Statistical Analysis Plan

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

Protocol Number: D9182C00001

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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
AST	aspartate transaminase
BSA	body surface area
CI	confidence interval
CSR	Clinical Study Report
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
eCRF	electronic case report form
EDC	electronic data capture
EDN	Eosinophil Derived Neurotoxin
E_{max}	maximum effect attributable to the drug
GEE	Generalized Estimating Equation
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IL	interleukin
IPD	Important protocol deviation
ITT	intent-to-treat
IXRS	interactive voice/web response system
IV	intravenous
mAb	monoclonal antibody
MCP-Mod	multiple comparison procedure with modelling techniques
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
NRS	Numerical Rating Scale
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
PD	pharmacodynamic(s)
PDP	protocol deviation plan
PGI-S	Patient Global Impression of Severity

Abbreviation or Specialized Term	Definition
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SNOT	Sino-nasal Outcome Test
SOC	system organ class
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TS	Translational Science
ULN	upper limit of normal
Q4W	every 4 weeks

1 INTRODUCTION

This document describes the statistical analysis for protocol D9182C00001, a Phase 2 proof-of-concept clinical study which aims to evaluate the efficacy and safety of MEDI3506 in subjects with moderate to severe Atopic Dermatitis (AD).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

The primary objective of the study is to assess the effects of MEDI3506 compared with placebo on AD disease severity, in adult subjects with moderate-to-severe AD.

2.1.2 Secondary Study Objectives

The secondary objectives are:

- To further assess the effects of MEDI3506 compared with placebo on AD disease severity and symptoms, in adult subjects with moderate-to-severe AD
- To assess the safety and tolerability of MEDI3506 compared with placebo, in adult subjects with moderate-to-severe AD
- To evaluate the PK of MEDI3506, in adult subjects with moderate-to-severe AD
- To evaluate the immunogenicity of MEDI3506, in adult subjects with moderate-to-severe AD.

2.1.3 Exploratory Study Objectives

The exploratory objectives are as follows:

- 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
- 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
- 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

- To assess the effect of MEDI3506 compared with placebo on the need for rescue therapy, in adult subjects with moderate-to-severe AD

- 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

- 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.

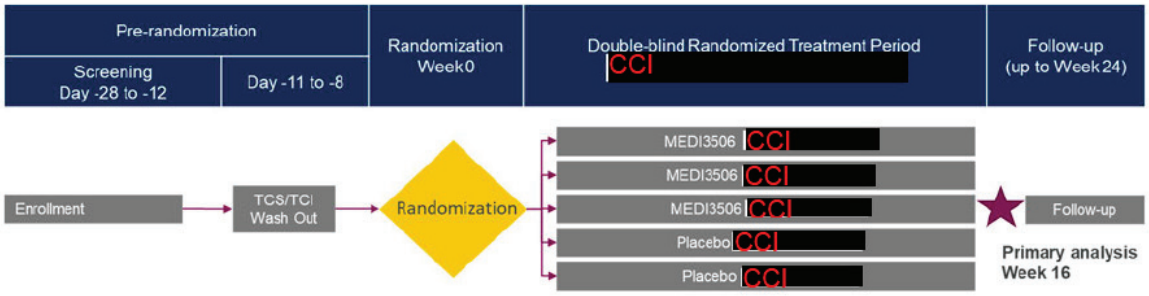
- To evaluate genetic markers that may predict an efficacy response in adult subjects with moderate-to-severe AD treated with MEDI3506 compared with placebo.

2.2 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 SC; or pooled placebo SC; in a 3:1:1:3 ratio overall, CCI The randomization ratio will change during the study. The first 72 subjects in the study will be randomized using a 3:3:3:1:2 ratio to receive CCI MEDI3506 SC; or placebo CCI SC, or placebo CCI SC. The remaining subjects will be randomized using a 1:1 ratio to receive CCI MEDI3506 SC or placebo CCI SC. The randomization will be stratified based on total IgE (< 150 kU/L or ≥ 150 kU/L) at screening.

Subjects will be enrolled in this study for approximately 6.8 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). Subjects will not be permitted to use TCSs and TCIs during these periods, except if medically necessary. The final dose of investigational product will be administered at Visit 9 (Week 12) and the primary endpoint assessment will occur at Visit 10 (Week 16).

Figure 1: Study Flow Diagram



2.3 Treatment Assignment, Blinding and Analysis Datasets

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).

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

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

The primary analysis will occur once all subjects have either completed the Visit 10 (Week 16) assessments or have withdrawn from the study. All the available data at the time of primary analysis will be included. 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.

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.

2.3.1 Analysis Datasets

The primary analysis datasets contain all data (efficacy, safety, ADA, and PK) from all randomized subjects through Visit 10 (Week 16), and all available safety data as of the data cut-off date.

The final analysis datasets contain all data collected in this study, including data in the primary datasets and data from the subjects who were ongoing in the study at the time when the primary datasets were locked.

2.4 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. The sample size calculations were performed using the R statistical computing software.

To allow for the possibility that ≤5% of the subjects per treatment group (for MEDI3506 CCI and placebo) may be ineligible for the ITT population, the total sample size will comprise approximately 152 subjects (58 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.

3 STATISTICAL METHODS

3.1 General Considerations

In general, unless specified otherwise, baseline is defined as the last non-missing assessment prior to dosing. If the baseline is missing following the above definition, baseline evaluations will not be imputed and will be considered as missing. All safety analyses will be performed on the As-treated population. All PK analyses will be conducted using the PK-population. Immunogenicity evaluation will be based on the As-treated population. All other analyses will be performed on the ITT population unless stated otherwise. All data will be provided in data listings sorted by treatment group and subject number. The placebo CCI groups will be pooled for planned analyses, except where stated otherwise. All 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. All statistical tests will be two-sided at an alpha = 0.1 significance level unless stated otherwise.

Day 1 is the first dosing date. Prior to Day 1, study days will be calculated as (sample collection date – Day 1). After Day 1, study days will be calculated as (sample collection date – Day 1 + 1).

3.1.1 General Computation Rules

3.1.1.1 Absolute and Percent Change from Baseline

Absolute change from baseline will be computed as (visit value – baseline value). Percent change from baseline will be computed as (visit value – baseline value)*100/baseline value.

If either a visit value or the baseline value is missing, then the absolute change from baseline value and the percent change from baseline will also be set to missing. If a visit value is non-zero while the baseline value is zero, then the absolute change from baseline will be computed but the percent change from baseline will be set to missing. If a visit value is zero and the baseline value is zero, the percent change will also be zero.

3.1.2 Visit Windows

Visit windows will be used for all scheduled assessments to allow for by-visit analyses, since not all assessments are performed on the scheduled day. The analysis visit windows will be calculated by bisecting the scheduled visit days. The lower limit of each window will be the mean of the two adjacent planned study days, rounded up to the nearest integer. The upper

limit of each window will be the mean of the two adjacent planned study days, rounded down to the nearest integer.

The visit result will be missing if no assessment was reported within the specified visit window around the scheduled date. If multiple readings are recorded within a single visit window, then rules will be applied, as follows:

- If there are 2 or more observations within the same visit window, the non-missing observation closest to the scheduled visit will be used in the analysis.
- If 2 observations are equidistant from the scheduled visit, the non-missing observation with the earlier collection date or time will be used in the analysis.
- If two observations are collected on the same date, the non-missing observation with the earlier collection time will be used in the analysis.
- Additional rules for cases not covered by the 2 rules above will be documented in the Analysis Conventions Document.

For EASI, IGA and SCORAD, adjusted protocol-defined visit windows will be used as defined in

Table 1.

Table 1 **Adjusted Protocol-defined Visit Windows for EASI, IGA, and SCORAD**

Visit Number	Name/Week Number	Scheduled Study Day in the Protocol	Visit Windows
1	Screening [a]	-28 to -12	Study Day ≤ -12
2	TCS/TCI Wash Out [a]	-11 to -8	-11 ≤ Study Day ≤ -8
3	Week 0 (Day 1) [a]	1	-7 ≤ Study Day ≤ 1
5	Week 1	8	2 ≤ Study Day ≤ 11
6	Week 2	15	12 ≤ Study Day ≤ 22
7	Week 4	29	23 ≤ Study Day ≤ 43
8	Week 8	57	44 ≤ Study Day ≤ 71
9	Week 12	85	72 ≤ Study Day ≤ 99
10	Week 16	113	100 ≤ Study Day ≤ 127
11	Week 20	141	128 ≤ Study Day ≤ 155
12	Week 24	169	Study Day ≥ 156

[a] The Screening and Week 0 (Day 1) visit windows are applicable only when the visit is present for descriptive statistics in the summary tables for EASI, IGA, and SCORAD. For analyses, baseline is defined as the last assessment value prior to dosing unless stated otherwise.

For the patient-reported questionnaires collected by electronic PRO, the data will be summarized based on the visit windows provided (Table 2).

Table 2 Visit Windows for PRO Data

Questionnaire	Collection Frequency and Scheduled Visits	Visit Windows
Pruritus NRS	• Daily	Not Applicable
Skin pain NRS	• Daily	Not Applicable
Moisturizer use	• Daily	Not Applicable
5-D Pruritus Scale	• Initial assessment at site: Day 1 • At site: Weeks 2, 4, 8, 12, 16, 20 and 24	Day 1: Study Day ≤ 1 Week 2: 2 ≤ Study Day ≤ 22 Week 4: 23 ≤ Study Day ≤ 43 Week 8: 44 ≤ Study Day ≤ 71 Week 12: 72 ≤ Study Day ≤ 99 Week 16: 100 ≤ Study Day ≤ 128 Week 20: 128 ≤ Study Day ≤ 155 Week 24: Study Day ≥ 156
DLQI	• Initial assessment at site: Day 1 • At site: Weeks 2, 4, 8, 12, 16, 20 and 24	Same as 5-D Pruritus Scale
PGI-S	• Initial assessment at site: Day 1 • At site: Weeks 2, 4, 8, 12, 16, 20 and 24	Same as 5-D Pruritus Scale
POEM	• Initial assessment at site: Day 1 • At site: Weeks 2, 4, 8, 12, 16, 20 and 24	Same as 5-D Pruritus Scale
ACQ	• Initial assessment at site: Day 1 • At site: Weeks 4, 8, 12, 16 and 24	Day 1: Study Day ≤ 1 Week 4: 2 ≤ Study Day ≤ 43 Week 8: 44 ≤ Study Day ≤ 71 Week 12: 72 ≤ Study Day ≤ 99 Week 16: 100 ≤ Study Day ≤ 141 Week 24: Study Day ≥ 142
SNOT-22	• Initial assessment at site: Day 1 • At site: Weeks 4, 8, 12, 16 and 24	Same as ACQ

3.2 Analysis Populations

There are 3 analysis populations defined for this study (Table 3). A summary of the analysis populations by treatment group will be provided.

Table 3 Analysis 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.

Table 3 Analysis Populations

Population	Description
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).

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

Summaries of subject eligibility, randomization, treatment received, and subjects randomized but not treated will be provided. In addition, subject disposition throughout the study and by visit with respect to treatment completion and follow-up completion will be provided. The summaries will be presented by treatment group and for all subjects combined. The denominators for this summary will include all subjects who were randomized into the study.

The number and percentage of subjects with one or more disruptions due to COVID-19 pandemic will be presented by treatment group. A listing of all subjects affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered, will be produced. COVID-19 related study disruptions can be:

1. Visit related (if visit is impacted by global/country situation, then contact mode will be specified);
2. Study drug related (if study drug action taken (except "Drug Withdrawn") was impacted by global/country situation; study drug administration or location was impacted by global/country situation; who performed a study drug administration);
3. Concomitant medication related (if when treatment was stopped due to any global/country related situations ie: epidemic/pandemic, healthcare crisis etc.);
4. Discontinuation of study drug due to COVID-19 pandemic (if study drug action taken "Drug Withdrawn" was impacted by global/country situation);
5. Withdrawal from study (if primary reason for ending study is related to global/country situation).

3.3.2 Important Protocol Deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or wellbeing (ICH E3 guidance). The category of IPDs for the study are:

1. Did not fulfil eligibility criteria
2. Developed discontinuation criteria but continued
3. Received incorrect investigational treatment/dose
4. Received prohibited concomitant medication
5. Protocol-required procedure not adhered to
6. Other reason

Details of the definition of IPDs will be provided in the protocol deviation plan (PDP), which will be developed for the study. The method for identifying IPDs will be documented in the PDP. The list of identified IPDs will be reviewed by the study statistician, medical monitor, study physician, lead data manager and study manager. All blinded IPDs will be agreed prior to study unblinding by blinded study personnel. The review will take place at the time of primary analysis and final analysis for the study. Unblinding IPDs (ie. those that relate to study medication/dosing and which could potentially unblind a reviewer to subject's treatment group) will be agreed by unblinded personnel. The finalized list of IPDs will be approved by the study statistician, medical monitor and study physician.

The number and percentage of subjects with at least one IPD, including and excluding COVID-19 related IPDs, will be summarized following the IPD categories for each study intervention group and overall. A listing of all identified IPDs will also be provided. All issues reported due to COVID-19 pandemic, regardless of whether the type of issue is considered an IPD or not, will be listed separately.

3.3.3 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, weight, height, and body mass index (BMI) will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics will include, but will not be limited to:

1. Stratification factor – Total immunoglobulin (Ig)E (< 150kU/L vs ≥ 150 kU/L)
2. Total serum IgE level (kU/L)
3. EASI score
4. EASI Score (≤ 25 points vs > 25 points)
5. Body surface area affected by AD (%)
6. Investigator's Global Assessment (IGA) score
7. SCORAD
8. DLQI
9. 5-D itch
10. PGI-S
11. POEM
12. Peripheral blood eosinophil count (cells/μL)
13. Peripheral blood eosinophil count (cells/μL) (<300 vs ≥ 300)
14. Plasma EDN level (ng/mL)
15. *Staphylococcus aureus* (< median vs ≥ median) (lesional and non-lesional skin separately) (at final analysis only)
16. TCS use at Screening (Low Potency TCS vs Medium to High Potency TCS vs No TCS)
17. Systemic therapy use in past 6 months (Yes vs No)
18. Topical medication use not tolerated or medically inadvisable (Yes vs No)

Medical history and AD history will be summarized by treatment group and for all subjects combined.

3.3.4 Investigational Product Exposure

Exposure to investigational product will be summarized by treatment group for the As-treated population. The summary of investigational product exposure will include descriptive statistics for the number of investigational product doses administered, total amount of investigational product exposure (in mg), and dose intensity for the entire study period. Also, total amount of investigational product administered by visit (in mg) will be summarized using descriptive statistics as well as for dose intensity. Dose intensity is defined as a percent of actual dose received versus total protocol planned dose.

3.3.5 Prior and Concomitant Medications

Prior and concomitant medications (including atopic dermatitis medications) will be coded using the WHODrug-Global-B3 Drug Dictionary. All prior and concomitant medications will be presented in a data listing. Prior medications include those medications that were stopped prior to the first dose of the investigational product. Concomitant medications exclude medications that were stopped prior to the first dose of investigational product. Summaries will be provided by preferred term and treatment group, as follows:

- Prior atopic dermatitis medications

- Prior other medications (ie. non-AD medications)
- Concomitant atopic dermatitis medications
- Concomitant other medications (ie. non-AD medications)

3.3.6 Prohibited and Rescue Concomitant Medications

If a subject receives prohibited or rescue AD therapy, which may impact their efficacy assessments, they should discontinue investigational product. Prohibited and rescue AD therapy will be identified prior to unblinding. All prohibited and rescue AD therapies identified will be reviewed and a list of medications deemed to influence the disease will be made before unblinding, the list will be approved by the medical monitor.

For the purpose of analyses, prohibited and rescue concomitant medications and therapies will be summarized. Cumulative summary of prohibited and rescue medication use by visit will also be provided. In addition, the cumulative distribution plot of the proportion of subjects receiving rescue therapy will be provided. A listing of all subjects who received prohibited rescue therapies will be provided specifying the prohibited therapy and the timing of use.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

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

EASI score is calculated as described (Table 4) (Hanifin et al, 2001).

Table 4 EASI Score Calculation

Body Region	Severity	Area	Score
Head/Neck (H)	The average degree of severity of each sign (erythema [E], induration/papulation [I], excoriation [EX], and lichenification [L]) is defined on a 4-point ordinal scale with half-steps (0.5, 1.5, and 2.5): 0 = none 0.5 1 = mild 1.5 2 = moderate 2.5 3 = severe	The area is defined on a 7-point ordinal scale: 0 = no eruption 1 = < 10% 2 = 10%-29% 3 = 30%-49% 4 = 50%-69% 5 = 70%-89% 6 = 90%-100%	(E + I + Ex + L) × Area × 0.1
Upper limbs (UL)			(E + I + Ex + L) × Area × 0.2
Trunk (T)			(E + I + Ex + L) × Area × 0.3
Lower limbs (LL)			(E + I + Ex + L) × Area × 0.4
EASI Score	NA	NA	Sum of scores for H, UL, T, and LL

NA = not applicable.

3.4.1.2 Handling of Dropouts and Missing Data

If any component of EASI is missing, the calculation of the score will be set to missing. For subjects who receive prohibited or rescue concomitant medications and therapies, the data obtained after the use of this therapy will be treated as missing and excluded from the primary analysis. In addition, sensitivity analyses will be performed in which the last response value recorded on the day of, or prior to, use of prohibited concomitant medications and therapies, and prohibited rescue therapies, will be carried forward.

3.4.1.3 Primary Efficacy Analysis

EASI score will be summarized with descriptive statistics (number of subjects with a valid value, mean, standard deviation, median, minimum, and maximum) by treatment group and visit. In addition, the change from baseline will be summarized with descriptive statistics for each post-baseline visit.

To assess dose response at Week 16, percent change from baseline to Week 16 in EASI score will be analyzed using a mixed-effects model for repeated measures (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 an alternative such as compound symmetry or first order auto-regressive will be used. 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. Details of the candidate models are provided in Appendix 1. 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. Data collected from subjects who discontinue the investigational product and did not use any rescue therapy afterwards will be included in 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 compared to placebo arm will be summarized together with a two-sided 90% CI, and p-value.

3.4.1.4 Additional Analyses of the Primary Efficacy Endpoint(s)

The following additional analyses will be performed to assess the sensitivity of the assumptions of the statistical methods used in the primary efficacy analysis. Firstly, 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. An MMRM followed by a MCP-Mod dose response model will be used for the analysis and the results from the fitted dose response model and the MMRM will be presented in a similar way as described above for the analysis of the primary efficacy endpoint (Section 3.4.1.3).

A second supplementary analysis will be performed using the ITT population. Data from assessments performed after prohibited or rescue therapies are received will be excluded and a last observation carried forward (LOCF) 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 from the fitted dose response model and the ANCOVA will be presented in a similar way as described above for the efficacy analysis for the primary endpoint (Section 3.4.1.3).

A third supplementary analysis will be performed using the ITT population, excluding data from subjects CCI whose treatment allocations were accidentally unblinded at the site. All other details of this analysis are the same as those for the primary analysis (Section 3.4.1.3).

A fourth supplementary analysis for percent change in EASI score will be performed using a MMRM as described above (Section 3.4.1.3), 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 each visit will be estimated along with the 90% CI and two-sided p-value. A plot of the adjusted mean percent change from baseline (± SE) in EASI by visit will be provided.

In addition, similar summary (MMRM) will be provided for each of the four components of EASI (ie. erythema, papulation, excoriation and lichenification).

3.4.1.5 Subgroup Analyses

The consistency of the overall treatment effect on the primary endpoint will be assessed in subgroups of subjects. A MMRM, as described in Section 3.4.1.3, including data from up to Week 16, will be used for each subgroup. The analyses will be performed for subgroups, as follows:

- Total serum IgE level at baseline (< 150 kU/L vs ≥ 150 kU/L).
- Baseline IGA score (3 vs 4).
- Baseline EASI (≤ 25 points vs > 25 points).
- *S aureus* in lesional skin at baseline (< median vs ≥ median) (at final analysis only).
- *S aureus* in non-lesional skin at baseline (< median vs ≥ median) (at final analysis only).
- Age (18 to 35 years of age vs 36 to 75 years of age).
- Age at onset of AD (< 18 years of age vs ≥ 18 years of age).
- Parent having a history of AD (presence vs absence).

- Sex (male vs female).
- Race (White vs non-White).
- Region (North America vs Europe/Australia).
- Blood eosinophil count at baseline (< 300 cells/μL vs ≥ 300 cells/μL).
- Aeroallergens (presence vs absence).
- Food allergies (presence vs absence).
- Contact allergies (presence vs absence).
- Asthma comorbidity (presence vs absence).

The MMRM will be fitted separately to each subgroup. The analysis for each subgroup will be performed if the subgroup has at least 20% of subjects in the ITT population.

3.4.2 Secondary Efficacy Endpoints and Analyses

3.4.2.1 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be measured up to Week 16 for on-therapy effects and at time points beyond the end of treatment for off-therapy effects.

IGA

The IGA consists of a 5-point severity scale from clear to severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, and 4 = severe disease). The secondary efficacy IGA endpoint is the percentage of subjects achieving both an IGA score of 0 (clear) or 1 (almost clear) and a reduction from baseline of ≥ 2 points at Week 16.

EASI including Percentage BSA Affected by AD

Secondary efficacy endpoints based on EASI include, as follows:

- 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
- Change from baseline to Week 16 in the percentage of BSA affected by AD, as assessed by EASI.

Pruritus NRS

Pruritus will be assessed using an NRS (0 to 10) with 0 = no itch and 10 = worst imaginable itch. 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. Baseline will be defined as an average of the last 7 days prior to study drug being administered. If more than 3 days have missing data in the baseline period, the baseline period will be shifted back to the last 7-day period which includes at least 4 non-missing days.

The secondary efficacy endpoints based on pruritus NRS include:

- Change from baseline to Week 16 in weekly mean of daily peak pruritus NRS, and
- Percentage of subjects achieving a reduction of ≥ 3 from baseline to Week 16 in weekly mean of daily peak pruritus NRS.

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. 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. Baseline will be defined as an average of the last 7 days prior to investigational product being administered. If more than 3 days have missing data in the baseline period, the baseline period will be shifted back to the last 7-day period which includes at least 4 non-missing days.

The secondary efficacy endpoint based on skin pain NRS is change from baseline to Week 16 in weekly mean of daily peak skin pain NRS.

SCORAD

The secondary efficacy endpoint based on SCORAD is the percent change from baseline to Week 16 in SCORAD, which is calculated as presented in Table 5 (European Task Force on Atopic Dermatitis, 1993).

Table 5 SCORAD Calculation

Component	Definition	Grading	Score
Extent (A)	• head and neck • upper limbs (anterior/posterior) • lower limbs (anterior/posterior) • anterior trunk • back • genitals • hand (right/left)	• head and neck: 9% • upper limbs: 9% each • lower limbs: 18% each • anterior trunk: 18% • back: 18% • genitals: 1% • hand: 1% each	Sum of each extent item score to give a total extent score A (range 0-102)
Intensity (B)	• erythema • edema/papulation • oozing/crusts • excoriations • lichenification • dryness	Each intensity item is defined on a 4-point ordinal scale: 0 = absent 1 = mild 2 = moderate 3 = severe	Sum of each intensity item score to give a total intensity score B (range 0-18)
Subjective Symptoms (C)	• pruritus • sleep loss	Each symptom has an NRS (0-10) where 0 is no pruritus/sleep loss and 10 is the worst imaginable pruritus/sleep loss.	Sum of each subjective symptom score to give a total symptom score C (range 0-20)
Objective SCORAD Score	NA	NA	(A/5) + (7×B/2)
SCORAD Score	NA	NA	(A/5) + (7×B/2) + C

NA = not applicable.

Patient Global Impression of Severity (PGI-S)

The PGI-S is a tool that allows patients to rate the severity of a condition. The PGI-S comprises a single question of, “Would you describe your AD or eczema as no symptoms, very mild, mild, moderate, severe or very severe?” The secondary efficacy endpoint based on this is PGI-S score at Week 16.

5-D Pruritus Score

A secondary efficacy endpoint includes change from baseline to Week 16 in 5-D pruritus score. 5-D pruritus score is calculated as presented in Table (Elman et al, 2010).

Table 6 5-D Pruritus Score Calculation

Domain	Definition	5-D Pruritus Score
Duration	Single-item domain score (range 1-5)	Range 1-5
Degree	Single-item domain score (range 1-5)	Range 1-5
Direction	Single-item domain score (range 1-5)	Range 1-5
Disability	Four items that assess the impact of itching on daily activities • sleep (range 1-5) • leisure/social (range 1-5) • housework/errands (range 1-5) • work/school (range 1-5)	Highest score on any of the four items
Distribution	Sixteen affected body parts (sum 0-16)	• 1 = sum of 0-2 • 2 = sum of 3-5 • 3 = sum of 6-10 • 4 = sum of 11-13 • 5 = sum of 14-16
5-D Pruritus	NA	Sum of five domains

NA = not applicable.

Patient-Oriented Eczema Measure (POEM)

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. Each item is scored on a 5-point scale with 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = every day. The total POEM score is calculated by summing the score of each item resulting in a maximum of 28 and a minimum of 0, with higher values indicating severe disease (Charman et al, 2004). The secondary efficacy endpoint based on this questionnaire is the change from baseline to Week 16.

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. 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 score is calculated by summing the score of each item resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The secondary efficacy endpoint based on DLQI is change from baseline in DLQI score to Week 16.

3.4.2.2 Handling of Dropouts and Missing Data

If any component of SCORAD, 5-D Pruritus Score, POEM, DLQI or EASI score is missing, the calculation of the score will be set to missing.

For the analysis of efficacy responder endpoints, including the proportion of subjects achieving both IGA score of 0 (clear) or 1 (almost clear) and a reduction from baseline of ≥ 2 points, EASI 50, EASI 75, EASI 90 and peak pruritus NRS responders, subjects who discontinue investigational product, withdraw from the study, or require rescue therapy will be considered as non-responders. For the EASI 75 and IGA endpoints, additional sensitivity analyses will be performed using the last non-missing post-baseline value carried forward approach to assess the impact of including efficacy data beyond the use of rescue therapies. For subjects who receive rescue therapies, the last response value recorded on the day of, or prior to, the subject received a prohibited rescue therapy will be carried forward.

The continuous efficacy endpoints, including, percent change from baseline to Week 16 in SCORAD, change from baseline to Week 16 in peak pruritus NRS, skin pain NRS, 5-D pruritus (itch) score, percentage of BSA affected by AD, POEM, and DLQI will be analyzed using MMRM. All data points for subjects in the ITT population will be included in the analysis, up to and including the day the rescue therapy is used.

3.4.2.3 Secondary Efficacy Analyses

IGA Score 0 or 1 with ≥ 2 Grade Reduction from Baseline to Week 16

The percentage of subjects achieving an IGA score of 0 (clear) or 1 (almost clear) and a reduction from baseline of ≥ 2 points at Week 16 will be analyzed using a logistic regression model 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). Details of the candidate models are provided in Appendix 1. 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.

A plot showing the percentage of subjects achieving IGA response in each treatment group by visit will be provided. In addition, barplot of IGA response rate at Week 16 in each treatment group will be provided.

Supplementary analyses will be performed to assess the sensitivity of the assumptions of the statistical methods used in the primary analysis for the IGA endpoint.

A logistic regression model of IGA response rate at Week 16 will be performed based on the ITT population. The model will include treatment group and randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L) as categorical factors, and baseline IGA score as a covariate. 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. 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).

An analysis based on 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. The analysis will be performed using the same MCP-Mod as described for as described above for the secondary efficacy analysis for IGA. In addition, a logistic regression analysis similar to that described above, will also be performed for this ITT population for all observed cases.

Another supplementary analysis will be performed using the ITT population in which data from assessments performed after rescue therapies are received are excluded and a last observation carried forward approach applied for missing data. The logistic regression and MCP-Mod dose response model used for this analysis and the presentation of results will be similar as described above for the secondary efficacy analysis for IGA. In addition, a logistic regression analysis like that described above, will also be performed for this ITT population with LOCF.

Another supplementary analysis will be performed using the ITT population excluding data from subjects CCI whose treatment allocations were accidentally unblinded at the site. The analysis will be performed using the same MCP-Mod as described above for the secondary efficacy analysis for IGA.

Furthermore, an analysis will be performed using a generalized estimating equation (GEE) 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 including exchangeable, unstructured, and autoregressive matrixes will be explored. From the model obtained, estimates of the treatment effect at each visit together with the associated standard errors, 90% CIs, and p-values will be provided.

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

The percentage of subjects achieving EASI 50, EASI 75, or EASI 90 at Week 16 will be analyzed separately 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).

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

Barplot of the percentage of subjects achieving EASI 50, EASI 75, or EASI 90 at Week 16 will be provided. A plot showing the percentage of subjects achieving an EASI 50 response

in each treatment group by visit will also be provided. Similar plot will be provided for EASI 75 and EASI 90.

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

The endpoint of change from baseline in % BSA affected by AD, as assessed by EASI, will be summarized descriptively and analyzed for the ITT population 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 3.4.1.3).

A plot of the adjusted mean change from baseline (± standard error) in %BSA by visit will be provided.

Peak Pruritus NRS at Week 16

The endpoint change from baseline to Week 16 in weekly mean of daily peak pruritus NRS will be summarized descriptively and 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 3.4.1.3)

The endpoint 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.

Skin pain NRS at Week 16

Change from baseline to Week 16 in weekly mean peak skin pain NRS will be summarized descriptively and 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 3.4.1.3).

Percent Change from Baseline to Week 16 in SCORAD

The endpoint of percent change from baseline to Week 16 in SCORAD will be analyzed 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 change from baseline to Week 16 in EASI score (Section 3.4.1.3).

A cumulative distribution plot of percent change from baseline in SCORAD will be presented. In addition, descriptive summary of the total SCORAD score at each visit will be provided by treatment group. In addition, similar summary will be provided for each of the components of SCORAD (extent, intensity, pruritus, sleep loss, objective). In addition, summary of change from baseline will be provided by visit for the total SCORAD score and separately for each of the components.

PGI-S at Week 16

The 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.

Change from Baseline to Week 16 in 5-D Itch

The endpoint change from baseline to Week 16 in 5-D itch will be summarized descriptively and analyzed using a MMRM, including data 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 change from baseline to Week 16 in EASI score (Section 3.4.1.3).

In addition, descriptive summary of the total 5-D itch score at each visit will be provided by treatment group. Similar summary will be provided for each of the domains of 5-D itch (duration, degree, direction, disability, distribution). In addition, summary of change from baseline will be provided by visit for the total 5-D itch score and separately for each of the domains.

Change from Baseline to Week 16 in POEM

The endpoint change from baseline to Week 16 in POEM will be summarized descriptively and analyzed using a MMRM, including data 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 change from baseline to Week 16 in EASI score (Section 3.4.1.3).

Change from Baseline to Week 16 in DLQI

The endpoint change from baseline to Week 16 in DLQI will be summarized descriptively and analyzed using a MMRM, including data 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 change from baseline to Week 16 in EASI score (Section 3.4.1.3).

In addition, descriptive summary of the total DLQI score at each visit will be provided by treatment group. Similar summary will be provided for each of the components of DLQI (daily activities, leisure, personal relationship, work or school, symptoms and feelings, treatment side effects). In addition, summary of change from baseline will be provided by visit for the total DLQI score and separately for each of the components.

3.4.2.4 Subgroup Analyses

The consistency of the detected overall treatment effect on the IGA response at Week 16 will be assessed in a subgroup of subjects. A logistic regression model including treatment group, randomization stratum (total serum IgE level < 150 kU/L or ≥ 150 kU/L), and baseline IGA as categorical factors, will be used in a similar way as described in Section 3.4.2.3 for the following subgroup populations of interest:

- Total serum IgE level (< 150 kU/L vs ≥ 150 kU/L).
- IGA score (3 vs 4).
- Baseline EASI (≤ 25 points vs > 25 points).
- *S aureus* in lesional skin (< median vs ≥ median) (at final analysis only).
- *S aureus* in non-lesional skin (< median vs ≥ median) (at final analysis only).
- Age (18 to 35 years of age vs 36 to 75 years of age).
- Age at onset of AD (< 18 years of age vs ≥ 18 years of age).
- Parent having a history of AD (presence vs absence).
- Sex (male vs female).
- Race (White vs non-White).
- Region (North America vs Europe/Australia).
- Blood eosinophil count (< 300 cells/µL vs ≥ 300 cells/µL).
- Aeroallergens (presence vs absence).
- Food allergies (presence vs absence).
- Contact allergies (presence vs absence).
- Asthma comorbidity (presence vs absence).

The logistic regression will be fitted separately to each subgroup. The analysis for each subgroup will be performed if the subgroup has at least 20% of subjects in the ITT population.

Similarly, the consistency of the detected overall treatment effect on the percentage of subjects achieving EASI 75 at Week 16 will be assessed in subgroup of subjects described above using a similar logistic regression model as described previously (Section 3.4.2.3).

3.4.3 Other Efficacy Analyses

Descriptions of the exploratory efficacy endpoints are provided (Section 3.4.2.1), except for SNOT-22 and ACQ-6, provided below.

The SNOT-22 is a validated questionnaire for assessing the impact of chronic rhinosinusitis on quality of life. 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 ACQ-6 is a questionnaire developed and validated to measure asthma control. 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.

3.4.3.1 Number and percentage of subjects achieving EASI 90, EASI 75, and EASI 50, at Weeks 2, 4, 8, 12, 16, 20, and 24

The number and percentage of subjects achieving EASI 90, EASI 75, and EASI 50 by Weeks 2, 4, 8, 12, 16, 20, and 24 will be summarized by visit separately for each endpoint. Analyses using a GEE model for repeated measures will be performed separately for each endpoint and will include all data up to Week 24. Details of the model are similar to those described for the additional analysis of the IGA response at Week 16 (Section 3.4.2.3).

3.4.3.2 Percentage change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in EASI score

The percent change from baseline to Weeks 2, 4, 8, 12, 16, 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 in a similar way as described for percent change from baseline to Week 16 in EASI score (Section 3.4.1.3).

3.4.3.3 Percentage of subjects achieving IGA 0/1 and ≥2 grade reduction from baseline at Weeks 2, 4, 8, 12, 16, 20, and 24

The number and percentage of subjects achieving an IGA response at Weeks 2, 4, 8, 12, 16, 20, and 24 will be summarized by visit, and analyzed using the GEE model as described for IGA response at Week 16 (Section 3.4.2.3).

3.4.3.4 Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in %BSA affected by AD

Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in percent BSA affected by AD will be summarized descriptively by visit, and analyzed using a MMRM as described for percent change from baseline to Week 16 in EASI score (Section 3.4.1.3).

3.4.3.5 Peak pruritus NRS: reduction of ≥3 from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24

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 GEE model as described above for IGA response at Week 16 (Section 3.4.2.3).

3.4.3.6 Peak pruritus NRS: reduction of ≥4 from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24

The number and percentage of subjects achieving reduction of ≥ 4 from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in weekly mean of daily peak pruritus NRS will be summarized by visit and analyzed using the GEE model as described above for IGA response at Week 16 (Section 3.4.2.3).

3.4.3.7 Peak pruritus NRS: change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24

Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in the weekly mean of daily peak pruritus NRS will be summarized descriptively by visit and analyzed using a MMRM as described for percent change from baseline to Week 16 in EASI score (Section 3.4.2.3)

3.4.3.8 Skin pain NRS: change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24

Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in the weekly mean of daily peak skin pain NRS will be summarized by visit and analyzed using a MMRM as described for percent change from baseline to Week 16 in EASI score (Section 3.4.2.3).

3.4.3.9 SCORAD: Percent change from baseline to Weeks 2, 4, 8, 12, 16, 20 and 24

Percent change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in SCORAD will be summarized descriptively by visit and analyzed using a MMRM as described for the percent change from baseline to Week 16 in EASI score (Section 3.4.2.3).

3.4.3.10 PGI-S at Weeks 2, 4, 8, 12, 16, 20 and 24

PGI-S at Weeks 2, 4, 8, 12, 16, 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.

3.4.3.11 Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in 5-D itch

Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in 5-D itch will be summarized by visit and analyzed using a MMRM as described for percent change from baseline to Week 16 in EASI score (Section 3.4.2.3).

3.4.3.12 Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in POEM

Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in POEM will be summarized by visit and analyzed using a MMRM as described for percent change from baseline to Week 16 in EASI score (Section 3.4.2.3).

3.4.3.13 Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in DLQI

Change from baseline to Weeks 2, 4, 8, 12, 16, 20, and 24 in DLQI will be summarized by visit and analyzed using a MMRM as described for percent change from baseline to Week 16 in EASI score (Section 3.4.2.3).

3.4.3.14 Change from baseline to Weeks 16 and 24 in SNOT-22

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

3.4.3.15 Change from baseline to Weeks 16 and 24 in ACQ-6

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

3.4.3.16 Subjects requiring rescue therapy during the treatment and follow-up period

The number and percentage of subjects requiring rescue therapy during the treatment period will be summarized by visit. Similarly, the number and percentage of subjects requiring rescue therapy during the treatment period and the follow-up period will also be summarized. In addition, a plot of the cumulative proportion of subjects receiving rescue therapy during the treatment and follow-up periods will be provided.

3.4.3.17 Time to first use of rescue therapy

Summary descriptive statistics (including number, minimum, maximum, median, 25th and 75th percentiles) will be provided for time to first use of rescue therapy either during the treatment or follow-up period. In addition, Kaplan-Meier analysis of the time to first use of rescue therapy will also be performed.

3.4.3.18 Incidence of skin infection TEAEs

The incidence of skin infection TEAEs requiring systemic treatment during the treatment and follow-up periods will be summarized descriptively by treatment group.

3.5 Biomarker Analyses

3.5.1 Blood Concentration of sST2 and CCI

The blood concentration of soluble ST2 (sST2) will be summarized by visit using descriptive statistics (number, mean, geometric mean, SD, median, coefficient of variation, minimum, and maximum). Change from (or ratio to) baseline to Week 16 in the concentrations of sST2 will be summarized descriptively by visit as described above. The concentration values will be log-transformed and analysis of change from baseline to Week 16 of the log-transformed data will be performed 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. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model. No imputation will be made for missing data. The results obtained will be back-transformed to the original scale. The estimated adjusted mean ratio to baseline (± standard error) for each treatment group will be provided. Also, the ratio of the adjusted mean ratio of each MEDI3506 group to placebo will be provided along with the 90% CI and p-value. The change from baseline to Week 16 in blood concentration of CCI will be explored and reported separately to the CSR.

3.5.2 Peripheral Blood Mononuclear Cell (PBMC) subset

The change from baseline in levels of PBMC subsets in whole blood at Week 16 may be explored and reported separately to the CSR.

3.5.3 Blood biomarker levels of Eosinophils, IL-33 bound to MEDI3506, IL-5, IL-13 and CCL17

Blood biomarker levels of eosinophils and IL-33 bound to MEDI3506 will be summarized descriptively (number, mean, geometric mean, median, coefficient of variation, minimum, and maximum) by visit for each treatment group. Change from (or ratio to) 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 also be summarized descriptively by visit and treatment group for each biomarker. In addition, for IL-33 bound to MEDI3506, the levels will be log-transformed and analysis of change from baseline to Week 24 of the log-transformed data will be performed using a MMRM as described for the percent change from baseline to Week 16 in EASI score (Section 3.4.1.3). The results obtained from the model will be back-transformed to the original scale. The estimated adjusted mean ratio to baseline (± standard error) for each treatment group will be provided. Also, the ratio of the adjusted mean ratio of each MEDI3506 group to placebo will be provided along with the 90% CI and p-value. The mean (± standard error) change from baseline through to Week 16 and to Week 24 for IL-33 bound to MEDI3506 of the log-transformed data will be plotted for each treatment group separately for each biomarker. For eosinophils, the analysis will be done on the original scale, that is, no log-transformation will be performed for this biomarker. The change from baseline up to Week 24 in levels of IL-5, IL-13 and CCL17 will be explored and reported separately to the CSR.

3.5.4 Serum IgE levels and Plasma Eosinophil Derived Neurotoxin (EDN) levels

Descriptive summary statistics (number, geometric mean, median, coefficient of variation, minimum, and maximum) will be provided separately for serum IgE levels and plasma EDN levels by visit and treatment group. Change from baseline to Weeks 2, 8, 16, and 24 in serum IgE levels and to Weeks 4, 16, and 24 in plasma EDN levels will be summarized descriptively by visit for each treatment group. In addition, the IgE levels and EDN levels will be log-transformed and similar analysis described in Section 3.5.1 above will be performed on the log-transformed data. Also, a plot of mean change (± standard error) from baseline through to Week 24 of log-transformed IgE levels and EDN levels will be provided.

3.5.5 Proinflammatory Gene Signatures in Blood

Change from baseline to Week 16 in proinflammatory gene signatures in whole blood will be reported separately from the CSR.

3.5.6 Colonization of Pathogenic Bacteria in Lesional and Non-lesional Skin

Colonization of pathogenic bacteria (ie, *Staphylococcus aureus*) in lesional and non-lesional skin at baseline and Week 16 will be summarized by visit using descriptive statistics (number, geometric mean, median, coefficient of variation, minimum and maximum). In addition, change from baseline to Week 16 in colonization of pathogenic bacteria (ie, *Staphylococcus aureus*) in lesional and non-lesional skin will be summarized using descriptive statistics by visit for each treatment group.

3.5.7 Gross inflammation evaluation

Gross inflammation evaluation in lesional and non-lesional skin at baseline and Week 16 may be explored and reported separately to the CSR.

3.5.8 Proinflammatory Gene Signatures in Lesional and Non-lesional Skin

The data on proinflammatory gene signatures in lesional and non-lesional skin at baseline and Week 16 will be assessed by the Translational Science (TS) group and the effect of the gene signatures on the primary efficacy endpoint will be explored and reported separately from the CSR.

3.5.9 CCI

CCI

3.6 Safety Analyses

3.6.1 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). The type, incidence, severity and relationship to study investigational product will be summarized by treatment group. Specific adverse events will be counted once for each subject for calculating percentages. In addition, if the same adverse event occurs multiple times within a particular

subject, the highest severity and level of relationship observed will be reported. The number and percentages of participants will also be summarized by SOC and PT for participants with COVID-19 related AEs and SAEs. All treatment-emergent adverse events (TEAEs) will be summarized overall, as well as categorized by MedDRA SOC and PT. A TEAE is any new sign, symptom, disease, or other untoward medical event that begins or worsens after the first dose of investigational product up to the FU visit.

Summaries of adverse events will be presented by subjects who are COVID-19 positive or negative where a subject is COVID-19 positive if they have a TEAE in the MedDRA COVID-19 SMQ. Summaries will include TEAEs, TEAEs by MedDRA preferred term and SOC, SAEs, and adverse events of special interest (AESI).

3.6.2 Adverse Events of Special Interest

The following are AESIs have been defined in the study protocol:

- Hepatic function abnormality meeting the definition of Hy's Law (HL), which is defined as any increase in alanine transaminase (ALT) or aspartate transaminase (AST) to greater than 3 × upper limit of normal (ULN) and concurrent increase in total bilirubin (TBL) to greater than 2 × ULN.
- Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions), including 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.

AEs will be assigned to a specific category based on investigator's judgement, using a checkbox on the AE CRF page. In addition, an AESI search strategy provided by Patient Safety will also be used to identify AESIs programmatically.

Subjects who meet the following criteria will be summarized by treatment group and separate listings of subjects will be presented:

- ALT/AST > 3 × ULN and any bilirubin > 2 × ULN
- ALT/AST > 5 × ULN for more than 2 weeks
- ALT/AST > 8 × ULN

All other AESIs will be summarized by treatment group and included in separate listings. In addition, the injection site reaction AE will be summarized by the placebo groups.

3.6.3 Deaths and Treatment Discontinuations due to Adverse Events

The number and percent of subjects with deaths and treatment discontinuation due to TEAEs will be summarized by treatment group, and separate listings of subjects will be presented.

3.6.4 Clinical Laboratory Evaluation

Hematology, urinalysis and serum chemistry parameters will be assessed at baseline as well as throughout the study. These laboratory parameters and change from baseline will be summarized descriptively by treatment group and visit. Also, the laboratory measurements will be presented as the number and percentage of subjects above or below the normal range for each laboratory test and shifts from baseline relative to the normal range for each treatment group. For laboratory values reported as lower than the limit of quantification (LLOQ), a value equal to half the limit of quantification will be imputed in the summaries. For each hematology and chemistry parameters, boxplots showing the distribution of each parameter by treatment arm and visit will be provided. All laboratory parameters will be provided in the by-subject listings as reported and values outside of the normal range will be flagged.

3.6.5 Vital Signs

Vitals signs will be summarized by treatment group and visit. Change from baseline to post-dose evaluations for vital signs will be summarized in a similar way.

3.6.6 ECGs and Left Ventricular Ejection Fraction

An electrocardiogram (ECG) will be performed to confirm that MEDI3506 does not affect cardiac electrophysiological intervals.

The computerized triplicate 12-lead ECG results and QT intervals (msec) will be summarized descriptively by treatment group and visit for each of the ECG variables collected (heart rate, RR interval, QRS interval, PR interval, QT interval (using both Fridericia's correction: QTcF[msec] = QT[msec]/(RR[sec]$^{1/3}$) and Bazett's correction: QTcB[msec] =

QT[msec]/(RR[sec]$^{1/2}$))). For the triplicate 12-lead ECG, an average of 3 reads will be used. Changes from baseline will be summarized by treatment group and visit into 3 categories: increase ≤ 30 msec, 30 msec < increase ≤ 60 msec, and increase > 60 msec. Shift tables for QTc intervals (QTc ≤ 450 msec, 450 < QTc ≤ 480 msec, 480 msec < QTc ≤ 500 msec, QTc > 500 msec) will be presented to compare the baseline ECG evaluation and the post-dose evaluations. In addition, descriptive summary of qualitative ECG results by visit will be provided.

Left ventricular ejection fraction, as measured by echocardiogram, will be summarized descriptively by treatment group and visit.

3.6.7 Other safety tests

NT-proBNP results will be summarized descriptively by treatment group at each visit and change from baseline summarized for each post-baseline visit. The summary based on the number and percentage of participants above or below the normal range will be produced as well as shifts from baseline relative to the normal range. A boxplot showing the distribution of NT-proBNP by treatment arm and visit will be provided. NT-proBNP results will be provided in the by-subject listings as reported and values outside of the normal range will be flagged.

3.7 Immunogenicity

Anti-drug antibodies (ADA) in serum will be assessed at baseline prior to MEDI3506 administration, and at multiple time points post MEDI3506 administration during the treatment and follow-up period of the study. Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by, or on behalf of, AstraZeneca, using an appropriately validated bioanalytical method. Tiered analyses will be performed to include screening, confirmatory, and titer assay components. ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titre will be reported as well.

ADA detection at subject level:

- A subject is considered ADA positive if a collected sample is tested positive at any time during the study, including baseline and/or post-baseline.
- A subject is considered ADA negative if collected samples are tested negative at all timepoints, including baseline and post-baseline.

Treatment-related ADA development at subject level:

- Treatment-emergent ADA positive (TE-ADA positive) is defined as the sum of treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive) and treatment-boosted ADA positive (ADA positive at baseline and boosted (≥4 fold) the pre-existing titre during the study period).
- Treatment-emergent ADA negative (TE-ADA negative) is defined as ADA positive but not fulfilling the definition of TE-ADA positive.

The following ADA responses variables will also be evaluated:

- Participants who are ADA positive at baseline
- Participants who are ADA positive at any post-baseline visit
- Participants who are ADA positive post-baseline and positive at baseline
- Participants who are ADA positive post-baseline and not detected (or missing) at baseline
- Participants with ADA negative post-baseline and positive at baseline
- Participants who are ADA positive at any time during the study, including baseline and/or post-baseline (also generally referred to as ADA prevalence).
- Participants who are TE-ADA positive, also known as ADA incidence.
- Participants who are ADA persistently positive, defined as ADA positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or ADA positive at last post-baseline assessment.
- Participants who are ADA transiently positive, defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥ 2 post-baseline assessments (with < 16 weeks between first and last positive).

For the ADA status across the study, the number and percentage of subjects with ADA responses will be summarized together with corresponding titre summaries by treatment group, according to the ADA categories defined above. For the time-course evaluation, the number of subjects with positive ADA result and ADA titres will be summarized at baseline and at all scheduled visits by treatment group. A listing of individual ADA results of all subjects will be provided.

For ADA summaries at a single time point the corresponding titre summary will be based on the titre of the positive sample for that particular visit, but for summaries across visits, the corresponding titre summaries will be based on the maximum titre of all positive samples for each subject. All valid assay results from subjects who receive any investigational product will be included in the ADA summaries. Blood samples collected at early discontinuation visit will be summarized at the closest nominal time point that does not already have a value.

To evaluate the effect of ADA on PK, descriptive statistics of MEDI3506 concentrations over time will be presented by ADA category (TE-ADA positive, ADA negative, TE-ADA negative).

Summaries of adverse events will be presented by ADA category (TE-ADA positive, ADA negative and TE-ADA negative). Summaries will include TEAEs, TEAEs by MedDRA preferred term and SOC, SAEs, and AESI. Also, the relationship between ADA category (TE-ADA positive, ADA negative and TE-ADA negative) and the percent change from baseline in EASI will be summarized.

3.8 Pharmacokinetics

Pharmacokinetic analysis will be based on the PK analysis set. Drug concentration data for MEDI3506 for all randomized subjects will be provided. Descriptive statistics of MEDI3506 serum concentrations by treatment group and visit and also over time by ADA category (TE-ADA negative, TE-ADA positive, ADA negative) will be reported. Individual serum MEDI3506 concentration over time plots will be provided. Spaghetti plots of individual serum MEDI3506 concentrations over time by dose and by ADA category (TE-ADA negative, TE-ADA positive, ADA negative) will be provided.

4 INTERIM ANALYSIS

There is no planned interim analysis.

5 EXPLORATORY ANALYSIS FOR RESPONDER SUBGROUP IDENTIFICATION

Exploratory analysis will be conducted *post hoc* to identify subgroup of patients that may have received enhanced benefits when treated with MEDI3506 vs placebo. The analysis will be based on a list of biomarkers that will be provided by the Translational Science group before the database lock for the primary analysis of the study. A post-hoc analysis plan will be developed prior to the conduct of the analysis and it will provide more details about the methods and analysis to be conducted. The results will not be reported in the CSR, and might be reported separately from the CSR.

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7 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	11DEC2019	Initial document	Initial document
2.0	09APR2020	• Changed the number of subjects that will be randomized into each treatment arm in the study design section (section 2.2) • Updated the sample size section (2.4) • Included an additional endpoint: EDN	• To align with Protocol Amendment #3 • To align with Protocol Amendment #3 • To align with Protocol Amendment #3

		• Included a section on exploratory analysis that will be performed post hoc	• To align with Protocol Amendment #3
3.0	08JUN2022	• Removed interim analysis	• To align with Protocol Amendment #7, #8
		• Added visit window calculation and updated visit window tables	• Clarification of how to calculate visit windows
		• Updated IPD categories	• To align with other Medi3506 studies
		• Added COVID-19 PD listings and summaries	• To align with Protocol Amendment #5
		• Added additional analyses excluding unblinded subjects (sections 3.4.1.4 and 3.4.2.3)	• Sensitivity analysis for unblinded subjects
		• Corrected MCP-Mod analysis of %change in EASI with LOCF to remove MMRM	• Correction of method
		• PGI-S categories updated to 6	• To match what is being collected
		• Removed PGI-S MMRM analysis from section 3.4.2.2	• Analysis not needed (not really continuous)
		• Updated IGA and EASI 75 MCP-Mod analyses to use coefficients from logistic regression	• Correction of method
		• Appendix I- corrected IGA MCP-Mod analysis and added EASI75	• Correction of method
		• Updated biomarker section	• Scope has changed
		• Removed section 3.5.9 Responder subgroup identification	• Information is covered in section 5
		• Added equations for QTcB and QTcF	• Was missing
		• Added additional ADA categories to section 3.7	• To align with AZ process
		• Updated PK section (3.8)	• To align with AZ process
		• Changed S aureus subgroups to use median	• Data is going to be continuous
		• Added AESI search strategy in section 3.6.2	• Requested by patient safety
		• Changed screening window to 4 weeks	• To align with PA #8
		• Added Plasma EDN to baseline disease characteristic list and removed serum IgE (pos vs neg)	• Update of list
		• Updated section 3.4.1.5 to remove sentences on subgroups	• Covered in section 5 already
		• Corrected SCORAD calculation	• Correction of error
		• Added extra biomarker endpoints to be reported separately to CSR	• To align with endpoints in protocol
		• Updated clinical lab evaluation section	• To remove lab toxicities as analysis not needed
		• Added Other safety tests section to include NT-proBNP analysis	• Analysis was missing
		• Added ADA safety and efficacy tables	• To evaluate safety profile
		• Added COVID-19 pos/neg safety analysis	• To evaluate impact of COVID-19 on the safety profile

		• Removed IL-5, IL-13 and CCL17 biomarker analyses from CSR • Removed PBMC analyses from CSR • Added comorbid asthma subgroup to 3.4.1.5 and 3.4.2.4	• Data will not be available, will be reported separately to CSR • Results may be reported separately to CSR • Genetic association between IL33 and asthma is strong so might be a difference in efficacy

Appendix 1 Determination of dose-response profile using MCP-Mod

To determine dose-response profile using MCP-Mod, the candidate models first need to be defined. For this study, four candidate models will be used for the MCP-Mod models and these are: Linear, E_{max} and 2 Hill-E_{max} models. The description of the function of each model and the parameters are specified below:

- Linear Model: $f(d,\theta) = E_0 + \delta d$
- E_{max} Model: $f(d,\theta) = E_0 + E_{max}\frac{d}{ED_{50} + d}$
- Hill-E_{max} Model: $f(d,\theta) = E_0 + E_{max}\frac{d^h}{ED_{50}^h + d^h}$

where d denotes the dose parameter; E_0 is the placebo effect; δ is the slope parameter for the linear model; E_{max} is the asymptotic maximum effect; ED_{50} is the dose giving half of the asymptotic maximum effect; h is the hill parameter which determines the steepness of the model as the ED_{50}.

For the percent change from baseline to Week 16 in EASI endpoint, the models are defined as follows:

fmodels=Mods(linear = NULL, emax = 150, sigEmax = rbind(c(150,3), c(450,3)),
doses = c([redacted]), placEff=0, maxEff=35, direction = c("decreasing")).

where *maxEff* is the maximum effect over placebo.

For the percentage of subjects achieving IGA response at Week 16 endpoint, the models are defined as follows on the logit scale:

fmodels=Mods(linear = NULL, emax = 150, sigEmax = rbind(c(150,3), c(450,3)),
doses = c([redacted]), placEff=logit(10), maxEff=logit(30)-logit(10),
direction=c("increasing"))

where *logit(x)* is log(x/(1-x)).

For the percentage of subjects achieving EASI 75 response at Week 16 endpoint, the models are defined as follows:

fmodels=Mods(linear = NULL, emax = 150, sigEmax = rbind(c(150,3), c(450,3)),
doses = c([redacted]), placEff=logit(15), maxEff=logit(35)-logit(15),
direction=c("increasing")).

Once the models are defined, then the MCP-Mod analysis is performed. For the percent change from baseline to Week 16 in EASI endpoint, the MCP-Mod analysis is performed as follows:

MM=MCPMod(dose=doses, EstEffects, S= vCov, models = fmodels, type = "general",
placAdj=FALSE, Delta=35, alpha=0.1, alternative=c("two.sided")).

where

- "*doses*" denotes the vector of doses,
- "*EstEffects*" denotes the vector of estimated coefficient obtained from the MMRM,
- "*vCov*" denotes the estimated variance-covariance matrix,
- "*fmodels*" is the specified candidate models,
- "type="general" " indicates that the estimates and their covariance matrix are specified,
- "placAdj =FALSE" indicates that the estimated specified are not placebo-adjusted,
- "*Delta*" is the target effect size over placebo,
- "*alpha*" is the significance level for the multiple contrasts.

For the percentage of subjects achieving IGA response at Week 16 endpoint, the MCP-Mod analysis is performed as follows:

MM=MCPMod(dose=doses, EstEffects , S= vCov, models = fmodels, type = "general",
placAdj=FALSE, Delta=logit(30)-logit(10), alpha=0.1, alternative=c("two.sided")).

where

- "*EstEffects*" denotes the vector of estimated coefficient obtained from the fitted logistic regression model,
- "*vCov*" denotes the estimated variance-covariance matrix.
- All the other parameters are the same as those described above for the EASI endpoint.

For the percentage of subjects achieving EASI 75 response at Week 16 endpoint, the MCP-Mod analysis is performed as follows:

MM=MCPMod(dose=doses, EstEffects , S= vCov, models = fmodels, type = "general",
placAdj=FALSE, Delta=logit(35)-logit(15), alpha=0.1,
alternative=c("two.sided"))

where the parameters are the same as those described for the IGA endpoint.

The IGA and EASI 75 results are then back transformed from the logit scale to percentages.

SIGNATURE PAGE

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