**Visit 11**	**Visit 12**	**Unscheduled/ Early Discontinuation Visit**
[redacted]	CCI [redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
sST2 and CCI [redacted]			
ADA (serum)		X	X
RNA PAXgene for quantifying proinflammatory gene signatures (whole blood)			
IgE (serum)		X	
EDN (plasma)		X	
IL-33 (serum)	X	X	
Additional exploratory biomarkers (serum)	X	X	
Lesional and non-lesional skin swabs for *Staphylococcus aureus*			
Application of stable dose of topical emollient (moisturizer)	Twice daily throughout follow-up period		
Assessment of SC injection sites			X

ACQ = Asthma Control Questionnaire; AD = atopic dermatitis; ADA = anti-drug antibody(ies); BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eDiary = electronic diary; EDN = eosinophil derived neurotoxin; Ig = immunoglobulin; IGA = Investigator's Global Assessment; IL = interleukin; NRS = Numerical Rating Scale; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PGI-S = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; PK = pharmacokinetic(s); SC = subcutaneous; SCORAD = SCORing Atopic Dermatitis; SNOT = Sino-nasal Outcome Test; sST2 = soluble ST2; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a] Specifications for moisturizer use prior to visits when SCORAD will be assessed are described in Section 4.3.1.3.

[b] SNOT-22 and ACQ-6 will be administered to a subset of subjects only as described in Sections 4.3.1.11 and 4.3.1.12, respectively.

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 EASI Including Percentage BSA Affected by AD

The EASI was designed by modifying the Psoriasis Area and Severity Index, which has been widely used in clinical studies and has been established as a well-accepted and standardized instrument for assessing therapeutic response in patients with psoriasis (Schmitt et al, 2013). The EASI is a one-dimensional scoring system, measuring only the clinical signs of AD not

including the symptoms. The EASI evaluates 4 anatomic regions for severity and extent of key disease signs and focuses on the acute and chronic signs of inflammation (ie, erythema, edema, papulation, excoriation, and lichenification). The maximum score is 72, with higher values indicating more severe disease.

The EASI including percentage BSA affected by AD will be assessed according to the schedule of study procedures (Table 6, Table 7, and Table 8). The EASI will be completed by the investigator on an electronic device supplied to the site, which will calculate the domain and total scores for the subject. Additional instructions for the investigator are described in Section 4.2. The percentage of subjects achieving a 75% reduction from baseline in Eczema Area and Severity Index score (EASI 75), 50% reduction from baseline in Eczema Area and Severity Index score (EASI 50), and 90% reduction from baseline in Eczema Area and Severity Index score (EASI 90) will be calculated from the EASI scores. The percentage BSA affected by AD is a component of EASI and will be analyzed separately from the composite EASI score.

4.3.1.2 IGA

The IGA allows investigators to assess overall AD disease severity at 1 given time point and consists of a 5-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, and 4 = severe disease; Appendix H). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment.

The IGA will be assessed according to the schedule of study procedures (Table 6, Table 7, and Table 8), and will be completed by the investigator on an electronic device supplied to the site. Additional instructions for the investigator are described in Section 4.2.

4.3.1.3 SCORAD

SCORAD is a clinical tool for assessing the severity of AD that evaluates the extent and intensity of AD lesions, in addition to subjective symptoms (Kunz et al, 1997). The maximum total score is 103, with higher values indicating more severe disease.

A suitable area of non-lesional skin will be designated at screening for SCORAD assessments of skin dryness at Visit 1. To allow for the assessment of skin dryness, moisturizers should not be applied to the designated area for ≥ 8 hours before visits when SCORAD will be assessed. This should be explained to subjects at Visit 1.

SCORAD will be assessed according to the schedule of study procedures (Table 7 and Table 8). SCORAD will be completed on an electronic device supplied to the site, which will calculate the domain and total scores for the subject. Additional instructions for the investigator are described in Section 4.2.

4.3.1.4 Peak Pruritus NRS

Peak pruritus (ie, worst itch experienced in the previous 24 hours) will be assessed using an Numerical Rating Scale (NRS; 0 to 10) with 0 = no itch and 10 = worst imaginable itch (Yosipovitch et al, 2019). Subjects will complete the pruritus NRS using an eDiary each morning according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.5 Skin Pain NRS

Skin pain (ie, worst skin pain experienced in the previous 24 hours) will be assessed using an NRS (0 to 10) with 0 = no pain and 10 = worst imaginable pain (Humphrey et al, 2017; Vakharia et al, 2017). Subjects will complete the pain NRS using an eDiary each morning according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.6 Moisturizer Use

Subjects will record their moisturizer use using an eDiary each morning according to the schedule of study procedures (Table 6, Table 7, and Table 8). The records of the subjects will be used to monitor compliance with daily moisturizer use.

4.3.1.7 5-D Itch

5-D itch is a questionnaire typically completed in < 5 minutes designed to assess itch or pruritus, with a recall period of 2 weeks. 5-D itch takes into account the multidimensional nature of pruritus and its impact on quality of life, and is capable of detecting changes over time (Elman et al, 2010). Subjects will complete the 5-D itch on an electronic device supplied to the site according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.8 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a 10-item, patient-completed, health-related quality of life assessment of dermatology conditions with a recall period of 1 week (Finlay and Khan, 1994). The DLQI captures perceptions of dermatology-related symptoms and feelings; impacts on daily activities, leisure, work or school, personal relationships; and the side effects of treatment. Each item is scored on a 4-point Likert scale with 0 = not at all/not relevant, 1 = a little, 2 = a lot, and 3 = very much (Basra et al, 2008). The DLQI can be completed in approximately 5 minutes.

Subjects will complete the DLQI on an electronic device supplied to the site according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.9 Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) is a tool that allows patients to rate the severity of a condition. The PGI-S will comprise a single question of, “Please select the response below that best describes the severity of your overall symptoms over the past 7 days.” with response options of “No symptoms”, “Very mild”, “Mild”, “Moderate”, “Severe”

or "Very severe". Subjects will complete the PGI-S on an electronic device supplied to the site according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.10 Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) is a 7-item questionnaire for assessing disease symptoms including dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping occurring in the past week with a scoring system of 0 (absent disease) to 28 (severe disease) (Charman et al, 2004). Subjects will complete POEM on an electronic device supplied to the site according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.11 SNOT-22

The SNOT-22 is a validated questionnaire for assessing the impact of chronic rhinosinusitis on quality of life (Hopkins et al, 2009). The SNOT-22 contains a list of 22 symptoms and social/emotional consequences of a patient's nasal disorder, and measures how severe each symptom is and the social/emotional consequences of symptoms over a 2-week period on a scale from 0 (no problem) to 5 (problem as bad as it can be). A total score is summed.

The SNOT-22 will be administered to subjects who have comorbid chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/rhinosinusitis, nasal polyps, allergic rhinitis). Subjects will complete the SNOT-22 on an electronic device supplied to the site according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.1.12 ACQ-6

The ACQ was the first questionnaire developed and validated to measure asthma control (Yosipovitch et al, 2019). The ACQ includes 6 questions regarding symptoms at night, in the morning, limitation of normal daily activities, dyspnea, wheezing, and beta-2 agonist use. Subjects are asked to recall how their asthma has been during the previous week and to answer questions using a 7-point scale with 0 = no impairment and 6 = maximum impairment). ACQ-6 does not include spirometry and is the equally weighted mean of 6 questions.

The ACQ-6 will be administered to subjects who have a medical history of comorbid asthma. Subjects will complete the ACQ-6 on an electronic device supplied to the site according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.2 Medical and Dermatology History, Physical Examinations, Weight, Height, Vital Signs, ECGs, and Echocardiograms

In addition to the medical and dermatology history, physical examinations, weight, height, vital signs, ECG and echocardiogram assessments described below, additional assessments may be performed at the investigator's discretion.

4.3.2.1 Medical and Dermatology History

Complete medical history will include history of and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders (including COVID-19 and COVID-19 vaccination).

The subject's dermatology history will also be collected including questions related to the subject's dermatology history, duration of AD, and AD medications (both past and current).

Medical and dermatology history will be assessed according to the schedule of study procedures (Table 6).

4.3.2.2 Physical Examinations, Weight, and Height

Full and abbreviated physical examinations will be performed by a licensed healthcare provider (eg, physician, physician's assistant, or licensed nurse practitioner). Full physical examinations will include, but are not limited to, assessment of general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Abbreviated physical examinations will include assessment of cardiovascular, respiratory, and nervous systems. Each clinically significant abnormal finding will be recorded in the medical history, and each treatment-emergent abnormality including injection site reactions identified by assessing SC injection sites will be recorded as a TEAE. Physical examinations, weight, and height will be performed according to the schedule of study procedures (Table 6, Table 7, and Table 8).

In addition, subjects will be assessed for the presence or absence of current alopecia areata at Visit 3 (Day 1) and Visit 10 (Day 113; Table 7). In subjects who had current alopecia areata at Visit 3 (Day 1), the presence or absence of an improvement in alopecia areata will be recorded at Visit 10 (Day 113).

4.3.2.3 Vital Signs

The nominal timing of vital signs, ECGs, and blood draws is described (Section 4.2). The subject should be in a resting supine position for at least 10 minutes prior to the collection of vital signs, as follows:

- Oral or tympanic temperature.
- DBP
- SBP
- Heart (pulse) rate
- Respiratory rate.

For the first 2 doses of investigational product, subjects are to remain at the site for ≥ 2 hours or until stable, whichever is later. In addition, vital signs will be taken before and immediately after administration of investigational product, and at 30, 60, and 120 minutes (± 5 minutes) thereafter or until stable, whichever is later. For the final 2 doses of investigational product, subjects are to remain at the site for ≥ 1 hour or until stable, whichever is later. In addition, vital signs will be taken before and immediately after administration of investigational product, and at 30 and 60 minutes (± 5 minutes) thereafter. Following the observation period, subject discharge will be at the discretion of the investigator. Vital signs will be recorded at visits according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.2.4 ECGs

The nominal timing of vital signs, ECGs, and blood draws is described (Section 4.2). The subject should be in a resting supine position for at least 10 minutes prior to the collection of ECGs. At baseline, pre-dose of investigational product at Visit 3 (Day 1), triplicate ECGs will be performed (all 3 ECGs within a 5-minute time period, at least 1 minute apart). The mean value of each parameter from the triplicate will be used as the baseline value. ECGs taken at all other times will be single assessments. ECGs will be recorded at visits according to the schedule of study procedures (Table 6, Table 7, and Table 8).

ECGs will be recorded with 12-lead digital ECG devices at a speed of 25 mm/second with amplitude recording of 10 mm/mV. Where possible the same make and model ECG device should be used for recording all ECGs for a particular subject. At least 3 full complexes must be recorded. Date and time settings should be checked regularly and following time changes for daylight savings time. Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placements.

ECG device software will be used to assess ECG parameters. All ECGs must be reviewed by the principal investigator or a qualified designee before the subject is permitted to leave the clinic. Abnormalities and obvious changes in ECG parameters from baseline will be assessed by the principal investigator for clinical significance.

ECG variables will be collected, as follows:

- Heart (pulse) rate.
- RR interval.
- QRS interval.
- PR interval.
- QT interval.

4.3.2.5 Echocardiograms

A transthoracic echocardiogram to assess left ventricular ejection fraction will be performed and read locally according to the schedule of study procedures (Table 6, Table 7, and Table 8).

4.3.3 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study. Clinical laboratory safety tests will be performed in a central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 6, Table 7, and Table 8 for the schedule of study procedures):

Serum Chemistry

- Potassium
- Sodium
- AST
- ALT
- ALP
- TBL (if result is > 1.5 ULN, indirect and direct bilirubin will be measured)
- GGT
- IgA, IgG, IgM, total Ig
- Creatinine
- Blood urea nitrogen
- Albumin
- Total protein
- Uric acid

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; TBL = total bilirubin; ULN = upper limit of normal.
Note for serum chemistry: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

Hematology

- WBC count with differential [a]
- RBC count
- Hematocrit
- Platelet count
- Hemoglobin

RBC = red blood cell; WBC = white blood cell.
Note for hematology: Blinding procedures for eosinophil, basophil, and monocyte data are described in Section 4.6.2.

[a] Whole blood samples will be collected concurrently for both hematology and exploratory biomarker (Section 4.3.7.1) assessments of eosinophils.

Urinalysis

- Color
- Appearance
- Specific gravity
- Glucose
- Ketones
- Blood

- pH
- Protein
- Microscopy including WBCs, RBCs, and casts
- Bilirubin
- Leukocytes

RBC = red blood cell; WBC = white blood cell.

Pregnancy Test (Female Subjects Only)

- Serum beta-human chorionic gonadotropin.
- Urine human chorionic gonadotropin.

Other Safety Tests

- Follicle-stimulating hormone (if needed to confirm post-menopausal status in female subjects aged < 50 years).
- HbA1c.
- Hepatitis B antibodies (HbsAg, anti-HBs, and anti-HBc) and hepatitis C virus antibody.
- HIV-1 and HIV-2 antibodies.
- IGRA (TB test). See Exclusion Criterion 2.
- Coagulation.
- Serum tryptase will only be taken in the event of suspected anaphylaxis (Appendix C and Appendix D).
- NT-proBNP.

Other Laboratory Tests

- Total IgE.
- CCI [redacted]
- EDN

4.3.4 PK Evaluation and Methods

The nominal timing of vital signs, ECGs, and blood draws is described (Section 4.2). The time of the first SC injection will be recorded for each subject as the timings will be required for analyzing the PK data. Serum will be collected to evaluate the PK of MEDI3506 according to the schedule of study procedures (Table 7 and Table 8). MEDI3506 concentration in serum will be measured utilizing a validated assay method.

Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected according to the schedule of study procedures (Table 7 and Table 8) to evaluate potential serum ADA responses to MEDI3506. Evaluations will be performed using a validated immunoassay. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naïve samples. Samples may be utilized for further characterization of the ADA response, including possible assessment of neutralizing antibody. Serum samples collected for ADA will be stored for 15 years following the issue of Clinical Study Report (CSR), and they may be utilized for further characterization of the antibody response.

Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

4.3.6 Genetic Evaluation and Methods

CCI [redacted]

On Day 1, a sample for DNA analysis will be taken. Participation in additional genetic research (ie, DNA analysis) is optional for subjects. The objectives, plan, and procedures for optional genetic research are described (Appendix F).

4.3.7 Biomarker Evaluation and Methods

The subject's consent to the use of donated biological samples is mandatory.

Biological samples (eg, serum) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of investigational product, clinical outcomes, and toxicity. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be tested in future research.

4.3.7.1 Blood Biomarkers

Blood samples for exploratory biomarker analyses will be collected at visits according to the schedule of study procedures (Table 7 and Table 8). Whole blood samples will be collected concurrently for both hematology (Section 4.3.3) and exploratory biomarker assessments of eosinophils. Plasma samples will be collected to evaluate EDN levels. Serum samples will be collected for all other exploratory biomarker analyses. A qualified immunoassay method will be used to analyze the biomarker samples.

4.3.7.2 RNA PAXgene

Whole blood for RNA PAXgene will be collected according to the schedule of study procedures (Table 7 and Table 8). RNA PAXgene will be used for the collection, transport, and storage of whole blood, and the stabilization of intracellular RNA. RNA transcript profiling analyses (Section 4.3.7.4) will be performed on RNA PAXgene samples.

4.3.7.3 Skin Punch Biopsies

Following provision of informed consent, skin punch biopsy samples will be collected from a subset of subjects according to the schedule of study procedures (Table 7).

Local anesthesia may be used in accordance with local practices. Skin punch biopsy samples will be collected from areas of lesional and non-lesional skin that are close in distance (≤ 5 cm) to each other. If possible, a 3 mm skin punch should be used. For the evaluation of the proinflammatory gene signature endpoint, RNA transcript profiling (Section 4.3.7.4) analyses will be performed on skin punch biopsy samples. For the evaluation of gross inflammation, hematoxylin and eosin staining analyses will be performed on skin punch biopsy samples.

At Visit 10, lesional and non-lesional skin biopsy samples should be taken from areas close in distance to where the lesional and non-lesional samples, respectively, were taken at Visit 3.

4.3.7.4 RNA Transcript Profiling of RNA PAXgene and Skin Punch Biopsy Samples

Intracellular RNA will be isolated and purified from whole blood RNA PAXgene (Section 4.3.7.2) and skin punch biopsy (Section 4.3.7.3) samples. Proinflammatory gene signatures will be quantified from the RNA. The expression levels of genes associated with disease activity, specific cell types, and signaling, including the IL-33/ST2 pathway will be quantified. The analyses will retrospectively evaluate transcript biomarkers predictive of subject response at baseline, prior to investigational product administration, as well as potentially identify additional biomarkers. In addition, these biomarker measurements will aid in the determination of which biological pathways are affected by treatment with MEDI3506.

4.3.7.5 *S aureus* Colonization

S. aureus has the potential to exacerbate AD skin disease through colonization, super-infection of the skin, and production of inflammation-inducing toxins. Skin swabs will be collected from subjects to assess *S. aureus* colonization and infection according to the schedule of study procedures (Table 7 and Table 8). Swabs will be rotated across non-lesional and lesional skin that are close in distance (≤ 5 cm) to each other. *S. aureus* colonization and infection will be characterized to determine whether differential benefit is observed among subjects in relation to *S. aureus* abundance, and if *S. aureus* colonization and infection are impacted by MEDI3506 treatment.

4.3.7.6 Peripheral Blood Mononuclear Cells

Whole blood will be collected to isolate peripheral blood mononuclear cells (PBMCs) according to the schedule of study procedures (Table 7). This exploratory biomarker may help identify a responder population based on the investigation of immune cell subset ratios at baseline and/or after MEDI3506 intervention.

4.3.7.7 Adhesive skin tape patches

Adhesive skin tape patches will be used to collect skin samples from all subjects for gene expression analysis according to the schedule of study procedures (Table 7). The worst target lesion and a non-lesional site (≤ 5 cm from the worst target lesional site) will be selected at baseline, both of which must not overlap with the selected sites for skin punch biopsies. Those two sites will then be used at both timepoints. This exploratory analysis may help identify a responder population based on transcript biomarkers, as well as to potentially identify additional pharmacodynamic biomarkers related to responders and non-responders to the investigational product.

Information regarding the handling/shipping of specimens will be provided in a separate manual.

4.3.8 Storage, Re-use, and Destruction of Biological Samples

Samples will usually be stored for a maximum of 15 years from the date of LSLV, after which they will be destroyed. If required, ADA samples might be stored for longer than 15 years based on the requirements described (Section 4.3.5).

4.3.9 Estimate of Volume of Blood to Be Collected

The estimated total volume of blood to be collected from each subject at each visit from screening through to the end of study will range from 25 to 55 mL. If repeats of any blood tests are required, the volume of blood collection will increase accordingly. The total blood volume to be collected throughout the study for each subject will not exceed 400 mL.

4.4 Study or Study Component Suspension or Termination

AstraZeneca reserves the right to temporarily suspend or permanently terminate this study or component of the study (eg, study site) at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1 The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
2 Subject enrollment is unsatisfactory.
3 Non-compliance that might significantly jeopardize the validity or integrity of the study.
4 Sponsor decision to terminate development of the investigational product for this indication.

If AstraZeneca determines that temporary suspension or permanent termination of the study or component of the study is required, AstraZeneca will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, AstraZeneca will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study or component of the study is suspended or terminated for safety reasons, AstraZeneca will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. AstraZeneca will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study or component of the study is suspended for safety reasons and it is deemed appropriate by AstraZeneca to resume the study or component of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Products

AstraZeneca will provide the investigators with investigational product (MEDI3506 or placebo; Table 9) using designated distribution centers.

Table 9 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI3506	AstraZeneca	2R vial with nominal 1 mL of 150 mg/mL MEDI3506 containing 20 mM L-histidine / L-histidine-hydrochloride, 220 mM L-arginine-hydrochloride, 0.03% (w/v) polysorbate 80, pH 5.5.
Placebo	AstraZeneca	3-cc vial with nominal 1 mL solution of 20 mM L-histidine / L-histidine-hydrochloride, 240 mM sucrose, 0.02% (w/v) polysorbate 80, pH 6.0

w/v = weight/volume.

Both MEDI3506 and placebo will be packaged into single vial kits with a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of the vial within the carton).

4.5.1.1 Investigational Product Handling

The MEDI3506 doses will be prepared by the site's designated unblinded investigational product manager using aseptic technique. MEDI3506 does not contain preservatives and therefore, any unused portion will be discarded.

The unblinded investigational product manager will select the appropriate kits allocated by the IXRS to prepare the subject's dose. The unblinded investigational product manager must ensure that only the unblinded team members have access to the areas of the pharmacy where the investigational product is being stored and prepared.

4.5.1.2 Investigational Product Inspection

Each vial allocated for dose preparation should be inspected. MEDI3506 is supplied as a clear to opalescent sterile liquid in a 2R glass vial at a concentration of 150 mg/mL. Placebo is supplied as a clear to opalescent sterile liquid in a 3cc glass vial.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

4.5.1.3 Dose Preparation Steps

No incompatibilities between MEDI3506 and plastics passing compatibility tests (ie, polypropylene and polycarbonate syringes) have been observed.

MEDI3506 and placebo do not contain preservatives and any unused portion must be discarded. Preparation of investigational product is to be performed aseptically. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials assigned by the IXRS.

Preparation of SC Doses

A vial should be used only 1 time to prepare a single dose.

To prepare the subject's dose, the unblinded investigational product manager will select investigational product for administration according to the kit identification numbers assigned by the IXRS. A summary of the investigational product volumes required and syringes to prepare for SC dose administration in each treatment group is provided (Table 10).

Table 10 Investigational Product Dose Preparation

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Do not mix MEDI3506 and placebo in the same syringe.

The dose preparation steps are, as follows:

1 Prepare the IXRS assigned MEDI3506 and/or placebo vials for the particular treatment group as per Table 10.
2 Withdraw the required volume of MEDI3506 or placebo from each vial using a separate, appropriately sized syringe and a separate 18-20-gauge 1-1.5 inch needle.
3 Remove the 18-20-gauge needle. Replace with a capped 27-gauge 0.5 inch needle until administration.

4.5.1.4 Treatment Administration

CCI [redacted]

Female subjects, regardless of childbearing potential, must have a negative urine pregnancy test prior to receiving each dose of investigational product.

MEDI3506 and placebo are not identical in appearance or viscosity. The syringes should be kept out of sight of all blinded persons, including the subject, to maintain the blind. Investigational product will be administered SC by unblinded site personnel via a 27-gauge 0.5-inch needle to the abdomen, back of the arms, or thigh. For multiple injections at the same visit, there should be an approximately 1-inch (2.5 cm) distance between injection sites in the same anatomical region. The unblinded site personnel administering the dose will wipe the skin surface of the administration sites with alcohol and allow the skin surface to air dry. The

skin will be pinched to isolate the SC tissue from the muscle. The needle will be fully inserted at a 45-degree angle into the SC tissue. The investigational product will be slowly injected (at least 5 seconds' duration is recommended). The area should not be massaged after injection.

It is advised that the site of injection be rotated so that the subject receives investigational product injections in different anatomical regions from one visit to the next. In cases when rotation of the injection site is not feasible and/or the subject prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents.

Each injection site must be documented on the electronic case report form (eCRF) and in the source documents at each treatment visit.

4.5.1.5 Monitoring Dose Administration

Post dose of investigational product, vital signs will be periodically assessed (Section 4.3.2.3), and SC injection sites will be assessed for injection site reactions (Section 4.3.2.2).

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis (Appendix C and Appendix D).

4.5.1.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the sponsor Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to the sponsor and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

Sponsor contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.3 Storage

Store investigational product at 2°C to 8°C (36°F to 46°F).

4.5.4 Treatment Compliance

Investigational product is administered by unblinded study site personnel, who will monitor compliance.

4.5.5 Accountability

The site's designated unblinded investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to AstraZeneca. All unused investigational product will be disposed of following site procedures and upon authorization by AstraZeneca, or will be returned to an AstraZeneca-authorized depot if a site is unable to dispose of unused investigational product.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers for the subject.

The first 72 subjects in the study will be randomized using a 3:3:3:1:2 ratio to receive CCI [redacted] MEDI3506 SC; or placebo CCI SC, or placebo CCI SC. The remaining subjects will be randomized using a 1:1 ratio to receive 600 mg MEDI3506 SC or placebo 4 mL SC. Randomization may be paused briefly to enable this change. The version of the Informed Consent Form (ICF) used will be dependent on the randomization ratio in operation at the time (Section 7.3).

The randomization will be stratified based on total IgE (< 150 kU/L or ≥ 150 kU/L) at screening.

The procedure for using the IXRS is, as follows:

- The investigator or designee contacts the IXRS and provides the SID number and the subject's baseline characteristic(s) used to verify that it is the same subject.

- The correct amount of kits of MEDI3506 and/or placebo will be assigned to the subject.
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log.
- Blinded study personnel will receive a notification containing a dose tracking number, that will not disclose how many kits are assigned to the subject.

Investigational product (MEDI3506 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the site monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This is a double-blinded study in which MEDI3506 and placebo are not identical in appearance or viscosity. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9; see Section 4.6.3.3 for unblinding related to planned analyses). Since MEDI3506 and placebo are not identical, investigational product will be handled by an unblinded investigational product manager at the site and will be administered by an unblinded study team member who will not be involved in the management of study subjects. An independent investigational product monitor will also be unblinded to perform investigational product accountability. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, AstraZeneca must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE (Section 4.6.3.1), the investigator must notify AstraZeneca *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product preparation and administration used to maintain the blind.

MEDI3506 could reduce eosinophil counts in blood over time. As a precaution, eosinophil, basophil, and monocyte data from the hematology laboratory tests (Section 4.3.3) will not be communicated to blinded sponsor or site personnel during the treatment and follow-up periods.

To facilitate the in-stream analysis of PK and ADA samples, the randomization schedule may be provided to limited personnel who have responsibility for analysing the samples. These unblinded sample analysts will not have any other involvement with the conduct of the study.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received MEDI3506. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this were the case, the investigational product allocation should not be unblinded. In the event there is unblinding, the investigator should promptly document and explain to AstraZeneca the reason for any premature unblinding.

AstraZeneca retains the right to unblind the treatment allocation for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.6.3.2 Unblinding for DSMB Purposes

If unblinding is required by the DSMB (Section 3.1.3), details of the methods for unblinding (sponsor will remain blinded) will be provided in a separate DSMB charter.

4.6.3.3 Unblinding for Primary Analysis Purposes

The primary analysis (Section 4.8.7) will be performed after all subjects have completed Visit 10 (Week 16) or have withdrawn from the study. The sponsor staff will be unblinded following database lock for the primary analysis. Investigators and site staff will not be made aware of unblinded treatment assignments for individual subjects who are in the follow-up period until these subjects have completed the study.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for prohibited medications and therapies (Section 4.7.3). Specifically, subjects should receive full supportive care during the study, including treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.7.2 Moisturizer Use

Subjects will be required to apply stable doses of moisturizers twice daily for at least 7 days before randomization at Visit 3 (Day 1) with a minimum of 85% compliance, through to the end of the follow-up period at Visit 12 (Week 24; Table 6, Table 7, and Table 8). Moisturizers should not be applied to the area of non-lesional skin designated for SCORAD assessments for ≥ 8 hours before visits when SCORAD will be assessed (Section 4.3.1.3). Use of certain moisturizers is not permitted (Section 4.7.3)

4.7.3 Prohibited Concomitant Medications and Therapies

Subjects are not permitted to receive any of the following (for the time periods stated):

- Systemic (oral or injectable) corticosteroids within 4 weeks of Visit 1 until the end of the follow-up period.
- TCSs and TCIs, and any other topical anti-inflammatory treatment for AD (eg, crisaborole) throughout the treatment and follow-up periods, except if medically necessary (Section 4.7.4).
- Any other immunosuppressive therapy within 3 months of randomization until the end of the follow-up period.
- Any immunotherapy within 3 months of randomization, except for stable maintenance dose allergen-specific immunotherapy started 4 weeks prior to Visit 1 until the end of follow-up period.
- Interferon gamma within 3 months of randomization until the end of the follow-up period.
- Investigational products other than MEDI3506 within 4 months or 5 half-lives, whichever is longer, of randomization until the end of the follow-up period.
- Marketed biologics including dupilumab within 4 months or 5 half-lives, whichever is longer, prior to randomization until the end of the follow-up period.
- Ig or blood products within 4 weeks of Visit 1 until the end of the follow-up period.
- Live or attenuated vaccines within 4 weeks of Visit 1 until the end of the follow-up period. (Note: Vaccines with adenoviral vectors that are unable to replicate, eg, ChAdOx1, are not considered live attenuated).
- Vaccination against COVID-19 (either first or subsequent dose) within 30 days before randomization or within 7 days before or after any dose of investigational product.
- Use of tanning beds or phototherapy including NBUVB, UVB, UVA1, or PUVA within 4 weeks prior to randomization until the end of the follow-up period.
- > 2 bleach baths per week within 4 weeks prior to randomization until the end of the follow-up period.
- Moisturizers containing additives including ceramide, hyaluronic acid, urea, or filaggrin degradation products from Visit 1 until the end of the follow-up period. Subjects may continue using stable doses of such moisturizers throughout the study if initiated at least 4 weeks prior to Visit 1.

Other than the permitted medications described in Section 4.7.1, use of concomitant medications or therapies from screening through to the early discontinuation visit/end of study is discouraged. Medications or therapies that are not prohibited and neither compromise subject safety nor affect study data, as judged by the investigator, will be permitted.

The activity of cytochrome P450 (CYP450) enzymes can be altered by increased levels of certain cytokines (eg, IL-1, IL-6, IL-10, tumor necrosis factor alpha, interferon) during chronic inflammation (Huang et al, 2010). Thus, MEDI3506, through its downstream mechanism of action, has the potential to normalize the formation of CYP450 enzymes indirectly, through the alteration of local and systemic cytokine levels. However, a role for IL-33 in the regulation of CYP450 enzymes has not been reported. As a precaution, upon initiation or discontinuation of MEDI3506, in patients who are receiving concomitant drugs that have a narrow therapeutic index and are CYP450 substrates (eg, warfarin), the investigator should consider whether (increased) monitoring is indicated.

4.7.4 Prohibited Concomitant Medications as Rescue Therapy

As this is a study of the effects of MEDI3506 in patients with AD not using TCS or TCI, inappropriate use of TCS, TCI or other prohibited concomitant medications as rescue therapy could undermine the validity/integrity of the trial. For example, use of rescue medication by a patient, before sufficient time has passed since first dose, to allow the opportunity for the investigational product to demonstrate beneficial effects on AD severity, may lead to those beneficial effects being undetected. Therefore, the following restrictions on the use of rescue therapy must be observed to ensure appropriate use.

If medically necessary for intolerable AD symptoms that occur throughout the study, rescue therapy with otherwise prohibited concomitant medications or therapies (Section 4.7.3) may be prescribed to subjects. In all other circumstances, rescue therapy should be restricted to subjects at or after Visit 7 (Day 29), who have:

- A worsening of EASI by ≥ 50% from baseline, or
- A clinically significant, disproportionate worsening of pruritus sustained for at least 7 days, that remains intolerable for the subject despite use of permitted medications (Section 4.7.1) and therapies for managing symptoms.

Rescue therapy should only be prescribed after assessment of the subject in the clinic, either at a scheduled or unscheduled visit. A justification for each subject who commences rescue therapy must be documented by the investigator in the clinical notes.

Rescue therapy should initially be restricted to topical therapies (ie, TCSs or TCIs, or any other topical anti-inflammatory treatment [eg, crisaborole]). TCSs should be prescribed at the lowest potency appropriate for the situation. TCIs should be reserved for problem areas only (eg, face, neck, or intertriginous and genital areas). Systemic rescue therapy should be

reserved for subjects who do not adequately respond to topical rescue therapy after ≥ 7 days of treatment.

Subjects who receive topical rescue therapy only may continue to receive investigational product provided no discontinuation criteria (Section 4.1.6) are met. Investigational product will be immediately discontinued in subjects who receive systemic rescue therapy, which is a prohibited medication (Section 4.7.3). All subjects should complete the schedule of study visits and assessments whether or not they continue treatment with investigational product, and whether or not they receive systemic rescue therapy. Investigators should make every attempt to conduct efficacy and safety assessments immediately before administration of any systemic rescue therapy. If it is not possible for the subject to complete the remaining visits, then the subject should complete the early discontinuation visit as outlined in the schedule of study procedures (Table 8).

4.7.5 COVID-19 Vaccination

If a subject receives a COVID-19 vaccination it should be recorded as a concomitant medication. Data regarding the date, dose, brand name, site of administration and lot number (if known) of each vaccine dose (eg, 10Feb2021; first dose; Pfizer-BioNTech COVID-19 Vaccine; left deltoid; Lot xxx) should be recorded in the patient's case notes.

Any AEs suspected to be due to the vaccination should be captured in the AE form including the causality assessment related to COVID-19 vaccine.

4.8 Statistical Evaluation

4.8.1 General Considerations

Unless specified otherwise, baseline is defined as the last assessment prior to dosing on Day 1 (Visit 3). The placebo CCI groups will be pooled for planned analyses, except where stated otherwise. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

The study populations that will be used in the reporting of the study include the intent-to-treat (ITT), As-treated, and PK populations (Table 11). The ITT population will be used to summarize demographic and baseline characteristics, concomitant medications, and efficacy endpoints. The As-treated population will be used to summarize safety endpoints (AEs, laboratory tests, ECGs, left ventricular ejection fraction, and vital signs), and will be used for other endpoints unless otherwise stated. The PK population will be used to summarize PK endpoints.

Table 11 Study Populations

Population	Description
ITT	Subjects who are randomized and receive any investigational product. Subjects will be analyzed according to their randomized treatment group.
As-treated	Subjects who are randomized and receive any investigational product. Subjects will be analyzed according to the treatment they actually receive.
PK	Subjects who receive at least 1 dose of MEDI3506 and have at least 1 detectable serum concentration measurement post first dose of treatment. Subjects will be analyzed according to the treatment they actually receive.

ITT = intent-to-treat; PK = pharmacokinetic(s).

Additional details of statistical analyses will be described in the Statistical Analysis Plan (SAP).

4.8.2 Sample Size

A sample size of 144 subjects in an overall 3:1:1:3 ratio of MEDI3506 CCI :MEDI3506 CCI :MEDI3506 CCI :pooled placebo, will provide at least 90% power to detect a statistically significant difference in the percent change from baseline to Week 16 in EASI score between the highest dose of MEDI3506 and pooled placebo in a responder subgroup, assuming a 35% point difference between placebo and MEDI3506 at the highest dose, based on a SD of 40% points, a two-sided 10% alpha level, and 50% of subjects in the responder subgroup. Based on identical assumptions, the sample size provides > 99% power to detect a statistically significant dose response in percent change from baseline to Week 16 in EASI score in all-comers.

The calculations for dose response assume that percent change from baseline to Week 16 in EASI score will increase monotonically with the administration of higher MEDI3506 doses. The power was calculated using a multiple comparison procedure with modelling techniques (MCP-Mod) (Bretz et al, 2005) with 4 candidate models for the dose response (linear, maximum effect attributable to the drug [E_{max}], and 2 Hill-E_{max} models). Randomization will be stratified by total IgE (< 150 kU/L or ≥ 150 kU/L) at screening.

To allow for the possibility that ≤ 5% of the subjects per treatment group may be ineligible for the ITT population, the total sample size will comprise approximately 152 subjects (58 for MEDI3506 CCI , 18 for MEDI3506 CCI , 18 for MEDI3506 CCI , and 58 for pooled placebo) randomized approximately to 3:1:1:3 ratio overall to the treatment groups.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

Percent Change in EASI Score

The primary efficacy endpoint is the percent change from baseline to Week 16 in EASI score.

To assess dose response at Week 16, percent change from baseline to Week 16 in EASI score will be analyzed using an MMRM including data from visits up to Week 16. The model will include treatment group, randomization stratum (total serum IgE < 150 kU/L or ≥ 150 kU/L), visit, and treatment group by visit interaction as categorical factors, with baseline EASI score as a covariate and the baseline*visit interaction term. Visit will be a repeated factor within a subject and an unstructured variance-covariance matrix will be used to describe the correlations between observations on a subject between visits. If the unstructured variance-covariance matrix will not fit, then suitable alternatives will be considered, with details provided in the SAP. The coefficient of the treatment effects at Week 16 obtained from the MMRM will then be incorporated into an MCP-Mod (Pinheiro et al, 2014), with 4 candidate models (linear, E_{max}, and 2 Hill-E_{max} models) to determine the dose response profile. As part of the MCP-Mod model, the testing of the 4 candidate dose response models will be adjusted for multiplicity using a family-wise error rate of 0.10. If more than 1 candidate model shows a statistically significant dose response, the final model will be selected based on the Akaike Information Criteria obtained from each model.

The estimand of primary interest is the difference in mean percent change from baseline to Week 16 in EASI score between MEDI3506 and placebo in the ITT population. Data that are collected after withdrawal from the study, or the use of rescue therapy will be treated as missing and excluded from the analysis. From the final model obtained from the MCP-Mod dose response analysis, the adjusted difference in mean percent change from baseline in EASI score between the placebo group and each MEDI3506 group at Week 16 will be estimated along with the 90% confidence interval (CI) and two-sided p-value. In addition, an estimate of the adjusted difference in mean percent change from baseline in EASI at each visit for each treatment group will be summarized together with a two-sided 90% CI, and p-value.

4.8.3.2 Additional Analyses of the Primary Endpoint Percent Change in EASI Score

A supplementary analysis using the ITT population will be done using all available data from subjects irrespective of whether or not they completed treatment, including data collected after subjects received rescue therapy. A MMRM followed by a MCP-Mod dose response model will be used for the analysis as described above for the analysis of the primary efficacy endpoint (Section 4.8.3.1).

A second supplementary analysis will be performed using the ITT population. Data from assessments performed after prohibited medications (eg, rescue therapies) are received will be excluded and a last observation carried forward approach will be applied for the missing data. An ANCOVA followed by a MCP-Mod dose response model including treatment group and randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L) as categorical factors and baseline EASI score as covariate, with 4 candidate models for the dose response (linear, E_{max}, and 2 Hill-E_{max} models) will be used for the analysis. The results will be presented in a

similar way as described above for the efficacy analysis for the primary endpoint (Section 4.8.3.1).

A third supplementary analysis for percent change in EASI score will be performed using a MMRM as described above (Section 4.8.3.1), including data from visits up to Week 24. The ITT population will be used for the analysis and data from visits after subjects receive rescue therapy will be excluded from the analysis. From the final model obtained from the fitted MMRM, the adjusted difference in mean percent change from baseline in EASI score between the placebo and each MEDI3506 group at Week 16 will be estimated along with the 90% CI and two-sided p-value.

4.8.3.3 Secondary Efficacy Analyses

IGA Response at Week 16

A key secondary efficacy endpoint is the percentage of subjects achieving an IGA response of 0 (clear) or 1 (almost clear) and at least a 2 grade reduction from baseline at Week 16.

IGA response at Week 16 will be analyzed for the ITT population using logistic regression including treatment group, randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L), and baseline IGA as categorical factors. The coefficient of the treatment effects at Week 16 obtained from the logistic regression will then be used in an MCP-Mod analysis with 4 candidate models for the dose response (linear, E_{max}, and 2 Hill-E_{max} models). As part of the MCP-Mod model, the testing of the 4 candidate dose response models will be adjusted for multiplicity using a family-wise error rate of 0.10. If more than 1 candidate model shows a statistically significant dose response, the final model will be selected based on the Akaike Information Criteria obtained from each model.

The composite estimand of primary interest is the difference in IGA response rate at Week 16 between MEDI3506 and placebo in the ITT population. Subjects who withdraw from the study or require rescue therapy will be considered as non-responders. From the final model obtained from the MCP-Mod dose response analysis, the difference in IGA response rate between the placebo and each MEDI3506 group will be estimated along with the 90% CI. For each MEDI3506 group versus placebo, the results will be presented as the difference in response rates, the 90% CI for the difference in response rates, and two-sided p-value.

Additional Analyses of the IGA Response at Week 16

A supplementary analysis using the ITT population will be done using all available data from subjects irrespective of whether or not they completed treatment, including data from subjects who received rescue therapy. Subjects who discontinue investigational product or withdraw from the study before Week 16 will be considered as non-responders.

A second supplementary analysis will be performed using the ITT population. Data from assessments performed after prohibited medications are received will be excluded and a last observation carried forward approach will be applied for missing data. The logistic regression and MCP-Mod dose response model used for the 2 supplementary analyses and the presentation of results will be similar as described above for the secondary efficacy analysis for IGA.

A third supplementary analysis will be performed using a generalized estimating equation model for repeated measures including treatment group, randomization stratum (total serum IgE < 150 kU/L or ≥ 150 kU/L), baseline IGA value, visit, and visit by treatment group interaction as covariates. The analysis will be conducted including data from visits up to Week 24. The model will use a logistic link function and an independence working correlation matrix. If the assumed working correlation matrix will not fit, then suitable alternatives will be considered, with details provided in the SAP. From the model obtained, estimates of the treatment effect at Week 16 together with the associated standard errors, 90% CIs, and p-values will be provided.

Percentage of Subjects Achieving EASI 50, EASI 75, and EASI 90 at Week 16

A subject is defined as achieving an EASI 50, EASI 75, or EASI 90 response if they have at least a 50%, 75%, or 90% reduction from baseline in EASI score, respectively.

EASI 50, EASI 75 and EASI 90 response at Week 16 will be analyzed using a logistic regression model including treatment group and randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L) as categorical factors, and baseline EASI score as a covariate for each endpoint. The composite estimand will be the difference between MEDI3506 and placebo in EASI 50, EASI 75, or EASI 90 response rate at Week 16 in the ITT population. Subjects who discontinue investigational product, withdraw from the study, or require rescue therapy will be considered as non-responders. For each MEDI3506 group compared with placebo, differences in response rates, 90% CIs for the differences in response rates (Ge et al, 2011), and two-sided p-values will be reported for each endpoint. If the number of responders is < 5 in any MEDI3506 group, the logistic regression model will not be used. Instead, the 90% CI and p-value for the difference in response rates will be calculated using an unconditional exact method (Chan and Zhang, 1999).

Additional Analyses of the EASI 75 response at Week 16

The percentage of subjects achieving an EASI 75 response at Week 16 will be analyzed for the ITT population using a logistic regression and MCP-Mod dose response model similar to that described above for IGA response at Week 16. Results obtained from the analysis will also be described in a similar way as described for the IGA response.

Change from Baseline to Week 16 in % BSA Affected by AD

Change from baseline to Week 16 in % BSA affected by AD, as assessed by EASI, will be analyzed for the ITT population using a mixed effects model for repeated measures, including data from visits up to Week 16. Data from visits after subjects receive rescue therapy will be excluded from the analysis. Details of the model are similar to those described above for the percent change from baseline to Week 16 in EASI score (Section 4.8.3.1).

Percent Change from Baseline to Week 16 in SCORAD

Percent change from baseline to Week 16 in SCORAD will be analyzed for the ITT population using a MMRM, including data from visits up to Week 16. Data from visits after subjects receive rescue therapy will be excluded from the analysis. Details of the model are similar to those described for percent of change from baseline to Week 16 in EASI score (Section 4.8.3.1).

Analysis of Peak Pruritus NRS at Week 16

Daily peak pruritus NRS assessments will be summarized as weekly means. The weekly mean score will be set to missing if > 3 assessments are missed in that 7-day period.

The percentage of subjects achieving a ≥ 3 point reduction from baseline to Week 16 in weekly mean of daily peak pruritus NRS will be analyzed using a logistic regression model including treatment group and randomization stratum (total serum IgE < 150 kU/L or ≥ 150 kU/L), and baseline weekly mean of daily peak pruritus score as a covariate. Other details of the model are similar to those described above for the analyses of the secondary efficacy endpoint of EASI 50.

Furthermore, change from baseline to Week 16 in the weekly mean of daily peak pruritus NRS will be analyzed using a MMRM. Data from visits after subjects receive rescue therapy will be excluded from the analysis. Details of the model are similar to those described for percent change from baseline to Week 16 in EASI score (Section 4.8.3.1).

Analysis of Skin Pain NRS at Week 16

Daily peak skin pain NRS assessments will be summarized as weekly means. The weekly mean score will be set to missing if > 3 assessments are missed in that 7-day period.

Change from baseline to Week 16 in weekly mean peak skin pain NRS will be analyzed using a MMRM. Data from visits after subjects receive rescue therapy will be excluded from the analysis. Details of the model are similar to those described for percent change from baseline to Week 16 in EASI score (Section 4.8.3.1).

Analysis of 5-D Itch, POEM, and DLQI at Week 16

Change from baseline to Week 16 in 5-D itch, POEM, and DLQI will be summarized descriptively, and analyzed using a mixed effects model for repeated measures. Data from visits after subjects receive rescue therapy will be excluded from the analysis. Details of the model are similar to those described for percent change from baseline to Week 16 in EASI score (Section 4.8.3.1).

Analysis of PGI-S at Week 16

The PGI-S is on a 3-point categorical response scale (mild, moderate, or severe). PGI-S will be summarized with descriptive statistics including number of subjects, mean, SD, median, minimum, and maximum at each visit. In addition, the number and percentage of subjects in each category will be summarized by visit.

4.8.3.4 Exploratory Analyses

The number and percentage of subjects achieving EASI 50 by Weeks 2, 4, 8, 12, 20, and 24 will be summarized by visit. Similar summary statistics will be provided for the percentage of subjects achieving EASI 75 and EASI 90. Furthermore, analyses using a generalized estimating equation model for repeated measures will be performed separately for each endpoint. Details of the model are similar to those described for the additional analysis of the IGA response at Week 16 (Section 4.8.3.3).

Percent change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in EASI score will be summarized descriptively by visit, and analyzed using a MMRM including data from visits up to Week 24 as described for the primary efficacy endpoint of percent change from baseline to Week 16 in EASI score (Section 4.8.3.1).

The number and percentage of subjects achieving an IGA response at Weeks 2, 4, 8, 12, 20, and 24 will be summarized by visit, and analyzed using the generalized estimating equation model as described for IGA response at Week 16 (Section 4.8.3.3).

For peak pruritus NRS, the number and percentage of subjects achieving reduction of ≥ 3 from baseline to Weeks 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak pruritus NRS will be summarized by visit and analyzed using the generalized estimating equation model as described above for IGA response. The number and percentage of subjects achieving reduction of ≥ 4 from baseline to Weeks 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak pruritus NRS will be summarized and analyzed similarly.

Change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in the weekly mean of daily peak pruritus NRS and change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in weekly mean of daily peak skin pain NRS will be summarized by visit and analyzed using a MMRM as described for the primary efficacy endpoint (Section 4.8.3.1).

Percent change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in SCORAD will be summarized descriptively by visit, and analyzed using a mixed effects model for repeated measures as described for the primary efficacy endpoint (Section 4.8.3.1).

PGI-S at Weeks 2, 4, 8, 12, 20, and 24 will be summarized by visit with descriptive statistics including number of subjects, mean, SD, median, minimum, and maximum. In addition, the number and percentage of subjects in each category will also be summarized by visit.

Change from baseline to Weeks 2, 4, 8, 12, 20, and 24 in percent BSA affected by AD, 5-D itch, POEM, and DLQI will be summarized descriptively by visit, and analyzed using a MMRM as described for the primary efficacy endpoint (Section 4.8.3.1).

The number and percentage of subjects requiring rescue therapy during the treatment and follow-up periods will be summarized by visit. Summary descriptive statistics (including number, mean, median, SD, minimum, and maximum) will be provided for time to first use of rescue therapy either during the treatment or follow-up period. Additional analyses that may be conducted for these endpoints will be described in the SAP.

Change from baseline to Week 16, and to Week 24, in SNOT-22 and ACQ-6 will be summarized using descriptive statistics including number of subjects, mean, median, SD, minimum, and maximum.

Additional details of the exploratory endpoint analyses will be described in the SAP.

4.8.3.5 Subgroup Analyses

Subgroup analyses may be performed, and will be described in the SAP as required.

4.8.4 Safety

4.8.4.1 Analysis of AEs

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. TEAEs will be summarized overall and by MedDRA SOC and PT, by severity, and relationship to investigational product. In addition, summaries of deaths, SAEs, and treatment discontinuations due to AEs will be provided.

4.8.4.2 Safety Laboratory Analysis

Laboratory parameters will be assessed at baseline and throughout the study (Table 6, Table 7, and Table 8). Frequencies of abnormal laboratory measurements will be presented for each

laboratory parameter. Also, laboratory parameters will be assessed by presenting tables containing information related to laboratory shifts from baseline relative to the normal range, as well as descriptively over time.

4.8.4.3 Analysis of Vital Signs, ECGs, and Echocardiograms

Vital signs, ECG parameters and left ventricular ejection fraction as measured by echocardiogram will be summarized descriptively.

4.8.4.4 Subgroup Analyses

Subgroup analyses may be performed, and will be described in the SAP as required.

4.8.5 Analysis of Immunogenicity and PK

The incidence rate of positive antibodies to MEDI3506 and ADA titer will be reported by treatment group. Depending on the incidence of ADA, further analysis of ADA effects may include the assessment of the relationship between ADA titer and:

- MEDI3506 exposure.
- Biomarker endpoints.
- Occurrence of AEs.

MEDI3506 serum concentrations will be tabulated and analyzed using descriptive statistics. Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported in the CSR.

4.8.6 Analysis of Biomarkers

Change from baseline to Week 16 in the concentrations of sST2 will be summarized descriptively by visit and analyzed using an ANCOVA model. The model will include treatment group and randomization stratum (total serum IgE < 150 kU/L or ≥ 150 kU/L) as categorical factors, with baseline sST2 as a covariate.

Change from baseline to Weeks 1, 2, 4, 8, 12, 16, 20, and 24 in eosinophils and change from baseline to Weeks 1, 2, 4, 16, 20, and 24 in IL-33 bound to MEDI3506 will be summarized descriptively by visit and treatment group. Change from baseline to Weeks 2, 8, 16, and 24 in IgE biomarker levels and change from baseline to Weeks 4, 16, and 24 in eosinophil derived neurotoxin levels will also be summarized by visit. In addition, descriptive plots will be provided to assess the association between primary efficacy endpoints and the changes in biomarker levels at each visit. Change from baseline to Week 16 in colonization of bacteria in lesional and non-lesional skin will be summarized using descriptive statistics. Additional analyses that may be conducted for these endpoints will be described in the SAP.

Analyses of biomarker endpoints will be further described in the SAP.

4.8.7 Primary and Final Analyses

No formal interim analyses are planned for this study.

The primary analysis will occur once all subjects have either completed the Visit 10 (Week 16) assessments or have withdrawn from the study and will include all available data. Details on unblinding for primary analysis purposes are described (Section 4.6.3.3).

The final analysis will occur when all subjects have completed the follow-up period at Visit 12 (Week 24) or have withdrawn from the study.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that fulfils 1 or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect in offspring of the subject.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse.

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the "important medical event" criterion (Appendix B) should be used. However, in certain situations medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to AstraZeneca. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

The following AESIs will be particularly monitored in this study (see the Safety Handling Plan for instructions and timing on completing any additional information required for specific types of events related to the categories noted below):

- Hepatic function abnormality meeting the definition of Hy's Law (HL) as described in Section 5.4.12.
- Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions), for example anaphylaxis and severe allergic reactions, and immune complex disease.
- Injection site reactions.
- Cardiac events (including angina or myocardial infarction, congestive heart failure, symptomatic atherosclerotic vascular disease, cor pulmonale, or arrhythmia).
- Serious infections (including opportunistic infections and viral reactivations), for example VZ/HSV, EBV/CMV, and TB.
- Gastrointestinal adverse events.
- Malignancy.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca (see Section 5.5). See Section 5.2 for the definition of SAEs and Appendix B for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious" it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from time of signature of informed consent at Visit 1, throughout the treatment period and including the follow-up period through Visit 12 (Week 24) or date of last contact.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- The AE causing the death must be reported as an SAE within 24 hours. The report should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca representative(s) within the usual timeframes (refer to Section 5.5 for additional information).

5.4.4 Recording of Serious Hypersensitivity (Including Type 1 to 4 Hypersensitivity Reactions)

For AESIs of serious hypersensitivity, narrative information will be recorded including the rationale for considering the event to be, or not to be, anaphylaxis (Appendix C).

5.4.5 Recording of Injection Site Reactions

For AESIs of injection site reactions, the sign or symptom, and diameter of area will be recorded.

5.4.6 Recording of Cardiac Events (Including Angina or Myocardial Infarction, Congestive Heart Failure, Symptomatic Atherosclerotic Vascular Disease, or Pulmonale or Arrhythmia)

For subjects with AESIs of cardiac events suggestive of new onset and/or progression of heart failure, left ventricular ejection fraction measured by echocardiogram and NT-proBNP will be recorded.

5.4.7 Recording of Serious Infections (Including Opportunistic Infections and Viral Reactivations

No additional information will be recorded beyond standard.

5.4.8 Recording of Gastrointestinal Adverse Events

No additional information will be recorded beyond standard.

5.4.9 Recording of Malignancy

No additional information will be recorded beyond standard.

5.4.10 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *"Have you had any health problems since the previous visit/you were last asked?"*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.4.11 Adverse Events Based on Examination and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. An abnormal laboratory finding (including echocardiogram or ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant, should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

5.4.12 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

5.5 Reporting of Serious Adverse Events

Prompt notification (within 24 hours) by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or and will notify the IRB/IEC, if appropriate according to local requirements.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is Section 5.6 Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions in the IB.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca investigational product occurs during the course of the study, then the investigator or other site personnel should inform appropriate sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

5.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor except if the pregnancy is discovered before the subject has received any investigational product.

5.6.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 calendar day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated study representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.2.2 Paternal Exposure

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until the end of the follow-up period (Visit 12 [Week 24]) or date of last contact should, if possible, be followed up and documented.

5.6.3 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca investigational product that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the investigational product, but rather a human- or process-related failure while the investigational product is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred.
- Was identified and intercepted before the subject received the investigational product.
- Did not occur, but circumstances were recognized that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion (ie, instead of receiving the investigational product, the subject received a medication that has a similar-sounding name).
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject.

- Investigational product not administered as indicated, for example, wrong route or wrong site of administration.
- Investigational product not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet.
- Investigational product not stored as instructed, eg, kept in the refrigerator when it should be at room temperature.
- Wrong subject received the investigational product (excluding IXRS errors).
- Wrong investigational product administered to subject (excluding IXRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IXRS- including those which lead to 1 of the above listed events that would otherwise have been a medication error.
- Subject accidentally missed investigational product dose(s), eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Subject failed to return unused investigational product or empty packaging.
- Errors related to background and rescue therapy, or standard of care medication in open label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.5) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

Investigational product accountability (Section 4.6.2) and any other unblinded monitoring activities will be conducted by an additional unblinded monitor.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The principal investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.5 and 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit (including telephone contact) for the last subject in the study (ie, LSLV).

6.4 Data Management

Data management will be performed by AstraZeneca Data Management staff or other party according to the Data Management Plan.

An EDC system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third-party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for each site must review and approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to AstraZeneca before enrollment of any subject into the study.

AstraZeneca should approve any substantive modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, AstraZeneca will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. AstraZeneca will provide safety updates/reports according to local requirements, including SUSARs where relevant, to regulatory authorities, IRB/IEC, and principal investigators.

Each principal investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. AstraZeneca will provide this information to the principal investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. AstraZeneca will develop a core ICF for use by all investigators in the clinical study. AstraZeneca must approve any modifications to the ICF that are needed to meet local requirements.

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each subject is notified that they are free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file.
- Ensure a copy of the signed ICF is given to the subject.
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC.
- Ensure that the ICF version used is appropriate for the randomization ratio in operation at the time. Subjects who have provided informed consent but are still in screening (ie, have not been randomized) when the randomization ratios change (Section 4.6.1) should be reconsented to the appropriate ICF version.

7.4 Changes to the Protocol and ICF

Study procedures will not be changed without the mutual agreement of the coordinating investigator and AstraZeneca. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, AstraZeneca will distribute amended versions of the protocol to the principal investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the ICF, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of

an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

9.1 Protocol Amendment 9

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 9. The principal reason for this amendment is to remove endpoints that are not being reported in the CSR or separately.

All changes to the protocol are considered to be non-substantial (Table 12) and are summarized below:

Table 12 Summary of Non-substantial Revisions in Protocol Amendment 9

Section of the Protocol Affected	Reason for Amendment
Title page	Change in Medical Monitor
Synopsis, 2.2 (Secondary Objectives and Associated Endpoints), 2.3 (Exploratory Objectives and Associated Endpoints), 4.8.3.3 (Secondary Efficacy Analyses), 4.8.3.4 (Exploratory Analyses)	The endpoint of assessing percent change from baseline to Week 8 in EASI score is moved from secondary to exploratory, as a consequence of removal of the interim analysis detailed in Protocol Amendment 7.
Synopsis, 2.2 (Secondary Objectives and Associated Endpoints)	Removal of the secondary endpoint assessing whether sinus rhythm had been recorded (yes/no) as this was not collected; other information collected from ECG, including heart rate, QT and overall evaluation, are sufficient to assess safety from ECG point of view
Synopsis, 2.3 (Exploratory Objectives and Associated Endpoints), 3.2.3.3 (Exploratory Endpoints), 4.3.7.5 (*S. aureus* Colonization), Table 7 (Schedule of Treatment Period Study Procedures), Table 8 (Schedule of Follow-up Procedures)	Removal of the exploratory assessment of *P. acnes* from skin swabs as it is no longer expected to be informative in the evaluation of MEDI3506. Note, assessment of *S. aureus* from skin swabs is retained.
Synopsis, 4.1.1 (Number of Subjects), 4.8.2 (Sample Size)	Updated to "approximately 152 subjects" to align with SAP.
Synopsis, 4.8.3.1 (Primary Efficacy Analysis)	Added "and the baseline*visit interaction term" to the primary efficacy analysis information to correct an omission.
4.8.3.1 (Primary Efficacy Analysis); 8 (References)	Updated the citation for Bretz et al 2005 to Pinheiro et al 2014 as this was a more appropriate reference, describing the method used.
Synopsis, 4.8.3.3 (Secondary Efficacy Analyses)	IGA response at Week 16 text corrected.
CCI [redacted]	[redacted]
4.3.3 (Clinical Laboratory Tests)	Amended the bullet in 'other safety tests' referring to hepatitis B and C antibodies to aid clarity.

Table 12 Summary of Non-substantial Revisions in Protocol Amendment 9

Section of the Protocol Affected	Reason for Amendment
4.3.5 (Immunogenicity Evaluation and Methods)	Updated the duration of storage for ADA samples from 2 years after marketing approval to 15 years following the issue of CSR, to be consistent with standard AstraZeneca processes and to allow easier tracking of sample lifecycle.
4.3.6 (Genetic Evaluation and Methods)	Text added to differentiate between the genetic samples collected during the study.
4.8.3.2 (Additional Analyses of the Primary Endpoint)	Use of ANCOVA added for the second supplementary analysis to be consistent with other MCP-Mod analyses.
4.8.6 (Analysis of Biomarkers)	Correction of statistical method used to analyse sST2 data from a mixed effects model for repeated measures to an ANCOVA model; the model was changed to ANCOVA due to the removal of some timepoints.
4.8.6 (Analysis of Biomarkers)	Removal of reference to how CCI , PBMC, IL-5, IL-13, CCL17, proinflammatory gene signatures, and gross inflammation data will be summarised as these data will be explored and reported separately to the CSR.
5.6.2.1 (Maternal Exposure), 5.6.2.2 (Paternal Exposure)	Congenital abnormality changed to congenital anomaly to meet regulatory requirements on good pharmacovigilance practices.

9.2 Protocol Amendment 8

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 8. The principal reason for this amendment is to update guidance on permitted vaccines in response to recent emergency use authorizations or approvals of vaccines against COVID-19.

All changes to the protocol are considered to be non-substantial (Table 13) and are summarized below.

Table 13 Summary of Non-substantial Revisions in Protocol Amendment 8

Section of the Protocol Affected	Reason for Amendment
Synopsis, 3.1.1 (Overview), Table 6 (Schedule of Screening and TCS/TCI Wash Out Procedures)	To extend the maximum duration of the screening period in response to investigator feedback that obtaining echocardiograms in the previously allowed period was challenging in the COVID-19 environment.

Table 13 Summary of Non-substantial Revisions in Protocol Amendment 8

Section of the Protocol Affected	Reason for Amendment
1.6.1.1 (Vaccination Against COVID-19)	New section added to inform investigators of the sponsor's approach to COVID-19 vaccination in Study D9181C00001, to provide clarification to investigators and to help ensure interpretability of safety data.
4.1.2 (Inclusion Criteria)	To lower the EASI threshold score at Screening Visit 1 so that subjects that worsen during the TCS/TCI wash out period could become eligible at Visit 3 prior to randomization, in order to improve recruitment.
4.1.3 (Exclusion Criteria) 4.7.3 (Prohibited Concomitant Medications and Therapies)	To clarify adenoviral vector vaccines are not considered live attenuated and to add certain restrictions on when vaccines against COVID-19 may be administered.
4.3.2.1 (Medical and Dermatology History) 4.7.5 COVID-19 Vaccination	To clarify the need for recording of history of COVID-19 and receipt of COVID-19 vaccination.
Synopsis, 3.1.1 (Overview), 4.1.2 (Inclusion Criteria), Table 6 (Schedule of Screening and TCS/TCI Wash Out Procedures), 4.7.2 (Moisturizer Use)	To alter required moisturizer use requirements prior to randomization to better approximate real-world use.
4.1.3 (Exclusion Criteria), Table 6 (Schedule of Screening and TCS/TCI Wash Out Procedures), 4.3.3 (Clinical Laboratory Tests)	To permit retesting of subjects with a positive IGRA test result, following investigator feedback. A negative IGRA test result is still required for eligibility.
4.1.3 (Exclusion Criteria)	To permit retesting of subjects with a NT-proBNP result greater than the upper limit of the laboratory reference range if this is clinically unexpected. An acceptable NT-proBNP result is still required.
Table 6 (Schedule of Screening and TCS/TCI Wash Out Procedures)	To allow for investigators to slightly delay randomization to maximize subject eligibility.
Table 6 (Schedule of Screening and TCS/TCI Wash Out Procedures), Table 7 (Schedule of Treatment Period Study Procedures), Table 8 (Schedule of Follow-up Procedures)	Clarification that all female subjects should have a pregnancy test.
4.6.2 (Methods to Ensure Blinding)	To facilitate in-stream analysis of PK and ADA samples.

ADA = anti-drug antibody(ies); COVID-19 = coronavirus disease 2019; EASI = Eczema Area and Severity Index; IGRA = interferon gamma release assay; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PK = pharmacokinetic(s); TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

9.3 Protocol Amendment 7

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 7. The principal reason for this amendment is to remove the interim analysis and add an additional PK sampling timepoint.

Changes to the protocol considered to be substantial (Table 14) and non-substantial (Table 15) are summarized below.

Table 14 Summary of Substantial Revisions in Protocol Amendment 7

Section of the Protocol Affected	Reason for Amendment
Synopsis, Table 7 (Schedule of Treatment Period Study Procedures) and Section 3.1.1 (Overview)	An additional PK sampling timepoint has been added for the 73rd and subsequent randomized subjects. This is to better characterize the pharmacokinetics (absorption phase) of MEDI3506 with the current formulation. The additional timepoint requires an additional visit to site early after the first dose, this (in addition to the clinical experience gained by that point) leaves the telephone call with the subject on Day 2 unnecessary and so it has been removed for applicable subjects.

Table 15 Summary of Non-Substantial Revisions in Protocol Amendment 7

Section of the Protocol Affected	Reason for Amendment
Section 4.1.3 (Exclusion Criteria)	Correction of typographical error leading to subjects who test positive for HIV but have not been treated, not being explicitly excluded.
Synopsis, Section 3.1.1 (Overview and Figure 1 [Study Flow Diagram]), Section 4.6.3.3 (Unblinding for Interim Analysis Purposes, entirely removed), Section 4.6.3.4 (Unblinding for Primary Analysis Purposes, this is now Section 4.6.3.3), Section 4.8.2 (Sample Size), and Section 4.8.7 (Interim, Primary, and Final Analyses, renamed)	The interim analysis was intended and expected to usefully serve internal administrative purposes. However, it is no longer expected to do so. Hence, the interim analysis and all references to it have been removed.
Table 7 (Schedule of Treatment Period Study Procedures)	Correction of an omission of a footnote from certain procedures.
Section 1.4 (Summary of Clinical Experience), Section 1.5 (Rationale for Conducting Study), and Section 1.6 (Risk-Benefit and Ethical Assessment)	Text updated in line with the fact that the Phase 1 study of MEDI3506 (Study D9180C00001) is now fully complete. However, no new or additional safety data have been added.

9.4 Protocol Amendment 6

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 6. The principal reason for this amendment is to allow for the collection of adhesive skin tape patches for exploratory purposes.

All changes to the protocol are considered to be non-substantial (Table 16) and are summarized below.

Table 16 Summary of Non-Substantial Revisions in Protocol Amendment 6

Section of the Protocol Affected	Reason for Amendment
Synopsis, Table 3 (Exploratory Objectives and Endpoints), Table 7 (Schedule of Treatment Period Study Procedures), Section 3.2.3.3 (Exploratory Endpoints) and Section 4.3.7.7 (Adhesive Skin Tape Patches)	Addition of one new exploratory biomarker at two timepoints as it may help identify a responder population based on skin transcriptomics.
Section 4.3.1.9 (Patient Global Impression of Severity)	In error a different wording of the question and responses was deployed in the study to the one stated in the original protocol. This error was discovered during the clinical conduct of the study. To ensure all responses are comparable and hence maintain the integrity of the study the protocol has been updated.

9.5 Protocol Amendment 5

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. The principal reason for this amendment is to provide a harmonised global protocol by incorporating changes from local amendments for Germany and the UK (feedback from the Paul Ehrlich Institute and the UK Medicines and Healthcare products Regulatory Agency, respectively). Changes are summarized by country/region.

Changes from Global Protocol Amendment 4

Changes include those detailed in Table 17 and Table 18.

Table 17 Summary of Substantial Revisions in Protocol Amendment 5

Section of the Protocol Affected	Reason for Amendment
1.6.1 (COVID-19), Section 4.1.2 (Inclusion Criteria) and Section 4.1.3 (Exclusion Criteria)	Addition of safety mitigations related to COVID-19 and description of benefit-risk balance.

COVID-19 = coronavirus disease 2019.

Table 18 Summary of Non-Substantial Revisions in Protocol Amendment 5

Section of the Protocol Affected	Reason for Amendment
Synopsis and 4.8.7 (Interim, Primary and Final Analyses)	Added clarification regarding the purpose of the interim analysis and study continuation after the analysis.
3.2.1 (Rationale for Dose and Dose Regimen)	Added further information on pharmacokinetic predictions.
4.1.3 (Exclusion Criteria)	Clarified that hereditary fructose intolerance is exclusionary, to address concerns from the PEI. Reduction in exclusionary threshold for total bilirubin.

Table 18 Summary of Non-Substantial Revisions in Protocol Amendment 5

Section of the Protocol Affected	Reason for Amendment
4.1.6 (Discontinuation of Investigational Product)	Clarified that incorrect randomization or use of prohibited medications should lead to discontinuation of investigational product except in defined circumstances, to address concerns from the PEI.
4.6.3.3 (Unblinding for Interim Analysis Purposes)	Clarified restrictions and requirements necessary to ensure the integrity of the trial to address concerns from the PEI and MHRA.
4.7.3 (Prohibited Concomitant Medications and Therapies)	Addition of possibility of indirect drug-drug interaction and related mitigation.
4.7.4 (Prohibited Concomitant Medications as Rescue Therapy)	• Added justification for restrictions on use of rescue therapy. • Revised wording regarding use of rescue therapy before Visit 7 (Day 29), to address concerns from the PEI.
4.8.2 (Sample Size)	Added justification for sample size and timepoint of interim analysis.
5.5 (Reporting of Serious Adverse Events)	Clarified the required timelines.
4.8.7 (Interim, Primary, and Final Analyses)	Clarified that the study will be continued and completed regardless of interim analysis results.

MHRA = Medicines and Healthcare products Regulatory Agency; PEI = Paul Erlich Institute.

Changes from UK Local Protocol Amendment 3

Changes include those detailed in Table 19 and Table 22.

Table 19 Summary of Non-Substantial Revisions in Protocol Amendment 5

Section of the Protocol Affected	Reason for Amendment
Synopsis and 4.8.7 (Interim, Primary and Final Analyses)	Added clarification regarding the purpose of the interim analysis and study continuation after the analysis.
3.2.1 (Rationale for Dose and Dose Regimen)	Added further information on pharmacokinetic predictions.
4.1.3 (Exclusion Criteria)	Clarified that hereditary fructose intolerance is exclusionary, to address concerns from the PEI.
4.1.6 (Discontinuation of Investigational Product)	Clarified that incorrect randomization or use of prohibited medications should lead to discontinuation of investigational product except in defined circumstances, to address concerns from the PEI.
4.7.4 (Prohibited Concomitant Medications as Rescue Therapy)	• Added justification for restrictions on use of rescue therapy. • Revised wording regarding use of rescue therapy before Visit 7 (Day 29), to address concerns from the PEI.

Section of the Protocol Affected	Reason for Amendment
4.8.2 (Sample Size)	Added justification for sample size and timepoint of interim analysis.
4.8.7 (Interim, Primary, and Final Analyses)	Clarified that the study will be continued and completed regardless of interim analysis results.

PEI = Paul Erlich Institute

Changes from Germany Local Protocol Amendment 2

Changes include those detailed in Table 20, Table 21, Table 22, Table 23 and Table 24.

Table 20 Summary of Substantial Revisions in Protocol Amendment 5

Section of the Protocol Affected	Reason for Amendment
1.6.1 (COVID-19), Section 4.1.2 (Inclusion Criteria) and Section 4.1.3 (Exclusion Criteria)	Addition of safety mitigations related to COVID-19 and description of benefit-risk balance.

COVID-19 = coronavirus disease 2019.

Table 21 Summary of Non-Substantial Revisions in Protocol Amendment 5

Section of the Protocol Affected	Reason for Amendment
4.1.3 (Exclusion Criteria)	Reduction in exclusionary threshold for total bilirubin.
4.7.3 (Prohibited Concomitant Medications and Therapies)	Addition of possibility of indirect drug-drug interaction and related mitigation.
5.5 (Reporting of Serious Adverse Events)	Clarified the required timelines.

9.6 Protocol Amendment 4

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The principal reason for this amendment is to allow for countries where spermicide is not available and to correct a miscalculation in the number of subjects in each treatment group.

All changes to the protocol are considered to be non-substantial (Table 22) and are summarized below.

Table 22 Summary of Non-Substantial Revisions in Protocol Amendment 4

Section of the Protocol Affected	Reason for Amendment
Protocol synopsis, Section 3.1.2 (Treatment Regimen), Section 4.1.1 (Number of Subjects), Section 4.8.2 (Sample Size)	Correction of a miscalculation in subject numbers for each treatment group, given the change in randomization ratio during the study introduced in Protocol Amendment 3. For each dose level of MEDI3506 and for the placebo groups combined the change is only 1 subject. The total sample size remains unchanged.
Protocol synopsis, Table 3 (Exploratory Objectives and Endpoints), Table 6 (Schedule of Treatment Period Study Procedures), Table 7 (Schedule of Follow-up Procedures), Section 4.3.7.6 (Peripheral Blood Mononuclear Cells) and Section 4.8.6 (Analysis of Biomarkers)	• Removal of certain timepoints from certain exploratory biomarkers (in schedule of assessments, endpoints and analysis) as no longer considered useful and to lower patient burden. • Addition of one new exploratory biomarker at two timepoints as it may help identify a responder population based on investigation of immune cell subset ratios in treated subjects.
Section 4.1.2 (Inclusion Criteria)	Amended to allow for participating countries where spermicide is not available. This change has no impact in countries where it is available.
Section 4.1.3 (Exclusion Criteria) and Section 4.7.3 (Prohibited Concomitant Medications and Therapies)	Clarified that for all prohibited medications where the minimum washout period is a specified number of months or a specified number of half-lives, the minimum washout is whichever is longer.
Section 4.3.7.1 (Blood Biomarkers)	Clarification added regarding plasma sample collection.
Section 4.3.7.3 (Skin Punch Biopsies)	Reduced the size of skin punch biopsy needle to align with other protocols using skin punch biopsies.
Section 4.3.7.6 (Peripheral blood mononuclear cells)	New subsection added to describe collection of peripheral blood mononuclear cells

9.7 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The principal reasons for this amendment are to introduce updates based on a preliminary report of a Phase 2b clinical study of etokimab that was not previously available, and to introduce changes suggested in the "Study May Proceed Letter" from the Food and Drug Administration (FDA).

Changes to the protocol considered to be substantial (Table 23) and non-substantial (Table 24) are summarized below.

Table 23 Summary of Substantial Revisions in Protocol Amendment 3

Section of the Protocol Affected	Reason for Amendment
[redacted]	CCI [redacted]
Protocol Synopsis (Study Design, Treatment Groups and Regimens, and Statistical Methods), Section 3.1.1 (Overview and Figure 1 Study Flow Diagram), Section 3.1.2 (Treatment Regimen), Section 4.1.1 (Number of Subjects), Section 4.6.1 (Methods for Assigning Treatment Groups), Section 4.6.3.3 (Unblinding for Interim Analysis Purposes), Section 4.8.2 (Sample Size), Section 7.3 (Informed Consent), and Section 8 (References)	To introduce updates based on a preliminary report of a Phase 2b clinical study of etokimab that was not previously available: • Increased the total number of subjects in the study. • Modified the randomization ratios. • Increased the number of study sites. • Modified the number of subjects in each treatment group. • Revised the description of the statistical analyses.
Section 1.2 (MEDI3506 Background) and Section 1.5 (Rationale for Conducting the Study)	Added text describing the preliminary report of a Phase 2b clinical study of etokimab that was not previously available to justify the substantial revisions made in Protocol Amendment 3.

AD = atopic dermatitis; IL = interleukin.

Table 24 Summary of Non-substantial Revisions in Protocol Amendment 3

Section of the Protocol Affected	Reason for Amendment
Protocol Synopsis (Objectives and Endpoints), Section 2.3 (Table 3 Exploratory Objectives and Endpoints), Section 4.2.2 (Table 6 Schedule of Treatment Period Study Procedures), Section 4.2.3 (Table 7 Schedule of Follow-up Procedures), Section 4.3.9 (Estimate of Volume of Blood to Be Collected), and Section 4.8.6 (Analysis of Biomarkers)	Upon further consideration after authoring the original protocol: • Added exploratory plasma EDN endpoint to introduce an assessment for measuring activated eosinophils. • Revised proinflammatory gene signatures in whole blood exploratory endpoint to clarify the text.
Protocol Synopsis (Statistical Methods), Section 4.8.3.1 (Primary Efficacy Analysis), and Section 4.8.3.3 (Secondary Efficacy Analyses)	Upon further consideration after authoring the original protocol, minor revisions were introduced to clarify the text.
Section 4.1.2 (Inclusion criteria)	Revised inclusion criterion 5b to remove corticosteroids "(b) A documented history, within the 6 months prior to screening Visit 1, of requiring intermittent or continuous systemic therapy,"
Section 4.1.3 (Exclusion Criteria)	Added an exclusion criterion (Criterion 9) that is a German legal requirement that was inadvertently not included in the original protocol.

Table 24 Summary of Non-substantial Revisions in Protocol Amendment 3

Section of the Protocol Affected	Reason for Amendment
Section 4.1.6 (Discontinuation of Investigational Product)	Revised criteria to introduce changes suggested in the "Study may proceed" letter from the FDA.
Section 4.2.3 (Table 7 Schedule of Follow-up Procedures)	Added assessment of SC injection sites at the unscheduled/early discontinuation visit to introduce a change suggested in the "Study may proceed" letter from the FDA.
Section 4.3.3 (Clinical Laboratory Tests)	Added serum chemistry assessment of GGT to introduce a change suggested in the "Study may proceed" letter from the FDA.
Section 4.8.7 (Interim, Primary and Final Analyses)	Added clarification of the interim analysis "No adjustments to the study design are planned based on the results of the interim analysis since…." To make it clear that the randomization ratio adjustment is not linked to the interim analysis.

EDN = eosinophil derived neurotoxin; FDA = Food and Drug Administration; GGT = gamma-glutamyl transferase; SC = subcutaneous.

9.8 Protocol Amendment 2

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. The principal reason for this amendment is to address feedback from the FDA.

Changes to the protocol considered to be substantial (Table 25) and non-substantial (Table 26) are summarized below.

Table 25 Summary of Substantial Revisions in Protocol Amendment 2

Section of the Protocol Affected	Reason for Amendment
Synopsis	Updates were made to the synopsis to maintain consistency with the safety endpoint alteration in the main protocol body.
Section 2.2 (Table 2 Secondary Objectives and Associated Endpoints), Section 4.8.1 (General Considerations), Section 4.8.4.3 (Analysis of Vital Signs, ECGs, and Echocardiograms), Section 5.4.11 (Adverse Events Based on Examination and Tests)	Left ventricular ejection fraction added to safety endpoints to capture data collected by echocardiogram assessments that were added to address safety concerns from the FDA.

Table 25 Summary of Substantial Revisions in Protocol Amendment 2

Section of the Protocol Affected	Reason for Amendment
Section 4.1.3 (Exclusion Criteria)	• Subjects with the following were excluded to address safety concerns from the FDA: ◦ Elevated NT-proBNP. ◦ Decreased left ventricular ejection fraction. ◦ Family history of heart failure. ◦ History of myocardial infarction. ◦ Systemic hypertension. ◦ History of treatment with cardiotoxic medications. • Exclusion criterion for diabetes mellitus was more tightly defined to address safety concerns from the FDA.
Section 4.2.1 (Table 5 Schedule of Screening and TCS/TCI Wash Out Procedures), Section 4.2.2 (Table 6 Schedule of Treatment Period Study Procedures) and Section 4.2.3 (Table 7 Schedule of Follow-up Procedures)	• To address safety concerns from the FDA: ◦ HbA1c added to screening Visit 1. ◦ NT-proBNP added to screening Visit 1, Visit 8 (Week 8), Visit 9 (Week 12), Visit 10 (Week 16), Visit 12 (Week 24), and for any unscheduled/early discontinuation visit. ◦ Echocardiogram added to TCS/TCI washout Visit 2, and Visit 9 (Week 12).
Section 4.3.2 (Medical and Dermatology History, Physical Examinations, Weight, Height, Vital Signs, ECGs, and Echocardiograms), Section 4.3.2.5 (Echocardiograms) and Section 4.3.3 (Clinical Laboratory Tests)	New subsection added to describe study procedure for echocardiogram, and echocardiogram removed from clinical laboratory tests section for clarity.

FDA = Food and Drug Administration; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.

Table 26 Summary of Non-substantial Revisions in Protocol Amendment 2

Section of the Protocol Affected	Reason for Amendment
Section 4.1.6 (Discontinuation of Investigational Product)	Reworded criterion on suspected new onset and/or progression of heart failure to clarify the default action is to discontinue investigational product.
Section 4.3.3 (Clinical Laboratory Tests)	Clarification that abnormal laboratory results that are not considered clinically significant are not required to be repeated.

9.9 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The principal reasons for this amendment are to correct errors inadvertently introduced in the original protocol and to introduce updates based on new information not available when drafting the original protocol.

Changes to the protocol considered to be non-substantial are summarized in Table 27.

Table 27 Summary of Revisions in Protocol Amendment 1

Section of the Protocol Affected	Reason for Amendment
Protocol Synopsis (Objectives and Endpoints), Section 2.3 (Table 3 Exploratory Objectives and Endpoints), Section 4.3.7.3 (Skin Punch Biopsies), and Section 4.8.6 (Analysis of Biomarkers)	Upon further consideration after authoring the original protocol, gross inflammation evaluation in lesional and non-lesional skin was added as an exploratory biomarker endpoint to add a standard assessment to the study.
Protocol Synopsis (Objectives and Endpoints), Section 2.3 (Table 3 Exploratory Objectives and Endpoints), and Section 4.8.6 (Analysis of Biomarkers)	Upon further consideration after authoring the original protocol, IL-33 bound to MEDI3506 was added as an exploratory biomarker endpoint to provide an assessment for confirming the new MEDI3506 formulation is able to bind to its IL-33 target.
Section 4.1.3 (Exclusion Criteria)	The formatting of bullet (c) of exclusion criterion 1 was changed to correct a formatting error inadvertently introduced in the original protocol.
Section 4.2.1 (Table 5 Schedule of Screening and TCS/TCI Wash Out Procedures)	Assessment of adherence to the completion of daily eDiary entries was added to Visit 2, to correct an error inadvertently introduced in the original protocol.
Section 4.2.2 (Table 6 Schedule of Treatment Period Study Procedures)	• The baseline echocardiogram assessment planned for Visit 3 (Day 1) was removed to correct an error inadvertently introduced in the original protocol. • Upon further consideration after authoring the original protocol, an ADA assessment was added to Visit 7 (Day 29) to: ◦ Further support PK modeling. ◦ Provide an additional opportunity for monitoring ADA between visits.
Section 4.2.2 (Table 6 Schedule of Treatment Period Study Procedures), Section 4.3.3 (Clinical Laboratory Tests), and Appendix D (Appendix D 2.3 Specific Measures to Consider after Epinephrine Injections, Where Appropriate)	The requirements for and the timing of the collection of serum tryptase samples changed based on new information that the stability period of the samples will be shorter than originally anticipated.

Table 27 Summary of Revisions in Protocol Amendment 1

Section of the Protocol Affected	Reason for Amendment
Section 4.2.3 (Table 7 Schedule of Follow-up Procedures)	• To correct errors inadvertently introduced in the original protocol: ◦ Added urinalysis and serum chemistry assessments to Visit 11 (Day 141) ◦ Added ECG assessment to the unscheduled/early discontinuation visit.
Section 4.3.3 (Clinical Laboratory Tests)	Revised description of pregnancy test specifications to correct an error inadvertently introduced in the original protocol.
Section 5.4.6 (Recording of Cardiac Events [Including Angina or Myocardial Infarction, Congestive Heart Failure, Symptomatic Atherosclerotic Vascular Disease, or Pulmonale or Arrhythmia])	Added how left ventricular ejection fraction is planned to be measured to clarify the text.
Section 4.5.1.4 (Treatment Administration)	Added a clause describing which female subjects must have negative urine pregnancy tests, to clarify the text.
Appendix E (Appendix E 7 Laboratory Tests)	Removed non-mandatory IgM anti-HCV test as the test is no longer recommended by the sponsor and the central laboratory is unable to provide the test.

ADA = anti-drug antibody(ies); ECG = electrocardiogram; eDiary = electronic diary; HCV = hepatitis C virus; Ig = immunoglobulin; IL = interleukin; PK = pharmacokinetic(s); TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Appendix A Contraception Guidance

Women are considered to be of childbearing potential unless they meet either of the criteria, as follows:

- Surgically sterilized (including bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or
- Post-menopausal.

For women aged < 50 years, post-menopausal is defined as having both:

- A history of ≥ 12 months amenorrhea, without an alternative cause, following cessation of exogenous sex-hormonal treatment and,
- A follicle-stimulating hormone level in the post-menopausal range.

For women aged ≥ 50 years, post-menopausal is defined as having a history of ≥ 12 months amenorrhea, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table A1.

Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

Table A1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) ° Oral (combined pill) ° Injectable ° Transdermal (patch) Progestogen-only hormonal contraception ° Desogestrel

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy medical testing of surgical success (ie, absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

Appendix B Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from an adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous (IV) hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5	Death as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

A Guide to Interpreting the Causality Question

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related:	The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
Not protocol related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix C National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Diseases (NAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

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

For the purpose of AE reporting, the above criteria should be used to guide retrospective judgment as to whether an event was true anaphylaxis. Guidance on the recognition of possible anaphylaxis at the time of the event is provided (Appendix D).

Appendix D Signs and Symptoms and Management of Acute Anaphylaxis

Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis. Local or national guidelines for the recognition and management of acute anaphylaxis should be followed where available. Where not available, guidance is provided below.

D 1 Signs and Symptoms of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema.
- Pruritus.
- Urticaria and/or angioedema.
- Bronchospasm.
- Laryngeal edema.
- Hypotension.
- Cardiac arrhythmias.
- Feeling of impending doom.
- Unconsciousness.
- Shock.

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles.
- Rhinorrhea.
- Change in voice.
- Metallic taste.
- Nausea, vomiting, diarrhea, abdominal cramps, and bloating.
- Lightheadedness.
- Headache.
- Uterine cramps.
- Generalized warmth.

D 2 Management of Acute Anaphylaxis

D 2.1 Immediate Intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation.

2 Administer epinephrine intramuscularly every 5 to 15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

D 2.2 Possibly Appropriate, Subsequent Measures Depending on Response to Epinephrine

1 Place patient in recumbent position and elevate lower extremities.
2 Establish and maintain airway.
3 Administer oxygen.
4 Establish venous access.
5 Normal saline IV for fluid replacement.

D 2.3 Specific Measures to Consider after Epinephrine Injections, Where Appropriate

1 Consider epinephrine infusion.
2 Consider H1 and H2 antihistamines.
3 Consider nebulized beta-2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.
4 Consider systemic corticosteroids.
5 Consider vasopressor (e.g. dopamine).
6 Consider glucagon for patient taking b-blocker.
7 Consider atropine for symptomatic bradycardia.
8 Consider transportation to an emergency department or an intensive care facility.
9 For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

If a suspected anaphylactic reaction occurs during or within a 24-hour period after administration of investigational product, blood samples for serum tryptase should be collected as soon as possible after the event, at 60 ± 30 minutes after the event, at discharge, and between 2 and 4 weeks post-discharge. Immediate care of the subject and treatment of the reaction must take priority over collecting blood samples.

Adapted from Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008;63(8):1061-70.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 5.4.12 of the protocol.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine transaminase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

E 2.1 Potential Hy's Law

Aspartate transaminase (AST) or ALT ≥ 3 × upper limit of normal (ULN) **together with** TBL ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase (ALP).

E 2.2 Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN.
- AST ≥ 3 × ULN.
- TBL ≥ 2 × ULN.

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to sponsor study representative).

The investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section E 2) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet PHL criteria the investigator will:

- Inform the study representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

E 4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the investigator will:

- Notify the sponsor study representative who will then inform the study team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol process for SAE reporting.

The medical monitor contacts the investigator, to provide guidance, discuss and agree on an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor. This includes deciding which the tests available in the HL lab kit should be used.
- Complete the relevant CRF Modules as information becomes available.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities per local requirements from the date PHL criteria were met. The medical monitor and global safety physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the sponsor's standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Send the updated SAE (report term "Hy's Law") according to the sponsor's standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL (report term now "Hy's Law case"), ensuring causality assessment is related to the investigational product and seriousness criteria are medically important, according to the clinical study protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following clinical study protocol process for SAE reporting, according to the outcome of the review and amend the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection, or liver disease.

If **No**: follow the process described in Section E 4.2, for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the subject's condition compared with when PHL criteria were previously met:

- If there is no significant change no action is required.
- If there is a significant change follow the process described in Section E 4.2, for reporting PHL as an SAE.

A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

E 7 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. If required, for additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction, consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA IgM anti-HEV HEV RNA

Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

REFERENCES

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix F Genetic Research

F 1 Rationale and Objectives

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

F 2 Genetic Research Plan and Procedures

F 2.1 Selection of Genetic Research Population

Study Selection Record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

F 2.2 Discontinuation of Subjects from this Genetic Research

Specific reasons for discontinuing a subject from this genetic research are:

- Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other

aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.1.8 of the protocol.

F 2.3 Collection of Samples for Genetic Research

The blood sample for genetic research will be obtained from the subjects at Visit 3 in the treatment period. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

F 2.4 Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the subject enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

F 2.5 Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 7 of the protocol.

F 2.6 Informed Consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for

the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

F 2.7 Subject Data Protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a global safety physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

F 2.8 Data Management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the Clinical Study Report or published in scientific journals.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization, or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

F 2.9 Statistical Methods and Determination of Sample Size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan for genetic research will be prepared where appropriate.

Appendix G Classification of Topical Corticosteroids

Topical corticosteroids (TCSs) are grouped into 7 classes based on vasoconstriction assays, with Class I TCSs the most potent and Class VII TCSs the least potent (Table G1). If a TCS not included in the table below is desired, the investigator should contact the medical monitor to confirm classification. These groups may vary depending on the formulation and concentration and should be considered approximate. In general, ointments are more potent than creams or lotions. Potency is also increased when TCSs are used under occlusive dressings or in intertriginous areas.

Table G1 Classification of Representative TCSs

Potency	Class	TCS	Formulation	Strength (%)
Very high	I	Augmented betamethasone dipropionate	O	0.05
		Clobetasol propionate	C, F, or O	0.05
		Diflorasone diacetate	O	0.05
		Halobetasol propionate	C or O	0.05
High	II	Amcinonide	C, L, or O	0.1
		Augmented betamethasone dipropionate	C	0.05
		Betamethasone dipropionate	C, F, O, or S	0.05
		Desoximetasone	C or O	0.25
		Desoximetasone	G	0.05
		Diflorasone diacetate	C	0.05
		Fluocinonide	C, G, O, or S	0.05
		Halcinonide	C or O	0.1
		Mometasone furoate	O	0.1
		Triamcinolone acetonide	C or O	0.5
Medium	IV	Betamethasone valerate	C, F, L, or O	0.1
		Clocortolone pivalate	C	0.1
		Desoximetasone	C	0.05
		Fluocinolone acetonide	C or O	0.025
		Flurandrenolide	C or O	0.05
		Fluticasone propionate	O	0.005
		Mometasone furoate	C	0.1
		Triamcinolone acetonide	C or O	0.1
Lower-medium	V	Hydrocortisone butyrate	C, O, or S	0.1
		Hydrocortisone probutate	C	0.1
		Hydrocortisone valerate	C or O	0.2
		Prednicarbate	C	0.1
Low	VI	Alclometasone dipropionate	C or O	0.05
		Desonide	C, G, F, or O	0.05
		Fluocinolone acetonide	C or S	0.01
Lowest	VII	Dexamethasone	C	0.1
		Hydrocortisone	C, L, O, or S	0.25, 0.5, or 1
		Hydrocortisone acetate	C or O	0.5-1

C = cream; F = foam; G = gel; L = lotion; O = ointment; S = solution; TCS = topical corticosteroid.

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Appendix H Investigator's Global Assessment

The Investigator's Global Assessment is not standardized, so the version provided should be used (Table H1).

Table H1 IGA

Score	Disease Severity	Standard IGA Scale	IGA Morphological Descriptors
0	Clear	No inflammatory signs of AD.	No erythema and no elevation (papulation/infiltration).
1	Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration.	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration) that is not widespread.
2	Mild disease	Mild erythema and mild papulation/infiltration.	Visible detectable, light pink erythema and very slight elevation (papulation/infiltration).
3	Moderate disease	Moderate erythema and moderate papulation/infiltration.	Dull red, clearly distinguishable erythema and clearly perceptible but not extensive elevation (papulation/infiltration).
4	Severe disease	severe erythema and severe papulation/infiltration.	Deep/dark erythema, marked and extensive elevation (papulation/infiltration).

AD = atopic dermatitis; IGA = Investigator's Global Assessment.

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