STATISTICAL ANALYSIS PLAN (SAP)

NCT05121480

A PHASE 2, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-COHORT STUDY INVESTIGATING THE EFFECT OF EDP1815 IN PARTICIPANTS FOR THE TREATMENT OF MILD, MODERATE AND SEVERE ATOPIC DERMATITIS

EDP1815-207 SAP

Version 2.0 / 24 April 2022

STATISTICAL ANALYSIS PLAN

Protocol: EDP1815-207
Protocol Version: V5.0 25APR2022

A Phase 2, Multicenter, Randomised, Double-Blind, Placebo-Controlled, Multiple-Cohort Study Investigating the Effect of EDP1815 in Participants for the Treatment of Mild, Moderate and Severe Atopic Dermatitis

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2 Abbreviations and Definitions

AD	Atopic Dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	Adverse Event
ALT	Alanine Aminotransferase
APP	Application
AST	Aspartate Aminotransferase
BSA	Body Surface Area
CDMS	Clinical Data Management System
CI	Confidence Intervals
CPM	Clinical Project Manager
CRF	Case Report form
CRO	Contract Research Organization
CSR	Clinical Study Report
DBL	Data Base Lock
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
DPS	Data Point Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA/EMEA	European Medicines Agency
EASI	Eczema Area and Severity Index
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLMM	Generalised linear mixed effects model
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
LS	Least Squares Mean Estimate
MCS	Mental Component Score
mL	Millilitre
MeDDRA	Medical Dictionary for Regulatory Activities

MMRM	Mixed Model for Repeated Measures
OLE	Open Label Extension
PCS	Physical Component Score
PBMC	Peripheral blood mononuclear cell
PCI	Potentially clinically important
POEM	Patient Oriented Eczema Measure
PP-NRS	Peak Pruritus Numerical Rating Scale
RNA	Ribonucleic Acid
SD-NRS	Sleep Disturbance Numerical Rating Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCORAD	Severity Scoring of Atopic Dermatitis (SCORing Atopic Dermatitis)
SF-12	12-Item Short Form Health Survey
SLS	Sodium Lauryl Sulfate
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
TLR	Top level results
TMF	Trial Master File
ULN	Upper Limit of Normal
vIGA	Validated Investigator Global Assessment
WGS	Whole Genome Sequencing
WHODD	World Health Organization Drug Dictionary
WOCBP	Woman of Child-Bearing Potential

3 Introduction

The purpose of this SAP is to provide all information that is necessary to perform the required statistical analyses of study EDP1815-207. It also defines the tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol. The SAP is based upon, and assumes familiarity, with the study protocol, version 5.0, dated 25-Apr-2022. The separate SAP addendum covers additional details related to the analysis of the cohort 4 efficacy data. The cohort 4 efficacy tables and figures to be included in the CSR are included in the SAP addendum.

Changes to the analyses described in the protocol are summarized in Section 13.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. The content of this SAP is compatible with the ICH E9 Guidance document.

4 Study Objectives and Endpoints

4.1 Study Objectives

The primary objective of the study is:

- To show superiority of EDP1815 over placebo in the proportion of participants achieving at least a 50% reduction in Eczema Area and Severity Index (EASI) score (EASI-50) in the absence of rescue medication for 28 days and in the absence of prohibited medications at any time.

The secondary objectives of the study are:

- To evaluate the clinical benefit of EDP1815 in the treatment of atopic dermatitis.
- To evaluate the safety and tolerability of EDP1815.

The exploratory objectives of the study are:

- To evaluate the time to onset of clinical response to EDP1815.
- To evaluate the most effective dose and dosing frequency of EDP1815 in the treatment of atopic dermatitis.
- To evaluate the effect of EDP1815 on patient reported outcomes.
- To evaluate the effect of early use of rescue therapy on Week 16 responder status.
- To evaluate the relationship of EDP1815 treatment with biomarkers such as immune protein markers, eosinophils, and immune cell RNA profile in blood.
- To evaluate correlation of genetic markers and EDP1815 treatment outcomes.
- To evaluate correlation of gut microbiome and EDP1815 treatment outcomes.

4.2 Endpoints

The primary efficacy endpoint for the study is:

- Achievement of an EASI-50 response at Week 16.

The secondary efficacy endpoints for the study will be evaluated at Weeks 4, 8, 12 and 16 (unless otherwise specified) and are:

- Percentage of participants achieving EASI-50 at Weeks 4, 8 and 12.
- Percentage of participants achieving EASI-75.
- Percentage of participants achieving EASI-90.
- Mean absolute change and percentage change from baseline in EASI Score.
- Percentage of participants achieving Validated Investigator's Global Assessment (vIGA) of 0 or 1 with a ≥2-point improvement from baseline.
- Percentage of participants achieving vIGA of 0 or 1.
- Percentage of participants achieving vIGA of 0 at Week 16.
- Mean absolute change and percentage change from baseline in vIGA*BSA (BSA=body surface area).
- Mean absolute change and percentage change from baseline in BSA.
- Percentage of participants achieving BSA-50.
- Percentage of participants achieving BSA-75.
- Percentage of participants achieving BSA reduction to 3% BSA or less.
- Mean absolute change and percentage change from baseline in SCORing Atopic Dermatitis (SCORAD) score.
- Percentage of participants achieving SCORAD-35.
- Percentage of participants achieving SCORAD-50.
- Percentage of participants achieving SCORAD-75.
- Mean absolute change and percentage change from baseline in Dermatology Life Quality Index (DLQI) score.
- Percentage of Participants achieving a reduction of ≥4 in the DLQI score, of those with a score of ≥4 at baseline at Week 16.
- Mean absolute change from baseline in Peak Pruritus Numerical Rating Scale (PP-NRS) score.
- Percentage of participants achieving a reduction of ≥2 in the PP-NRS, of those with a score of ≥2 at baseline.
- Percentage of participants achieving a reduction of ≥4 in the PP-NRS, of those with a score of ≥4 at baseline at Week 16.
- Mean absolute change from baseline in Sleep Disturbance Rating Scale (SD-NRS) score.
- Percentage of participants achieving a reduction of ≥2 in SD-NRS score, of those with a score of ≥2 at baseline at Week 16.
- Mean absolute change and percentage change from baseline in Patient Oriented Eczema Measure (POEM) score.
- Percentage of participants achieving a reduction of ≥4 in the POEM score, of those with a score of ≥4 at baseline at Week 16.
- Number of courses of TCS/TCI rescue therapy per participant in Weeks 1-8, 9-16 and for Weeks 1-16.
- Number of days of treatment with TCS/TCI rescue therapy per participant in Weeks 1-4, 5-8, 9-12 and 13-16 and for Weeks 1-16.
- Proportion of participants requiring TCS/TCI rescue therapy in Weeks 1-4, 5-8, 9-12 and 13-16 and for Weeks 1-16.

The secondary safety endpoints for the study are:

- Adverse events and serious adverse events.
- Change from baseline in vital signs.
- Change from baseline in ECG parameters.
- Change from baseline in clinical laboratory parameters.
- Change from baseline in physical examination findings.
- Worst-case change from baseline with respect to potentially clinical important criteria for vital signs, QTcF and clinical laboratory parameters.
- Worst-case change from baseline with respect to values outside the normal ranges for clinical laboratory parameters.

Exploratory endpoints to evaluate the time to onset of clinical response are:

- Time to first achievement of EASI-50.
- Time to first achievement of sustained EASI-50.
- Time to first achievement of EASI-75,
- Time to first achievement of vIGA of 0 or 1 with a 2-point improvement from baseline.
- Time to first achievement of vIGA of 0 or 1.
- Time to first achievement of a ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline.
- Time in days to first sustained ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline.
- Time to first achievement of a ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline.
- Time in days to first sustained ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline.
- Time to first achievement of a ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline.
- Time in days to first sustained ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline.

Exploratory endpoints to evaluate the effect of early use of topical corticosteroid rescue therapy on Week 16 responder status are defined in the following subgroups: the subgroup of participants with no rescue use at any time before Week 16 will be compared to subgroups of participants with rescue therapy use within only the first 4, 8, 12 and 14 weeks of treatment and to participants with rescue therapy use within the 2 weeks and 4 weeks prior to the Week 16 visit. For these subgroups, the following endpoints will be summarized:

- Percentage of participants achieving EASI-50, EASI-75 and EASI-90
- Percentage of participants achieving IGA 0 or 1, with and without a 2-point improvement from baseline
- Percentage of participants achieving BSA-50, and BSA-75

Other exploratory endpoints will be evaluated at Weeks 2, 4, 8, 12 and 16 (unless otherwise specified) and are:

- Percentage of participants achieving vIGA of 0 or 1 with a ≥2 Point Improvement from screening.

- Mean absolute change and percentage change from Screening in EASI Score.
- Percentage of participants requiring topical antimicrobial or systemic antibiotic treatment for skin infections by Week 16.
- Changes from baseline in SF-12 Mental Component Score (MCS) and Physical Component Score (PCS) at Weeks 4, 12 and 16.
- Changes from baseline in HADS anxiety and depression scores at Weeks 4, 12 and 16.
- Changes from baseline in ADCT scores at Weeks 4, 12 and 16.
- Daily changes from baseline in the PP-NRS and SD-NRS (Timescale: Days 2 to 140).
- Percentage of participants achieving a reduction of ≥2, ≥4 in the PP-NRS, of those with a score of ≥2, ≥4 at baseline daily from Day 2 to 112.
- Percentage of participants achieving a reduction of ≥2 in SD-NRS score, of those with a score of ≥2 at baseline daily from Day 2 to 112.

Note that analyses of the other exploratory endpoints including the following biomarkers exploratory endpoints will be addressed in a separate analysis plan and will not be further discussed in this document:

- Changes from baseline in eosinophils at Weeks 2, 16 and 20.
- Changes from baseline in serum immune protein markers including IgE at Week 16.
- Changes from baseline in immune cell RNA profile at Weeks 2, 16 and 20.

5 Study Methods

5.1 General Study Design and Plan

This is a randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of EDP1815 as compared to placebo in participants with mild, moderate and severe atopic dermatitis.

Cohorts 1, 2 & 3 will be run concurrently, and Cohort 4 recruitment will commence after enrollment for Cohorts 1, 2, & 3 are completed. During the Cohorts 1, 2, & 3 enrollement after eligibility is confirmed during the screening period (Protocol Sections 5.1 and 5.2), participants will be randomly assigned in a 1:1:1 ratio to 1 of the cohorts 1, 2 or 3. Once recruitment to first three cohorts is completed all participants will enrol cohort 4:

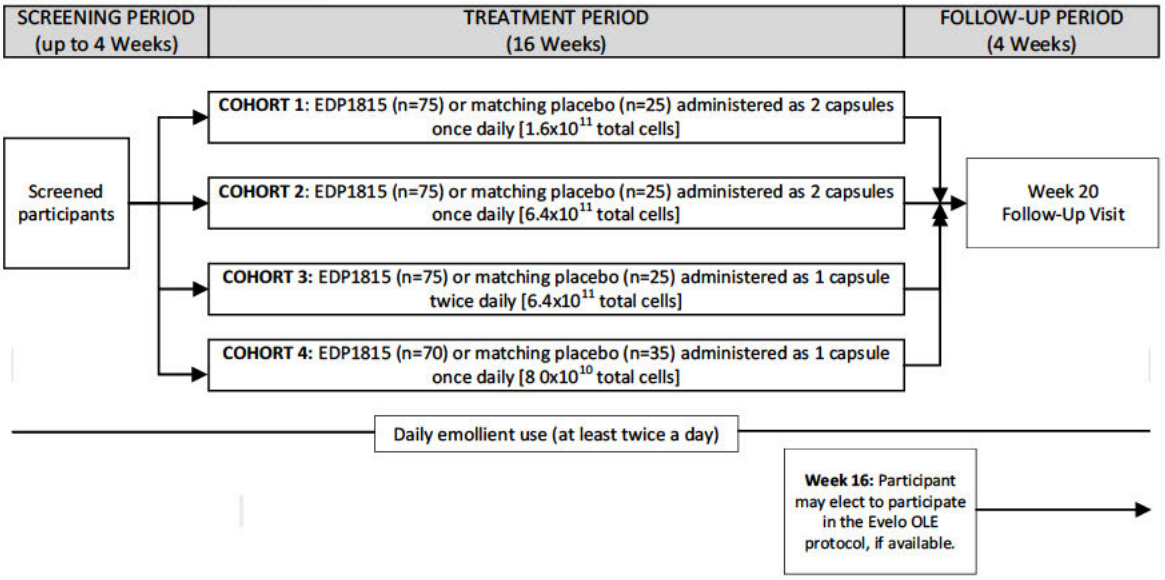
- **Cohort 1**: $1.6x10^{11}$ total cells of EDP1815 or matching placebo administered as 2 capsules once daily.
- **Cohort 2**: $6.4x10^{11}$ total cells of EDP1815 or matching placebo administered as 2 capsules once daily.
- **Cohort 3**: $6.4x10^{11}$ total cells of EDP1815 or matching placebo administered as 1 capsule of $3.2x10^{11}$ cells twice daily.
- **Cohort 4**: $8.0x10^{10}$ total cells of EDP1815 or matching placebo administered as 1 capsule once daily.

Participants in Cohorts 1, 2, & 3 will be randomised in a 3:1 ratio (approximately 75 to EDP1815 and 25 to placebo within each cohort, 300 in total). Participants in Cohort 4 will be randomised in a 2:1

ratio (approximately 70 to EDP1815: 35 to placebo, 105 in total). So approximately 405 participants will be randomised in total.

As shown in Figure 1, the study comprises a screening period of up to 4 weeks, a treatment period of 16 weeks, and a 4-week post-treatment follow-up period, which results in a maximum study duration of up to 24 weeks. Should a participant elect to participate in an Open Label Extension (OLE) protocol for EDP1815, the follow-up period will be skipped, and the study duration would be a maximum of 20 weeks.

Figure 1 Study Schema



An interim analysis may be undertaken prior to the end of recruitment in cohorts 1-3. The purpose of this interim analysis is to check that the treatment groups have remained balanced and that the use of stratified randomisation has not led to issues caused by multiple incomplete blocks of randomisation. A separate interim analysis process plan is available which provides all relevant details.

5.2 Randomisation and Blinding

Cohorts 1, 2 & 3

At the baseline visit (Visit 2), participants will be randomly allocated, in a 1:1:1 ratio to one of the three cohorts. Within the cohort, participants will then be randomly assigned in a 3:1 allocation ratio to receive either EDP1815 or matching placebo treatment. The randomisation schedule will be stratified by vIGA at Day 1 to ensure that the cohorts and treatment groups within cohort are balanced with respect to disease severity.

Cohort 4

Participants will be randomly assigned in a 2:1 ratio to receive either EDP1815 or matching placebo treatment. The randomisation schedule will also be stratified by vIGA at Day 1. In order to match as closely as possible the severity of Cohorts 1, 2 & 3. Cohort 4 may also limit the numbers of

participants recruited to each strata to match the proportions of each vIGA strata in Cohorts 1, 2 & 3.

Interactive response technology (IRT) will be used for assigning eligible participants to a treatment regimen (cohort and treatment within cohort) based on a predetermined production randomisation and/or packaging schedule.

The allocation to cohort is not blinded, however, treatment allocation within cohort will be fully blinded to participants, study staff and the sponsor with the exception of the personnel supporting the IRT system, the independent randomisation team, the clinical supplies team, the clinical safety team at [redacted], and an unblinded team within [redacted] who will produce the interim analysis but have no other involvement in the reporting of the study.

A participant's treatment assignment will not be unblinded for the investigator or study site staff until EOS unless medical treatment of the participant depends on knowing the study treatment the participant received. Participants who are unblinded will be allowed to continue their participation in the study; however, the impact of unblinding will be assessed in the supplementary analysis where EDPS5 is used.

Cohorts 1-3 data may be unblinded before the end of the study, after the cohorts 1-3 database lock (DBL) which will occur once all cohorts 1-3 participants have completed 4 weeks of post-treatment follow-up (Week 20 or Early Termination Visit) or entered the OLE study. Cohort 4 data will be unblinded at the end of study.

5.3 Derived variables

5.3.1 General

5.3.1.1 Relative Day and Time

The relative day of an assessment will be calculated as:

- For measurement performed on or after the date of first dose:
  Date of assessment – date of start of treatment +1

- For measurements performed before the date of first dose:
  Date of assessment – date of start of treatment

5.3.1.2 Baseline

The last non-missing value collected before first study dose will be taken as the baseline measurement for all parameters collected at scheduled visits. If data is collected on Day 1 it will be assumed to be pre-dose regardless of an associated time.

For the daily endpoints baseline will be taken as average of the 7 days before Day 1 (including Day 1 assessment) and will be calculated if there will be at least 4 non-missing values.

5.3.1.3 Change and Percentage Change from Baseline

Change from baseline will be calculated as:

change from baseline = value at timepoint – baseline value

Change from baseline will be presented to the same level of precision as the original value in the listings.

Percentage change from baseline will be calculated as:

percentage change from baseline = 100*(change from baseline / baseline value)

Percentage change from baseline will be presented to 1 decimal place (dp) in the listings.

5.3.2 Demographic and Background Data

Height may be recorded in cm or inches. Height in inches will be converted to height in cm as follows:

Height (cm) = Height (inches)*0.3937

Height (cm) will be presented to 1 dp in the listings.

Weight may be recorded in kg or pounds. Weight in pounds will be converted to weight in kg as follows:

Weight (kg) = Weight (pounds) * 0.4536

Weight (kg) will be presented to 1 dp in the listings.

Body mass index (BMI) will be calculated as:

BMI (kg/m^2) = Weight (kg) / [height (cm)/100]^2

BMI (kg/m^2) will be presented to 1 dp in the listings.

BMI will also be categorised as:

- ≥30 kg/m2
- <30 kg/m2

5.3.2.1 Study Drug Compliance

Participants in cohorts 1 and 2 will be expected to dose once daily with 2 capsules per dose (2 capsules per day); in cohort 3 – twice daily with 1 capsule (2 capsules per day).

Compliance will be calculated across the whole treatment period.

Compliance calculation will be based on the daily diary and drug accountability data.

Expected capsules

Expected capsules for the treatment period will be calculated as:

Expected capsules = 2*(End date of treatment period – Start date of treatment period + 1).

End date of treatment period = Date of the last dose of study drug.
Start date of treatment period = Day 1.

Actual capsules taken

Actual capsules taken will be calculated from the dosing diary using entries between the start and end days inclusively and drug accountability data.

Dosing diary number of capsules definitely not taken will be calculated as:

Number of capsules not taken from dosing diary days where participant specifically chose the answer 'did not take dose' or 'took some of dose'.

Drug accountability number of capsules definitely not taken will be calculated as:

Expected capsules – (Number of capsules dispensed* – Number of capsules returned*)

* Through the whole treatment period.

Actual capsules taken will be then calculated as:

Actual capsules taken = Expected capsules – max(Dosing diary number of capsules definitely not taken, Drug accountability number of capsules definitely not taken)

Study drug compliance

Study drug compliance will be calculated as:

Study drug compliance (%) = 100*Actual capsules taken/Expected capsules taken.

Study drug compliance will also be categorised as:

- <75%
- ≥75%

5.3.2.2 Emollient Compliance

All participants must use an emollient twice daily for at least 14 consecutive days immediately prior to randomisation and should continue the background emollient treatment twice daily until the the end of the study.

Compliance will be calculated across the whole treatment period.

Expected number of applications for the treatment period will be calculated as:

Expected number of applications = 2*(End date of period – Start date of period +1).

End date of period = End of study treatment day.
Start date of period = Day 1.

Actual number of applications will be calculated from the emollient usage diary using entries between the start and end days inclusively. In case of more than two applications per day participant will be considered compliant for that day and only two applications will be considered for compliance calculation.

Emollient compliance will be calculated as:

Emollient compliance (%) = 100*Actual number of applications/Expected number of applications.

Emollient compliance will also be categorised as:

- <75%
- ≥75%

5.3.2.3 Prohibited Concomitant Medications

The following medications are not allowed at any point during the study:

- Live (attenuated) vaccinations (a non-replicating / non-live vaccine when the first dose of IMP was not taken within a 7-day window of the administration of vaccine is allowed).

Type 1 prohibited medications are prohibited concomitant medications which may affect efficacy requiring the concomitant medication to be immediately discontinued where possible once the use is discovered. If the prohibited medication cannot be discontinued for any reason, then the IMP should be discontinued:

- Emollients containing additives including SLS.
- Topical Corticosteroids (TCS) or Topical Calcineurin Inhibitors (TCI) (unless considered a rescue therapy).
- Topical PDE-4 Inhibitors.
- Bleach baths.
- Tanning beds.
- Leukotriene Receptor Antagonists.
- Allergen Immunotherapy.

Type 2 prohibited medications are prohibited concomitant medications which may affect efficacy requiring IMP discontinuation:

- Phototherapy treatment
- Systemic treatments that may lead to clinical improvements in atopic dermatitis, e.g., oral or injectable corticosteroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, JAK-inhibitors, biologic therapy, and other systemic immunosuppressive therapy (note single dose intra-articular or intra-lesional corticosteroid therapy is permitted).

If a prohibited medication is found to have been used, this will be captured into the protocol deviations log.

Prohibited medications will be identified by the sponsor in a separate spreadsheet.
Any medications taken during the study and classified as type 1 prohibited medications in the spreadsheet will be considered as type 1 prohibited medications with exception for

1. Medications which stopped at least 14 days before Day 1
2. Medications which started strictly before screening and carried on throughout study to week 16
3. Medications which are emollients and started on or after screening, but before Day 1
4. Medications which are emollients and started before screening and stopped before Day 1

Any medications taken during the study and classified as type 2 prohibited medications in the spreadsheet will be considered as type 2 prohibited medications with exception for medications which stopped at least 14 days before Day 1.

5.3.3 Efficacy

5.3.3.1 General

Participants who used permitted rescue therapy less than 28 days before Week 16 or discontinued study due to treatment related reason should be considered as non-responder in the primary estimand for the primary endpoint.

5.3.3.2 Eczema Area and Severity Index (EASI)

The Eczema Area and Severity Index (EASI) will be calculated within the [redacted] system and taken directly from the supplied data. EASI score ranges from 0 to 72. Further information on the scoring of the EASI is provided in Section 16.

EASI -50, EASI -75 and EASI -90 responses are defined respectively by at least a 50%, 75% and 90% decrease from Baseline in the EASI score.

Sustained EASI-50 response is defined as one which is present on at least two consecutive visits. The sustained response is considered to have been first achieved at the first of the consecutive visits.

5.3.3.3 The Percent of Body Surface Area Involvement (BSA)

The Body Surface Area (BSA) will be calculated as part of EASI score in the [redacted] system and taken directly from the supplied data. The percent of BSA involvement will be estimated for each participant, where 1% is approximately the area of the participant's handprint.

BSA-50 and BSA-75 responses are defined respectively by at least a 50% and 75% reduction from Baseline in the BSA.

5.3.3.4 Validated Investigator's Global Assessment (vIGA)

The Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA) will be calculated within the [redacted] system and taken directly from the supplied data. There is a standardised grading system based on an overall assessment of the degree of erythema, papulation/induration, lichenification, and oozing/crusting. In indeterminate cases, extent will be used to differentiate between scores - but otherwise extent is not used in the scoring system. The vIGA score ranges from 0 to 4.

5.3.3.5 SCORing Atopic Dermatitis (SCORAD)

The SCORing Atopic Dermatitis (SCORAD) will be calculated within the [redacted] system and taken directly from the supplied data. There is an investigator-rated area score which uses the rule of

nines to assess disease extent, and a disease intensity score comprising erythema, swelling, oozing/crusting, excoriation, lichenification, and dryness. Additionally, there is a subjective symptoms component which considers itch and sleeplessness scored using a visual analogue scale. These scores combine to give a SCORAD score between 0 and 103.

SCORAD-35, SCORAD-50 and SCORAD-75 responses are defined respectively by at least a 35%, 50% and 75% reduction from Baseline in the SCORAD score.

5.3.3.6 Patient Oriented Eczema Measure (POEM)

The Patient Oriented Eczema Measure (POEM) will be calculated within the [redacted] system and taken directly from the supplied data. It includes a series of 7 questions, measuring itch, sleep, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness over the last week, and is scored by the participant. Each of the 7 questions is scored from 0 (no days) to 4 (every day), giving a POEM score range from 0 to 28, with higher scores representing higher disease severity.

POEM response is defined as a reduction of ≥4 in the POEM score if a participant has a score of ≥4 at baseline.

5.3.3.7 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item questionnaire with each item scored from 0 to 3.

The DLQI score is the sum of the 10 individual items and ranges from 0 to 30, with higher scores indicating greater impairment of quality of life. Further information on the scoring of the DLQI is provided in Section 20.

DLQI response is defined as a reduction of ≥4 in the DLQI score if a participant has a score of ≥4 at baseline (a 4-point change from baseline is considered the minimal clinically important difference threshold).

5.3.3.8 Peak Pruritus Numerical Rating Scale (PP-NRS)

The Peak Pruritus Numerical Rating Scale (PP-NRS) is a scale from 0 to 10 for participants to rate their worst itch that they have experienced over the previous 24 hours. The PP-NRS will be completed as a part of daily symptom diary from the Screening Visit to end of study.

PP-NRS score at each visit is calculated as the mean itch daily score for the 7 days prior to and including the visit date. At least 4 daily scores must be available for the score at the relevant visit to be considered evaluable.

PP-NRS responses are defined as a reduction of ≥2 and ≥4 in the PP-NRS score if a participant has a score of ≥2 and ≥4, respectively, at baseline (a ≥2-4-point change from baseline is considered the minimal clinically important difference threshold).

Sustained PP-NRS response is defined as one which is present at all available assessments within at least 14 days period. Sustained response is considered to have been first achieved at the first of the consecutive days.

5.3.3.9 Sleep Disturbance Numerical Rating Scale (SD-NRS)

The Sleep Disturbance Numerical Rating Scale (SD-NRS) is a scale from 0 to 10 for participants to rate their worst sleep that they have experienced over the previous 24 hours. The SD-NRS will be completed as a part of daily symptom diary from the Screening Visit to end of study.

SD-NRS score at each visit is calculated as the mean sleep daily score for the 7 days prior to and including the visit date. At least 4 daily scores must be available for the score at the relevant visit to be considered evaluable.

SD-NRS response is defined as a reduction of ≥2 in the SD-NRS score if a participant has a score of ≥2 at baseline (a 2-point change from baseline is considered the minimal clinically important difference threshold).

Sustained SD-NRS response is defined as one which is present at all available assessments within at least 14 days period. Sustained response is considered to have been first achieved at the first of the consecutive days.

5.3.3.10 Time to First Achievement of Daily Time-to-Event Endpoints

The daily time-to-event endpoints are based on a daily questionnaire and include:

- Time to first achievement of a ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline
- Time to first achievement of a sustained ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline
- Time to first achievement of a ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline
- Time to first achievement of a sustained ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline
- Time to first achievement of a ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline
- Time to first achievement of a sustained ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline

Time to event is defined as the time in days from the first dose of study drug until the date when event occurred.

Participants who complete the study up to Week 16 visit without experiencing the relevant event will be censored on the date of Week 16 visit. Participants who prematurely withdraw from the study before Week 16 without experiencing the relevant event will be censored on the date of treatment discontinuation.

For sustained response endpoints censoring rules are adjusted to consider that sustained response cannot be achieved less than 14 days before the end of the relevant period. Therefore, participants who complete 16 weeks of study or prematurely withdraw from the study without experiencing the relevant event will be censored 14 days before the date of Week 16 visit/withdrawal, if before Week 16.

Time to the relevant event will be calculated as:

Time to event (days) = Date of event/censoring – date of the first study drug (Day 1) +1

5.3.3.11 12-Item Short Form Health Survey (SF-12)

The 12-Item Short Form Health Survey (SF-12) is a PRO instrument consisting of twelve questions used to measure non-disease related outcomes in 8 health domains, including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social functioning, and mental health. The score (ranging from 0 to 100) is presented in two components: a mental composite scale (MCS) and physical composite scale (PCS). The higher the score, the better the physical and mental health functioning.

5.3.3.12 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a PRO instrument used to measure anxiety and depression over the past week. It is comprised of 7 questions for anxiety and 7 questions for depression and each are scored using a 4-point Likert scale (e.g., 0-3). Scores for each domain therefore, range from 0-21, where 8-10 is mild, 11-14 is moderate and 15-21 is severe anxiety or depression.

5.3.3.13 Atopic Dermatitis Control Tool (ADCT)

The Atopic Dermatitis Control Tool (ADCT) is a 6-question PRO instrument used to detect change of disease activity in a person over time. There are six main areas that assess the multi-dimensional aspects of disease control over the course of a week, scored between 0-4. ADCT scores range from a minimum score of 0 and a maximum score of 24. A higher score indicates lower AD control.

5.3.3.14 Rescue Therapy

Rescue therapy use is allowed throughout the entire study: selected topical corticosteroids and calcineurin inhibitors systemic antimicrobials and topical antibacterial may be prescribed. An unscheduled visit will be performed to collect skin assessments prior to administering any rescue therapy, if needed.

Rescue therapy use will be documented as concomitant medication once prescribed and in a daily symptom diary during the whole course. Each rescue therapy course will be recorded in concomitant medication CRF separately, resulting in a one record in a concomitant medication dataset for each course.

Any medications taken during the study and classified as TCS/TCI rescue therapy medications in the sponsor provided spreadsheet with total course duration no more than 8 days (adjusted for dosing

frequency – only days with planned medication usage are counted in course duration) will be considered as rescue therapy with exception for medications which stopped at least 14 days before Day 1 – these cannot be rescue therapy.

For the number of courses of TCS/TCI rescue therapy in Weeks 1-4, 5-8, 9-12, 13-16, course will only be counted at the start day of course. If the rescue therapy course starts in one period and continues to the next period it will be counted only in the first period where the start of the course belongs. The number of courses of rescue therapy will be also evaluated for the whole period of Weeks 1-16.

For the same periods, rescue therapy use will be evaluated. In case of rescue therapy course overlap with the period, the participant will be considered as those who used rescue therapy in this period.

The number of days requiring TCS/TCI rescue therapy in Weeks 1-8, 9-16, 1-16 will be calculated as:

Number of days requiring rescue therapy (days) = min(therapy stop date, the end of the period date) – max(therapy start date, the start of the period date) + 1

In case of multiple rescue therapy medications concurrently, the day still will be counted only once.

5.3.4 Safety

5.3.4.1 Duration of Exposure

The duration of exposure will be calculated as

Duration of exposure (days) = Treatment stop date – Treatment start date + 1

5.3.4.2 Treatment-Emergent Adverse Events

An adverse event (AE) will be classified as 'treatment-emergent' if the onset date/time was on or after the start date/time of study treatment. Where dates or times are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates/times, see Section 7.3.1) to suggest that the AE started prior to dosing.

AEs will be classified into the following study phases based on the onset date/time of the AE after any imputations:

- Pre-Treatment Phase: All AEs with onset date/time prior to the first dose of randomised study treatment
- Treatment Phase: All AEs with onset date/time at the time of or after the first dose of randomised study treatment (Day 1) up to and including the date of the last dose of treatment received.
- Follow-up Phase: All AEs with onset date after the date of the last dose of treatment received.

For participants who complete 16 weeks of dosing per protocol, the Treatment Phase will be from Day 1 to the Week 16 visit, and the Follow-up Phase will start after the Treatment Phase and last until their last day in the study. In all cases the day will be assumed to start at 00:00 hours and end at 23:59 hours. Adverse events occurring in both the Treatment Phase and Follow-up Phase are classified as treatment emergent.

The onset phase of all AEs will be included in the relevant data listings.

6 Sample Size

Cohorts 1-3

The sample size was calculated using the assumption that data from the placebo participants in the three cohorts can be pooled prior to comparison with the EDP1815 treatment groups. No adjustments for multiple testing have been made.

The primary efficacy endpoint is the achievement of EASI-50 at Week 16. The pooled placebo response rate is estimated to be approximately 25% and a doubling of this to 50% for EDP1815 would be considered as clinically meaningful.

Using a two-sided test at the 5% level of significance, 58 participants in each treatment group would give 80% power to detect a difference in one of the EDP1815 cohorts compared to the pooled placebo group. There would also be more than 90% power to compare the pooled EDP1815 group to the pooled placebo group.

Under the assumption of a 20% drop-out of participants prior to Week 16 this will require a total of at least 73 participants to be enrolled in each treatment group. In order to allow for the 3:1 randomisation in each cohort this has been adjusted to 75 participants per treatment group to give a total of 300 participants recruited. With 75 EDP1815 participants and 25 placebo participants in each of the three cohorts.

Cohort 4

Using the same assumptions relating to the placebo rate, clinically meaningful difference, significance level, and drop-out rate as above for Cohorts 1-3, approximately 70 participants are required in each of the EDP1815 $8.0x10^{10}$ and Cohort 4 Matched Placebo groups to provide approximately 80% power in detecting a difference between EDP1815 and placebo in Cohort 4.

In order to allow 50% of the placebo control group to be concurrent controls and 50% to be historic matched controls from Cohorts 1-3, a 2:1 randomization will be used to enroll 70 EDP1815 $8.0x10^{10}$ subjects and 35 placebo participants to Cohort 4.

If sensitivity analyses indicate that pooling of the Cohort 4 placebo group with the Cohort 1-3 matched placebo data is inappropriate, then the power of the comparison between the Cohort 4 EDP1815 and placebo groups is approximately 65% if only Cohort 4 placebo participants could be used in the treatment comparisons.

7 General Considerations

7.1 Analysis Populations

7.1.1 Participant Analysis Populations

7.1.1.1 Enrolled Population

The enrolled set will consist of all participants who sign the ICF.

7.1.1.2 Full Analysis Population

The full analysis population will consist of all participants who were randomised to treatment.

All analyses using the full analysis population will group participants according to randomised treatment.

7.1.1.3 Safety Population

The safety population will consist of all participants who received any study drug.

All analyses using the safety population will group participants according to actual treatment received. If participants received multiple treatment during the study, they will be assigned to treatment group in the following manner:

- If participant received both active EDP and placebo treatments, they will be assigned to the active treatment group.
- If participant received 2 or more different active dose levels, they will be assigned to the highest dose they received.

7.1.2 Defined Data Point Sets

Efficacy data point sets 1-6 were designed to replicate the corresponding primary endpoint estimands intercurrent event strategies:

- EDPS1 corresponds to primary estimand 1.
- EDPS2 corresponds to supplementary estimand 1.
- EDPS3 corresponds to supplementary estimand 2.
- EDPS4 corresponds to supplementary estimand 3.
- EDPS5 corresponds to supplementary estimand 4.
- EDPS6 corresponds to supplementary estimand 5.

The following definitions and computational methods applied to the data point sets:

* TCS/TCI rescue therapy – is the rescue therapy when topical corticosteroid or calcineurin inhibitors medication was prescribed. Rescue therapy is reported in both the CRF and patient diary. For the analysis purposes rescue therapy recorded on CRF page will be used.

Multiple periods with rescue therapy are allowed during the study. All periods with rescue therapy are considered in EDPS definitions.

** Study withdrawal reasons related to study medication are lack of efficacy, treatment failure, adverse event (if related). Also, withdrawal of consent may be considered related to study medication based on the clarification text provided, that will be assessed by the Evelo team and provided in a separate spreadsheet. Type 2 prohibited medication will be considered as treatment withdrawal due to related reason at the date of medication start. Non-related reasons are all other reasons.

[1]Last off-rescue observation is defined as the last off-rescue observation in the period before the corresponding intercurrent event plus early termination visit in case of early study discontinuation (off-rescue is defined as data collected at least 28 days after use of rescue medication or type 1 prohibited medication).

Categorization of all concomitant medications prescribed during the study will be done by Evelo clinician in order to identify TCS/TCI rescue therapy, antimicrobial rescue therapy and prohibited medications of type 1 and 2.

7.1.2.1 Efficacy Data Point Set 1 (EDPS1)

EDPS1 consists of all data collected at a scheduled timepoint that is at least 28 days after use of TCS/TCI rescue therapy* or type 1 prohibited medication and before use of type 2 prohibited medication. Data collected less than 28 days after such use or data missing due to withdrawal from the study for reasons considered related to study medication** or data collected after use of type 2 prohibited medications will be replaced as follows:

- Continuous endpoints: value will be imputed with the last off-rescue[1] observation in the period before the event plus early termination visit in case of early study discontinuation (off-rescue is defined as data collected at least 28 days after use of rescue medication or type 1 prohibited medication)
- Responder endpoints: value will be imputed as non-response.
- Count endpoints: N/A (no count endpoint will use this DPS).

Data missing for other reasons, including early withdrawal from the study due to reasons not considered related to study medication will not be replaced and will be considered as missing.

Example 1: if patient completed 16 weeks of study with rescue therapy during week 3 and then during week 10 then responder endpoints will be analysed as shown in table:

Week 0	Week 2	Week 4	Week 8	Week 12	Week 16
As collected	As collected	Imputed as non-responder *because there was a rescue therapy within 28 days before Week 4 visit*	As collected	Imputed as non-responder *because there was a rescue therapy within 28 days before Week 12 visit*	As collected

Example 2: if patient completed 16 weeks of study with rescue therapy from Day 25 to Day 31 then responder endpoints will be analysed as shown in table:

Week 0	Week 2	Week 4	Week 8	Week 12	Week 16
As collected	As collected	Imputed as non-responder *because there was a rescue therapy within 28 days before Week 4 visit*	Imputed as non-responder *because there was a rescue therapy within 28 days before Week 4 visit*	As collected	As collected

Example 3: if patient withdrew study early due to the lack of efficacy after 12 weeks of treatment with rescue therapy during week 3 (unscheduled rescue therapy visit was not done) and then during week 10 (unscheduled rescue therapy visit was done at Week 9 prior to the rescue therapy start) then continuous endpoints will be analysed as shown in table:

Week 0	Week 2	Week 4	Week 8	Week 12	Week 16
As collected	As collected	Imputed with Week 2 data *because there was a rescue therapy within 28 days before Week 4 visit and the last off-rescue data is at Week 2 visit*	As collected	Imputed with Week 9 data *because there was a rescue therapy within 28 days before Week 12 visit and the last off-rescue data is at unscheduled Week 9 visit*	Imputed with Week 9 data *because visit is missing due to reasons considered related to study medication and the last off-rescue data is at unscheduled Week 9 visit*

7.1.2.2 Efficacy Data Point Set 2 (EDPS2)

EDPS2 consists of all data collected at a scheduled timepoint that is at least 28 days after use of TCS/TCI rescue therapy* or type 1 prohibited medication and before use of type 2 prohibited medication. Data collected less than 28 days after such use will be considered as missing and excluded from the analysis. Data missing due to withdrawal from the study for reasons considered related to study medication** and data after use of type 2 prohibited medication will be imputed as per EDPS1. Data missing for other reasons will not be replaced.

7.1.2.3 Efficacy Data Point Set 3 (EDPS3)

EDPS3 consists of EASI-50 responses collected at Week 16 that were evaluated at least 14 days after use of TCS/TCI rescue therapy* or type 1 prohibited medication and before use of type 2 prohibited medication. Data collected less than 14 days after such use or missing due to withdrawal from the study for reasons considered related to study medication** or data after use of type 2 prohibited medication will be imputed as non-response.

EASI-50 response missing for other reasons, including early withdrawal from the study due to reasons not considered related to study medication will not be replaced and will be considered as missing.

7.1.2.4 Efficacy Data Point Set 4 (EDPS4)

EDPS4 consists of EASI-50 responses collected at Week 16 that were evaluated at least 28 days after use of TCS/TCI rescue therapy* or type 1 prohibited medication and before use of type 2 prohibited medication. Data collected less than 28 days after such use will be replaced as per EDPS1. Data missing due to other reasons including early withdrawal from the study for any reason will not be replaced and be considered as missing. Data after use of type 2 prohibited medication will be considered missing.

7.1.2.5 Efficacy Data Point Set 5 (EDPS5)

EDPS5 is a subset of EDPS1 for the EASI-50 response data only, excluding any data collected or imputed after the unblinding of a participant or other protocol deviations affecting efficacy (whichever occurs first) and excluding all data from subjects who take <75% of expected doses (Section 5.3.2.1) or whose compliance with emollient use was <75% (Section 5.3.2.2).

7.1.2.6 Efficacy Data Point Set 6 (EDPS6)

EDPS6 consists of data collected in the absence of TCS/TCI rescue therapy* and type 1 prohibited medication at any time since Day 1 for the responder endpoints relating to EASI, vIGA and PP-NRS. Data collected after such use will be imputed as non-response. Data missing due to withdrawal from the study for reasons considered related to study medication** and data after use of type 2 prohibited medication will be imputed as per EDPS1.

Responses missing for other reasons, including early withdrawal from the study due to reasons not considered related to study medication will not be replaced and will be considered as missing.

7.1.2.7 Efficacy Data Point Set 7 (EDPS7)

EDPS7 contains all data collected. A treatment policy strategy will be used for all intercurrent events other than discontinuation from the study which will use a while on treatment strategy (i.e., the collection period will be ended at the time of study discontinuation).

7.1.2.8 Safetyagree Data Point Set 1 (SDPS1)

SDPS1 consists of all observed data collected at a scheduled visit.

7.1.2.9 Safety Data Point Set 2 (SDPS2)

SDPS2 consists of all observed data collected, including data from scheduled and unscheduled visits.

7.2 Covariates and Subgroups

Subgroups based on baseline severity of disease will be defined as follows:

- Using baseline vIGA score of 3 for efficacy analysis
- Using baseline vIGA score other then 3 for summaries only (2, 4)

For the inferential models defined in Section 9, in addition to the baseline vIGA score and relevant baseline score where applicable, the following covariates will be considered:

- Body mass index (<30 kg/m^2, ≥30 kg/m^2)
- Sex (male, female)
- Race (Non-Hispanic white and Hispanic or Non-White)
- Region (North America, Europe, Asia Pacific)

Covariates selection will be done separately for cohorts 1-3 analyses and cohort 4.

7.3 Missing Data

Missing efficacy data such as individual item scores will be dealt with as detailed in Section 5.3.3. Imputation of missing efficacy data due to intercurrent events will be performed in EDPS1, EDPS2, EDPS3, EDPS4 and EDPS5 as described in Section 7.1.2.

7.3.1 Partial Dates/Times

Partial dates and times for AEs, medical conditions and concomitant medications will be imputed for the purpose of assigning study phases and calculating duration. Listings will always include the reported date/time information rather than any imputations.

Partial AE onset and concomitant medication (from concomitant medications CRF page) start dates will be imputed as follows:

- If only the month and year are specified, and the month and year of the start of treatment are not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified, and the month and year of the start of treatment are the same as the month and year of the start date, then use the date of start of treatment. If this results in a start date after a known or partial end date, then use the 1st of the month.
- If only the year is specified, and the year of the start of treatment is not the same as the year of the start date, then use January 1 of the year of the start date.

- If only the year is specified, and the year of the start of treatment is the same as the year of the start date, then use the date of the start of treatment. If this results in a start date after a known or partial end date, then use January 1 of the year of the start date.
- If the start date is completely unknown, then use the date of the start of treatment. If this results in a start date after a known or partial end date, do not impute the start date.

Concomitant medication (from atopic dermatitis past treatments CRF page) start dates will be imputed as follows:

- If only the month and year are specified, then use the 1st of the month.
- If only the year is specified, then use January 1 of the year of the start date.
- If the start date is completely unknown, then do not impute the start date.

Partial AE onset start times will be imputed as follows:

- If the actual or imputed start date is the same as the treatment start date, and the start time is completely missing, then use the time of start of treatment.
- If the actual or imputed start date is not the same as the treatment start date, and the start time is completely missing, then use 00:00.
- If the actual or imputed start date is the same as the treatment start date, and the start time is partially missing (hh:XX) then use the following:
    - If the hour is the same as the hour of the start of treatment time then use the complete time of the start of treatment (i.e., both hours and minutes)
    - If the hour is not the same as the hour of the start time than use hh:00.
- If the actual or imputed start date is not the same as the treatment start date, and the start time is partially missing (hh:XX) then use hh:00

Partial medical conditions start dates will be imputed as follows:

- If only the month and year are specified, then use the 1st day of the month.
- If only the year is specified, then use January 1st of that year.
- If the start date is completely unknown, do not impute the start date.

Partial AE resolution, medical condition stop dates and concomitant medication (from concomitant medications CRF page) stop dates and date last smoked will be imputed as follows:

- If the event, condition or medication is flagged as ongoing, do not impute the stop date
- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

Concomitant medication (from atopic dermatitis past treatments CRF page) stop dates will be imputed as follows:

- If the event, condition or medication is flagged as ongoing, do not impute the stop date
- If only the month and year are specified, and the month and year of the screening visit are not the same as the month and year of the end date, then use the last day of the month.
- If only the month and year are specified, and the month and year of the screening visit are the same as the month and year of the end date, then use the date of screening visit.

- If only the year is specified, and the year of the screening visit is not the same as the year of the end date, then use December 31 of that year.
- If only the year is specified, and the year of the screening visit is the same as the year of the end date, then use the date of screening visit.
- If the stop date is completely unknown, do not impute the stop date.

Partial AE resolution and concomitant medication stop times will be imputed as follows:

- If the actual or imputed stop date is non-missing, and the stop time is completely missing, then use 23:59 on that date.
- If the actual or imputed stop date is non-missing, and the stop time is partially missing, then hh:59 for missing minutes.
- If the actual or imputed stop date is missing, do not impute the stop time.

7.3.2 Adverse Event Information

AEs with missing relationship will be considered 'Related' for summary purposes but recorded as missing in the listings.

7.4 Interim Analyses and Data Monitoring

7.4.1 Purpose of Interim Analyses

Interim analysis

The Interim analysis will be performed to check that no imbalance of treatment groups has occurred due to stratified randomisation leaving multiple incomplete blocks.

If an imbalance is detected, the randomisation schedule may be slightly adapted for the final participants to ensure that all treatment groups have enrolled at least 73 participants.
No other decisions regarding study conduct will be made based on the interim results and the study will not be stopped if superior efficacy or futility is found.

Cohorts 1-3 analysis

After the last patient last visit in cohorts 1-3, DBL and cohorts 1-3 specific analysis will be performed. No decisions regarding the study conduct will be made based on the cohorts 1-3 analyses, but the results may be shared externally. Also, cohorts 1-3 efficacy tables and listings will be considered final and included in CSR at the end of study.

7.4.2 Planned Schedule of Interim Analyses

The interim analysis will be performed after approximately 290 participants have been randomised..

Cohorts 1-3 specific analysis will be performed after the cohorts 1-3 DBL.

7.4.3 Endpoints to be Included in the Interim Analysis

Interim analysis
No endpoints will be evaluated. Only the distribution of participants in each of the treatment groups (Active cohort 1-3 and pooled placebo) will be considered.

Cohorts 1-3 analysis
All analyses planned for the study will be done, but will only include cohorts 1-3 participants.

7.4.4 Adjustment of Confidence Intervals and p-values

Interim analysis
No comparisons of efficacy will be performed so no adjustments for alpha-spending are required.

Cohorts 1-3 analysis
Efficacy tables and figures will be considered final so no adjustments for alpha-spending are required.

7.4.5 Practical Measures to Minimise Bias

Interim analysis
Outputs featuring unblinded treatment assignments will be created by the unblinded analysis team within [redacted] and shared with the unblinded personel at [redacted] (Interactive Response Technology Vendor) who will implement the required changes to the randomisation schedule in their system.. Unblinded results will not be shared with any study site staff, participants, or any members of the study team who will be involved in the collection, review or analysis of individual study data.

The members of the unblinded team will not be involved in any aspects of study conduct, including in the development of the final summaries and analyses for the study. No data which may have the potential to unblind will be released beyond the unblinded personnel.

Cohorts 1-3 analysis
Cohorts 1-3 data will be unblinded to the [redacted] study team and the sponsor after the cohorts 1-3 DBL. Cohort 4 data will remain blinded till the end of study.

7.4.6 Documentation of Interim Analyses

Interim analysis
All unblinded data and summaries, together with any meeting minutes in which unblinded data is discussed will be held in a restricted file structure by the unblinded statistician until after the study has finished and the data has been unblinded after DBL.

Cohorts 1-3 analysis
Unblinded summaries will be shared with the sponsor as cohorts 1-3 data will be unblinded after the cohorts 1-3 DBL.

7.5 Multi-centre Studies

Results will be presented for all centres combined. For the inferential analyses the effect of region will be assessed for significance in the models.

7.6 Multiple Testing

The focus of this study is on model estimation of treatment effects and as such no adjustments will be made for multiple testing in this study.

7.7 Visit Windows

All data will be reported according to nominal visits. For example, if a Week 2 visit occurred on Day 16 instead of the nominally expected Day 14 it will be reported and included in the summary statistics/statistical analyses for Week 2.

Scheduled visits which occur outside the protocol-specified visit window (e.g., if the Week 2 visit occurred on Day 19 outside of the Day 12-18 window), this will be noted as a protocol deviation but data collected will still be included in all summary and analysis tables.

Unscheduled visits and Early Termination visit will not be included in summary or analysis tables, unless they are baseline measurements, provide data towards a safety endpoint which looks at worst-case post-baseline, or if a visit is a rescue therapy unscheduled visit.

Week 20 visit will be included in the summaries, but no analysis will be done at this visit.

For the rescue therapy, subjects who started rescue therapy outside of a scheduled visit should complete assessments required for the rescue therapy unscheduled visit. This data will only be included in tables and figures in cases where the last off-rescue observation carried forward imputation method is used to account for the intercurrent event of rescue therapy.

All listings will include all collected data even if they are from an unscheduled visit.

8 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, SD, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

In general, all data will be listed, sorted by cohort (1, 2, and 3 for the cohorts 1-3 analysis and 1-4 for the final analysis), randomised treatment (Placebo, EDP1815), site number and participant number. Relevant listings will include whether the assessment was performed and the date, study day/visit and time of the assessment as applicable.

Unless otherwise specified below, all summary tables will be structured with a column for each treatment. Where appropriate, columns combining all placebo participants, all EDP1815 participants and an overall total column may also be presented.

For summaries of study disposition, demographic and baseline data and study treatment compliance, columns will be ordered and labelled as follows:

- Cohort 1 Placebo
- Cohort 1 EDP1815
- Cohort 2 Placebo
- Cohort 2 EDP1815
- Cohort 3 Placebo
- Cohort 3 EDP1815
- Cohort 4 Placebo (final analysis only)
- Cohort 4 EDP1815 (final analysis only)
- All Placebo
- All EDP1815
- Total

For cohorts 1-3 efficacy outputs, columns will be ordered and labelled as follows:

- All Placebo
- Cohort 1 EDP1815
- Cohort 2 EDP1815
- Cohort 3 EDP1815
- Cohorts 2+3 EDP1815
- All EDP1815

For cohort 4 efficacy outputs, columns will be ordered and labelled as follows:

- Cohort 4 Placebo
- Cohort 4 Matched Placebo
- Cohort 4 EDP1815
- Cohort 1 EDP1815

For concomitant medication and safety outputs, columns will be ordered and labelled as follows:

- All Placebo
- Cohort 1 EDP1815
- Cohort 2 EDP1815
- Cohort 3 EDP1815
- Cohort 4 EDP1815 (final analysis only)
- All EDP1815

For the analysis:

- For study disposition summaries where it is appropriate to report information on participants who failed screening, the enrolled population will be used.

- For safety summaries, where data is assigned to specific scheduled visits, the safety population with SDPS1 will be used.

- For safety summaries, where all other safety data is presented (including adverse events and worst-case change from baseline endpoints), the safety population with SDPS2 will be used.

- For the primary estimand and all secondary and exploratory estimands, full analysis population with EDPS1 will be used.

- For the supplementary estimands for the primary endpoint, full analysis population with EDPS2-EDPS5 will be used.

- Selected secondary response endpoints will also have secondary supplementary estimands: full analysis population with EDPS2 and EDPS6 will be used for endpoints based on EASI, vIGA and PP-NRS.

- For the secondary count endpoints, full analysis population with EDPS7 will be used.

- For the exploratory endpoints, full analysis population with EDPS1 will be used.

- For all other summaries and analyses the full analysis population will be used.

8.1 Study Disposition

Completion/withdrawal from the study and completion/discontinuation from treatment, together with reasons for withdrawal from the study or discontinuation from treatment will be listed and the following will also be tabulated:

- Number and percentage of participants who completed the study
- Number and percentage of participants withdrawn from the study and the reported reason for withdrawal
- For the interim analyses, the number and percentage of participants still ongoing in the study will also be presented
- Number and percentage of participants who completed the 16-week treatment period
- Number and percentage of participants who discontinued treatment early and reason for discontinuation

For participants who fail screening, the reasons for screen failure including details on which inclusion/exclusion criteria were not met will be summarised and listed.

The number and percentage of participants enrolled within each region, country and site will be summarised.

For the enrolled population, the number and percentage of participants in each analysis population will be presented. Inclusion/exclusion in each study population will also be listed, together with reasons for exclusion.

The number and percentage of participants with data available for each scheduled visit (including the early termination visit) will be summarised.
Missed visits due to COVID-19 will also be summarised and listed.

8.2 Protocol Deviations

The number and percentage of participants in the full analysis population with at least one significant protocol deviation will be summarised by deviation category.

All protocol deviations will also be listed.

8.3 Demographic and Baseline Variables

Demography data of age, sex, race, ethnicity will be summarised together with height, weight and BMI at screening.

Baseline vIGA score (randomisation stratification factor from the IRT system and CRF data), baseline EASI score and baseline BSA will be summarised.

Time since diagnosis (years) will be summarised.

Separately atopic dermatitis medications taken pre-treatment will be summarised.

8.4 Medical History

Medical history and concurrent illnesses will be captured and coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The dictionary will be updated through the life of the study with version 24.0 used initially.

Concurrent illnesses and medical conditions will be classified as ‘current’ if the end date is on or after the date of first dose of study drug, or the condition has been marked as ongoing. Otherwise, they will be classified as ‘past’.

Past and current medical history will be summarised separately by System Organ Class (SOC) and Preferred Term (PT). Summary tables will contain the number and percentage of patients. A patient who has multiple conditions in the same SOC or with the same PT will be counted only once in the patient counts. Medical history summaries will be sorted by the internationally agreed SOC order (Table 5) and decreasing frequency of PT within SOC in the Total column.

All medical history data will be listed.

8.5 Prior and Concomitant Medications

Medications will be coded according to the World Health Organization Drug Dictionary (WHODD). The dictionary will be updated through the life of the study with the version dated 01Mar2021 used initially. Medical procedures will not be coded.

Concomitant medications are defined as any medications taken during the treatment period or follow-up period after treatment. This includes any medications started before the first dose and ongoing after the first dose. Prior medications are defined as any medication taken before or during the screening period which were stopped before the first dose of study medication.

Missing and partial start and stop dates will be imputed using the rules specified in Section 7.3.1 before classifying therapies as prior or concomitant. If the classification is still ambiguous after missing and partial dates have been imputed, then the medication will be considered concomitant.

Medications will be summarised by WHODD Anatomical Main Group (Level 1), Therapeutic Subgroup (Level 2) and preferred term. The summaries will report incidence within each relevant level so that a participant taking multiple medications coded to the same relevant Level 1, Level 2 or preferred term would only be counted once within the incidence count for that level or term.

Separate summaries will be produced for each of the following:

- Prior medications
- All concomitant medications
- Concomitant medications started pre-treatment
- Concomitant medications during the treatment period (including any which started pre-treatment)
- Concomitant medications started during the follow-up period

All prior and concomitant medications will be listed.

8.6 Treatment Compliance

Treatment compliance will be summarised for the whole 16-week treatment period.

Summary statistics (n, mean, SD, median and range) will be produced together with the number and percentage of participants within each of the categories defined in Section 5.3.2.1. Percentages will use the number of participants who started the treatment period as the denominator.

Data from the dosing diary, drug accountability and the calculated treatment compliance will also be listed.

8.7 Emollient Compliance

Emollient compliance will be summarised for the whole treatment period.

Summary statistics (n, mean, SD, median and range) will be produced together with the number and percentage of participants within each of the categories defined in Section 5.3.2.2. Percentages will use the number of participants who started the period as the denominator.

Data from the daily diary and the calculated emollient compliance will also be listed.

9 Efficacy Analyses

All efficacy analyses outputs will be created separately for cohorts 1-3 and cohort 4.

In addition to the inferential analyses described below, descriptive statistics will be provided to summarize all efficacy endpoints by treatment group.

For categorical variables, summary tabulations of frequency and percentage of participants within each category will be presented.

For continuous variables and duration endpoints, the number of participants, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

For daily time to event endpoints, the number of participants with the event, the number of participants censored will be presented together with Kaplan-Meier estimates of the proportion of responders in each study week, the estimated median and quartiles for time to response. Kaplan-Meier curves of time to event will also be presented.

All efficacy data will be listed, including both individual item scores and calculated questionnaire summary scores.

9.1 Pooling of Placebo Cohorts

For all cohorts 1-3 efficacy analyses, the cohorts 1-3 placebo groups will be pooled into a single ‘all placebo’ group and will be used as a common control group for the pooled EDP1815 treatment group and each individual EDP1815 treatment group.

For cohort 4 the process is described in the separate SAP Addendum.

9.2 Selection of Additional Covariates

For all cohorts 1-3 efficacy analyses, the covariates described in Section 7.2 will be considered and included in the primary efficacy model 1 described in Section 9.3.3 for the primary estimand if found to be significant ($p<0.05$). A forward stepwise selection method will be used to include the covariates after the baseline vIGA score and baseline EASI score have already been fitted.

The covariates selected for this primary model will also be used in all other analytical models including covariates.

For cohort 4 the process is described in the separate SAP Addendum.

9.3 Primary Efficacy Analysis

All efficacy analysis details in this section are provided for cohorts 1-3 analysis.
For cohort 4 analysis the same approach will be used. Any differences and additional analyses will be described in the SAP Addendum.

9.3.1 Primary Efficacy Estimand

The primary efficacy estimand will be the effect of each individual EDP1815 cohort compared to the pooled placebo group on the percentage of participants achieving EASI-50 at Week 16. The population summary measure of interest will be the odds ratio between each active EDP1815 treatment group and pooled placebo.

Intercurrent events will be accounted for in the following manner:

Table 1 Intercurrent Event Strategies for the Primary Estimand (EDPS1)

Intercurrent event		
Use* of Permitted TCS/TCI Therapy or Type 1 Prohibited Medications[1]	Study Discontinuation Before Week 16 Visit or Type 2 Prohibited Medications[2] Use	Noncompliance or Unblinding or Other Protocol Deviations Affecting Efficacy Before Week 16
<u>If <28 days before Week 16 visit: Composite strategy</u> Participant will be considered a non-responder <u>If ≥28 days before Week 16 visit: Treatment policy strategy</u> Data will be used as collected	<u>If type 2 prohibited medication[2] used: Composite strategy</u> Participant will be considered a non-responder from the date of medication start <u>If due to related** reason: Composite strategy</u> Participant will be considered a non-responder from the time of treatment discontinuation in case of missing data <u>If due to non-related** reason: While-on-treatment strategy</u> No replacement of missing data (data after treatment discontinuation will be used as collected)	<u>Treatment policy strategy:</u> Data will be used as collected

* Consider the last day with therapy for participant before Week 16.

** Treatment discontinuation reasons will be checked. Reasons related to study medication are lack of efficacy, treatment failure, adverse event (if related). Also, withdrawal of consent may be considered related to study medication based on the clarification text provided, that will be assessed by the Evelo team and provided in a separate spreadsheet. Non-related reasons are all other reasons.

[1]Prohibited concomitant medications which may affect efficacy requiring the concomitant medication to be immediately discontinued where possible once the use is discovered. Such medications use will be recorded as protocol deviation. Classification will be provided by the sponsor in a separate spreadsheet.

[2]Prohibited concomitant medications which may affect efficacy requiring IMP discontinuation. Such medications use will be recorded as protocol deviation. Classification will be provided by the sponsor in a separate spreadsheet.

If multiple events occurred, composite and while-on-treatment strategies are prioritized over treatment policy strategy. If multiple events requiring composite and while-on-treatment strategies occurred, study discontinuation due to treatment related reason and type 2 prohibited medication

strategy will be prioritized. If data does not change after applying composite strategy (for example, there is a treatment discontinuation due to related reason event and scheduled visit after treatment discontinuation was performed and so data from this visit will not be replaced), other events strategies still may be applied.

9.3.2 Supplementary Estimands for the Primary Endpoint

For the primary analysis, five supplementary estimands will be considered in order to assess the impact of intercurrent events.

Table 2 Supplementary Estimands for the Primary Endpoint

		Intercurrent event		
Estimand	EDPS	Use* of Permitted TCS/TCI Rescue Therapy or Type 1 Prohibited Medications[1]	Study Discontinuation Before Week 16 Visit or Type 2 Prohibited Medications[2] Use[3]	Noncompliance or Unblinding or Other Protocol Deviations Affecting Efficacy Before Week 16
Supplementary Estimand 1	EDPS2	If <28 days before Week 16 visit: While-on-treatment strategy Data will be considered missing If ≥28 days before Week 16 visit: Treatment policy strategy (as per primary estimand)	If type 2 prohibited medication[2] used: Composite strategy (as per primary estimand) If due to related** reason: Composite strategy (as per primary estimand) If due to non-related** reason: While-on-treatment strategy (as per primary estimand)	Treatment policy strategy (as per primary estimand)

Estimand	EDPS	Intercurrent event		
		Use* of Permitted TCS/TCI Rescue Therapy or Type 1 Prohibited Medications[1]	Study Discontinuation Before Week 16 Visit or Type 2 Prohibited Medications[2] Use[3]	Noncompliance or Unblinding or Other Protocol Deviations Affecting Efficacy Before Week 16
Supplementary Estimand 2	EDPS3	<u>If <14 days before Week 16 visit: Composite strategy</u> Participant will be considered a non-responder <u>If ≥14 days before Week 16 visit: Treatment policy strategy</u> Data will be used as collected	<u>If type 2 prohibited medication[2] used: Composite strategy</u> (as per primary estimand) <u>If due to related** reason: Composite strategy</u> (as per primary estimand) <u>If due to non-related** reason: While-on-treatment strategy</u> (as per primary estimand)	<u>Treatment policy strategy</u> (as per primary estimand)
Supplementary Estimand 3	EDPS4	<u>If <28 days before Week 16 visit: Composite strategy</u> (as per primary estimand) <u>If ≥28 days before Week 16 visit: Treatment policy strategy</u> (as per primary estimand)	<u>If type 2 prohibited medication[2] used: While-on-treatment Strategy</u> Data will be considered missing from the date of medication start <u>If study discontinuation: While-on-treatment strategy</u> Data will be considered missing from the date of treatment discontinuation	<u>Treatment policy strategy</u> (as per primary estimand)

Estimand	EDPS	Intercurrent event		
		Use* of Permitted TCS/TCI Rescue Therapy or Type 1 Prohibited Medications[1]	Study Discontinuation Before Week 16 Visit or Type 2 Prohibited Medications[2] Use[3]	Noncompliance or Unblinding or Other Protocol Deviations Affecting Efficacy Before Week 16
Supplementary Estimand 4	EDPS5	As per primary estimand unless data is already excluded due to non-compliance or unblinding or other protocol deviations affecting efficacy	As per primary estimand unless data is already excluded due to non-compliance or unblinding or other protocol deviations affecting efficacy	<u>While-on-treatment strategy</u> Data collected after the intercurrent event will be excluded
Supplementary Estimand 5	EDPS6	<u>Composite strategy</u> Participants with use at any time between Day 1 and the Week 16 visit will be considered as non-responders at all visits after the relevant medication was used.	<u>If type 2 prohibited medication[2] used: Composite strategy</u> (as per primary estimand) <u>If due to related** reason: Composite strategy</u> (as per primary estimand) <u>If due to non-related** reason: While-on-treatment strategy</u> (as per primary estimand)	<u>Treatment policy strategy</u> (as per primary estimand)

* Consider the last day with therapy for participant before Week 16.

** Treatment discontinuation reasons will be checked. Reasons related to study medication are lack of efficacy, treatment failure, adverse event (if related). Also, withdrawal of consent may be considered related to study medication based on the clarification text provided, that will be assessed by the Evelo team and provided in a separate spreadsheet. Non-related reasons are all other reasons.

[1]Prohibited concomitant medications which may affect efficacy requiring the concomitant medication to be immediately discontinued where possible once the use is discovered. Such medications use will be recorded as protocol deviation. Classification will be provided by the sponsor in a separate spreadsheet.

[2]Prohibited concomitant medications which may affect efficacy requiring IMP discontinuation. Such medications use will be recorded as protocol deviation. Classification will be provided by the sponsor in a separate spreadsheet.

[3]Type 2 prohibited medication will be considered as treatment withdrawal due to related reason at the date of medication start for the intercurrent event strategy.

9.3.3 Main Analytical Approach

The primary analysis will be performed using a logistic regression model. The model will include parameters for treatment group, baseline vIGA score and baseline EASI score. As described in Section 9.2 additional covariates for baseline factors will be assessed using this model for inclusion in all efficacy models. Only Week 16 data will be included in the model.

Treatment will consist of 4 levels (all placebo, cohort 1 EDP1815, cohort 2 EDP1815, cohort 3 EDP1815). Baseline vIGA will consist of 3 levels (2, 3 and 4).

The following treatment differences will be of estimated:

- Cohort 1 EDP1815 vs Pooled placebo
- Cohort 2 EDP1815 vs Pooled placebo
- Cohort 3 EDP1815 vs Pooled placebo
- Cohorts 2+3 EDP1815 vs Pooled placebo*
- All EDP1815 vs Pooled placebo*
- Cohort 2 EDP1815 vs Cohort 3 EDP1815**
- Cohort 1 EDP1815 vs Cohort 2 EDP1815**

* Comparisons between pooled EDP1815 groups and pooled placebo will be considered as secondary analysis.
** Comparisons between EDP1815 treatment groups will be considered as exploratory analysis.

The comparisons between pooled EDP1815 groups* and comparisons between EDP1815 treatment groups** will be done using contrasts (LSMESTIMATE statement) within the relevant SAS procedures.

The actual and predicted probability of EASI-50 response at Week 16 in each treatment group together with the estimated odds ratios and associated confidence intervals for each treatment difference will be displayed. P-values will be displayed for the comparisons of active treatment (individual and pooled) vs pooled placebo.

Vertical bar plots for the actual and predicted probabilities of EASI-50 at Week 16 for each treatment group will be plotted.

The primary analysis approach will be repeated using the 4 supplementary estimands described in Section 9.3.2.

9.3.4 Sensitivity Analyses

Secondary estimand generalised linear mixed effects model (GLMM) analysis of EASI-50 (including all timepoints as described in Section 9.4.2.2) will be considered a sensitivity analysis for the primary endpoint.

9.3.5 Subgroup Analyses

The analyses described in Section 9.3.3 will be repeated on the primary estimand using the subgroup of baseline vIGA score of 3 as defined in Section 7.2.

For the subgroups of baseline vIGA score other then 3 (baseline vIGA score of 2; baseline vIGA score of 4), number of patients with EASI-50 response will be summarized, but no analysis will be done, as the sample sizes are not expected to be large enough for meaningful comparisons to be made.

There will be no figures for the subgroup analyses.

9.4 Secondary Efficacy Analyses

All efficacy analysis details in this section are provided for cohorts 1-3 analysis.
For cohort 4 analysis the same approach will be used. Any differences and additional analyses will be described in the SAP Addendum.

All continuous and response secondary estimands will use EDPS1 (the primary estimand approach).

Secondary continuous and response endpoints based on the EASI, vIGA and PP-NRS will be analysed with a supportive estimands using EDPS2 (the supplementary estimand 1 approach) and EDPS6 for the response endpoints only (the supplementary estimand 5 approach).

Count secondary endpoints will use EDPS7 (estimand includes all data as collected prior to completion or withdrawal from the study).

The following treatment differences will be estimated:

- Cohort 1 EDP1815 vs Pooled placebo
- Cohort 2 EDP1815 vs Pooled placebo
- Cohort 3 EDP1815 vs Pooled placebo
- Cohorts 2+3 EDP1815 treatment group vs all placebo
- All EDP1815 treatment group vs all placebo
- Cohort 2 EDP1815 vs Cohort 3 EDP1815*
- Cohort 1 EDP1815 vs Cohort 2 EDP1815*

* Comparisons between EDP1815 treatment groups will be considered as exploratory analysis.

The comparisons between pooled EDP1815 groups and comparisons between EDP1815 treatment groups* will be done using contrasts (LSMESTIMATE statement) within the relevant SAS procedures.

Summary statistics only will be presented for Week 20 for those participants who completed treatment but did not wish to participate in the OLE.

9.4.1 Continuous Secondary Endpoints

The following secondary endpoints will be analysed in the same manner as described below:

- Mean absolute change from baseline in EASI score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in EASI score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in vIGA*BSA score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in vIGA*BSA score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in BSA score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in BSA score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in SCORAD score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in SCORAD score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in POEM score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in POEM score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in PP-NRS score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in SD-NRS score at Weeks 4, 8, 12, and 16

If a participant has a zero score for any of the secondary scores at baseline, that participant will be excluded from any of the percentage change from baseline summaries and analyses as the percentage change from baseline cannot be calculated.

9.4.1.1 Estimands

The population summary measure of interest will be the mean difference between treatment groups specified in Section 9.4.

Where intercurrent event strategy is composite, for continuous endpoints value will be imputed with the last off-rescue observation.
Last off-rescue observation is defined as the last off-rescue observation in the period before the corresponding intercurrent event plus early termination visit in case of early study discontinuation (off-rescue is defined as data collected at least 28 days after use of rescue medication or type 1 prohibited medication).

Note, for PP-NRS and SD-NRS intercurrent event strategy should be applied for daily scores before the weekly scores are calculated.

9.4.1.2 Main Analytical Approach

A mixed model for repeated measures (MMRM) with parameters for treatment group, visit (excluding Week 20), baseline vIGA score, baseline relevant questionnaire score and the interaction for treatment*visit will be used.

Treatment will consist of 4 levels (all placebo, cohort 1 EDP1815, cohort 2 EDP1815, cohort 3 EDP1815). Baseline vIGA will consist of 3 levels (2, 3 and 4).

As described in Section 9.2, any baseline covariates fitted into the primary analysis model will also be fitted in the models for these endpoints.

An unstructured covariance structure will be used. If there are issues with model convergence, other covariance structures may be considered (e.g. compound symmetry).

Distributional assumptions underlying the model used for analysis will be examined by a normal probability plot of the residuals and a plot of residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Least squares mean estimates and their 95% confidence intervals (CI) will be presented for the endpoint value at each visit. Treatment differences between each EDP1815 group (including cohorts 2+3 EDP1815 and all EDP1815 groups) and the pooled placebo group will be estimated using LS mean differences, 95% CI and p-values. Pairwise treatment differences between EDP1815 groups will be estimated with LS mean differences and 95% CI.

Least square mean (95% CI) estimates will be plotted against visit. Least square mean (95% CI) treatment differences between each EDP1815 treatment group and the pooled placebo group will also be plotted against visit. Waterfall plots at Week 16 will be presented as panels for individual treatment groups.

In addition, for the secondary endpoints based on the EASI, vIGA and PP-NRS only, a supportive analysis will be performed using the EDPS2.

9.4.2 Response Endpoints

The following endpoints will be analysed in the same manner as described below:

- Percentage of participants achieving EASI-50, EASI-75, EASI-90 at Weeks 4, 8, 12 and 16
- Percentage of participants achieving vIGA of 0 or 1 with a ≥2-point improvement from baseline at Weeks 4, 8, 12 and 16
- Percentage of participants achieving vIGA of 0 or 1 at Weeks 4, 8, 12 and 16
- Percentage of participants achieving vIGA of 0 at Weeks 12 and 16
- Percentage of participants achieving BSA-50, BSA-75 at Weeks 4, 8, 12 and 16
- Percentage of participants achieving BSA reduction to 3% or less at Weeks 4, 8, 12 and 16
- Percentage of participants achieving SCORAD-35, SCORAD-50, SCORAD-75 at Weeks 4, 8, 12 and 16
- Percentage of participants achieving improvement of ≥4 points in DLQI score from baseline at Weeks 4, 8, 12 and 16
- Percentage of participants achieving improvement of ≥2, ≥4 points in PP-NRS score from baseline at Weeks 4, 8, 12 and 16

- Percentage of participants achieving improvement of ≥2 points in SD-NRS score from baseline at Weeks 4, 8, 12 and 16
- Percentage of participants achieving improvement of ≥4 points in POEM score from baseline at Weeks 4, 8, 12 and 16
- Proportion of participants requiring TCS/TCI rescue therapy in periods Weeks 1-4, 5-8, 9-12, 13-16 and Weeks 1-16.

9.4.2.1 Estimands

The population summary measure of interest will be the odds ratio between treatment groups specified in Section 9.4 for the achievement of response at the relevant time point.

Note, for PP-NRS and SD-NRS intercurrent event strategy will be applied after weekly scores at scheduled visits are calculated from daily scores.

9.4.2.2 Main Analytical Approach

Endpoints evaluated at selected visits

A generalised linear mixed effects model (GLMM) with a logit link function will be fitted using data from all visits (excluding Week 20). Treatment, visit, baseline vIGA score and the appropriate baseline questionnaire score (if different from vIGA) terms will be included in the model as fixed effects together with treatment*visit interaction.

Endpoints evaluated in periods

A generalised linear mixed effects model (GLMM) with a logit link function will be fitted using data from all periods (Weeks 1-4, 5-8, 9-12 and 13-16). Treatment, period, baseline vIGA score terms will be included in the model as fixed effects together with treatment*period interaction. The analyses will be repeated for the weeks 1-16 period dropping the terms for period and treatment*period interaction.

As described in Section 9.2, any baseline covariates fitted into the primary analysis model will also be fitted in the models for these endpoints.

An unstructured covariance structure will be used. If there are issues with model convergence, other covariance structures may be considered (e.g., compound symmetry).

If responder numbers are low and there are visits/periods at which not all treatment groups have at least one response, the analysis may be modified to exclude one or more of the earlier visits/periods to ensure model convergence. For endpoints evaluated in periods, periods may be pooled in order to have more patients data in periods and ensure model convergence.

Alternatively, the mixed effects model may be replaced with an individual logistic regression models at Week 16 if this approach appears to be more appropriate for the available data. Note that if there are insufficient responders to run the model with the Week 16 visit included then no inferential analysis should be performed.

The number and percentage of responders will be reported at each visit/period together with 95% CI for the percentage of responders, calculated using the exact method for binomial proportions. At each visit/period, the adjusted odds ratio, with 95% CI and associated p-value will also be presented for each EDP1815 group (including cohorts 2+3 EDP1815 and all EDP1815 groups) compared to the pooled placebo group. For comparison between EDP1815 groups, at each visit/period, the adjusted odds ratio with 95% CI will be presented.

If the analysis is changed to exclude visits/periods, then only the summary statistics for the number of subjects with data, the number and percentage of participants with a response and the 95% CI for the percentage of responders will be shown for any visits/periods which were excluded from the model. Table footnotes will be added as appropriate to detail any changes to the planned analysis.

For Week 20 visit, only the summary statistics for the number of subjects with data, the number and percentage of participants with a response and the 95% CI for the percentage of responders will be shown.

The proportions of responders and the 95% CI will be displayed graphically. The adjusted odds ratios (with 95% CI) will be plotted by visit.

In addition, for the secondary endpoints based on the EASI, vIGA and PP-NRS only, a supportive analysis will be performed using the EDPS2.

9.4.3 Count Endpoints

The following endpoints will be analysed in the same manner as described below:

- Number of courses of TCS/TCI rescue therapy
- Number of days requiring TCS/TCI rescue therapy

9.4.3.1 Estimands

The population summary measure of interest will be the rate ratio between treatment groups specified in Section 9.4.

Additionally, participants with rescue therapy courses recorded in CRF but with duration of more than 8 days (adjusted for dose frequency) will be excluded from the analysis due to the potentially incorrect rescue therapy data record.

9.4.3.2 Main Analytical Approach

A Poisson regression model fitted with treatment and baseline vIGA as covariates. An offset of log(days in study) will also be included in the model to account for any data from participants who withdrew early from the study. For participants who withdrew treatment early days in study will be calculated up to the end of treatment date or the end of period whichever occurs first. For

participants who completed treatment up to Week 16 days in study will be calculated up to the end of period.

In case of a greater variability among counts than expected for Poisson distribution, other models may be used (including negative binomial and zero inflated Poisson (ZIP)).

Number of courses of TCS/TCI rescue therapy endpoint will be evaluated for the following periods: Weeks 1-4, 5-8, 9-12, 13-16 and for Weeks 1-16.

Number of days requiring TCS/TCI rescue therapy endpoint will be evaluated for the following periods: Weeks 1-8, 9-16 and Weeks 1-16.

The model will be run separately for each period. Only participants with at least one visit performed in a period will be included in this period model. An offset of log(days in the period) will also be included in the model based on the number of days from the first visit in the period to the last visit in the period.

Model predicted event rates and their 95% CIs will be presented for each treatment group. Rate ratios with 95% CIs and p-values for each EDP1815 group (including cohorts 2+3 EDP1815 and all EDP1815 groups) compared to the relevant pooled placebo group at each visit will be presented. Rate ratios and 95% CIs will be presented for any comparisons between two EDP1815 treatment groups. If ZIP model will be used, odds ratios for no rescue medication used and the 95% CIs will also be presented.
Number of courses of TCS/TCI rescue therapy in each period will be also plotted as histogram.

9.5 Exploratory Efficacy Analyses

All efficacy analysis details in this section are provided for cohorts 1-3 analysis.
For cohort 4 analysis the same approach will be used. Any differences and additional analyses will be described in the SAP Addendum.

9.5.1 Exploratory Efficacy Endpoints

The exploratory endpoints will be summarised using statistics appropriate to the endpoint as described below.

Continuous, time to event and response exploratory endpoints estimands will use the same intercurrent event strategy as the primary estimand (EDPS1 will be used). Where intercurrent event strategy is composite, for continuous endpoints value will be imputed with the last off-rescue observation.
Last off-rescue observation is defined as the last off-rescue observation in the period before the corresponding intercurrent event plus early termination visit in case of early study discontinuation (off-rescue is defined as data collected at least 28 days after use of rescue medication or type 1 prohibited medication).

Count exploratory endpoints and response subgroup endpoints will use EDPS7 (estimand includes all data as collected prior to completion or withdrawal from the study).

Exploratory estimands will be evaluated at all timepoints at which the relevant endpoints are collected.

9.5.1.1 Continuous Exploratory Endpoints

Continuous exploratory endpoints:

- Mean absolute change and percentage change from Screening in EASI Score.
- Changes from baseline in SF-12 MCS and PCS scores.
- Changes from baseline in HADS anxiety and depression scores.
- Changes from baseline in ADCT scores.
- Daily changes from baseline in the PP-NRS and SD-NRS (Timescale: Days 2 to 112).

The population summary measure of interest will be the mean value in each treatment group.

Endpoints other than PP-NRS and SD-NRS will be summarized as described in Section 8.

Daily PP-NRS and SD-NRS endpoints will be listed and plotted.

9.5.1.2 Time to Event Exploratory Endpoints

Time to event exploratory endpoints:

- Time to first achievement of EASI-50.
- Time to first achievement of sustained EASI-50.
- Time to first achievement of EASI-75.
- Time to first achievement of vIGA of 0 or 1 with a 2-point improvement from baseline.
- Time to first achievement of vIGA of 0 or 1.
- Time to first achievement of a ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline.
- Time to first sustained ≥2 point in improvement in PP-NRS score, in participants with a score of ≥2 at baseline.
- Time to first achievement of a ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline.
- Time to first sustained ≥4 point in improvement in PP-NRS score, in participants with a score of ≥4 at baseline.
- Time to first achievement of a ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline.
- Time to first sustained ≥2 point in improvement in SD-NRS score, in participants with a score of ≥2 at baseline.

PP-NRS and SD-NRS time to event endpoints

The population summary measure of interest for the PP-NRS and SD-NRS endpoints will be the Kaplan-Meier estimates of proportion of responders at each week from 1 to 16 in each treatment group.

Censoring rules for these time to event endpoints are defined in Section 5.3.3.10.

The total number of responders throughout the period and number of participants censored will be presented together with Kaplan-Meier estimates of proportion of responders at each week from 1 to 16 and the estimated median and quartiles for time to response.

A figure showing the estimated survival curves of each treatment group will also be presented.

Sustained PP-NRS and SD-NRS time to event endpoints

The population summary measure of interest for the PP-NRS and SD-NRS endpoints will be the Kaplan-Meier estimates of proportion of responders at each week from 1 to 14 in each treatment group.

Censoring rules for these time to event endpoints are defined in Section 5.3.3.10.

The total number of responders throughout the period and number of participants censored will be presented together with Kaplan-Meier estimates of proportion of responders at each week from 1 to 14.

A figure showing the estimated survival curves of each treatment group will also be presented.

Other time to event endpoints

The population summary measure of interest for other endpoints will be the cumulative proportion to have achieved the event at each visit in each treatment group.

The number of participants meeting the criteria for the endpoint, and the number of participants 'at risk' of meeting the criteria at each visit will be presented together with the cumulative incidence and associated 95% CI. Cumulative incidence is calculated as the total number of events on or before the visit divided by the total number of participants at risk of the event.

For each endpoint, the cumulative incidences for each treatment group will be plotted against time as bars (with an 'error bar' for the corresponding 95% CI).

9.5.1.3 Response Exploratory Endpoints

Response exploratory endpoints:

- Percentage of participants achieving Investigator's Global Assessment (vIGA) of 0 or 1 with a ≥2 Point Improvement from screening.
- Percentage of participants achieving a reduction of ≥2, ≥4 in the PP-NRS, of those with a score of ≥2, ≥4 at baseline daily from Day 2 to 112.

- Percentage of participants achieving a reduction of ≥2 in SD-NRS score, of those with a score of ≥2 at baseline daily from Day 2 to 112.

The population summary measure of interest will be the proportion of responders at each timepoint in each treatment group.

The number and percentage of participants who achieve a response will be summarised by timepoint. Exact 95% CIs for the percentage of participants will also be displayed at each timepoint.

Daily PP-NRS and SD-NRS endpoints, will be listed and plotted.

9.5.1.4 Response Subgroup Exploratory Endpoints

For the primary and secondary responder endpoints relating to EASI, IGA and BSA, summaries will be provided comparing the number and percentage of participants in each treatment group who respond at Week 16 between the following subgroups:

- Participants with no rescue therapy use
- Participants with no rescue therapy use after the Week 4 visit
- Participants with no rescue therapy use after the Week 8 visit
- Participants with no rescue therapy use within 4 weeks of the Week 16 visit
- Participants with no rescue therapy use within 2 weeks of the Week 16 visit
- Participants with rescue therapy use within 4 weeks of the Week 16 visit
- Participants with rescue therapy use within 2 weeks of the Week 16 visit

The population summary measure of interest will be the proportion of responders in each subgroup in each treatment group.

9.5.1.5 Count Exploratory Endpoints

Response exploratory endpoints:

- Number of uses of topical antimicrobial or systemic antibiotic treatment for skin infections by Week 16.

The population summary measure of interest will be the proportion of participants reporting at least one infection on or before the Week 16 visit in each treatment group.

The number and proportion of participants with skin infection requiring topical or systemic antibiotic treatment at least once during the study will be presented. Histogram of the number of courses will be plotted.

10 Safety Analyses

The Safety population will be used for all summaries of Safety. All safety endpoints will be listed.

10.1 Extent of Exposure

The duration of exposure (days) and number of doses taken will be summarized using summary statistics for continuous data. The number and percentage of participants with at least 4, 8, 12 and 16 weeks (28, 56, 84 and 112 days respectively) will also be presented.

Treatment start and stop dates, exposure duration (days), number of doses administered, number of capsules taken and reasons for dose adjustments and dose interruptions will be listed by participant.

10.2 Adverse Events

Adverse events will be reported from the date of signed informed consent and through the Week 16 visit for participants entering the OLE study/28 days after cessation of dosing for participants who don't enter OLE. Adverse events occurring after the 28 days post-treatment would only be reported if the investigator considers it to be related to the study treatment.

Only treatment emergent AEs (TEAEs) will be included in the summaries, pre-treatment AEs will be included in the listings of all AEs.

All AEs will be coded using MedDRA. The dictionary will be updated through the life of the study with version 24.0 used initially. Severity of event will be coded using the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).

An overview of TEAEs will be produced showing the number and percentage of participants with:

- Any TEAEs
- Any TEAE of CTCAE grade 2 or above
- Any TEAE of CTCAE grade 3 or above
- Any TEAE of CTCAE grade 4 or above
- Any fatal TEAE
- Any serious TEAE
- Any TEAE leading to permanent discontinuation of study drug
- Any TEAE leading to withdrawal from the study
- Any related TEAE
- Any related TEAE of CTCAE grade 2 or above
- Any related TEAE of CTCAE grade 3 or above
- Any related TEAE of CTCAE grade 4 or above
- Any related fatal TEAE
- Any related serious TEAE
- Any related TEAE leading to permanent discontinuation of study drug
- Any related TEAE leading to withdrawal from the study

Related events are those which were considered by the investigator to be possibly, probably or definitely related to study drug.

TEAEs will also be summarized by system organ class (SOC) and preferred term (PT). Summary tables will contain the number and percentage of participants and the number of events. A participant who has multiple events in the same SOC or the same preferred term will be counted only once in the participant counts but all events will be counted in the event counts. Adverse event summaries will be sorted by the internationally agreed SOC order (Table 5) and decreasing incidence of preferred term within SOC in the EDP1815 column.

Related TEAEs and TEAEs of CTCAE Grade 3 or above will also be summarized by SOC and PT in the same manner as described above.

Non-serious TEAEs will be also summarised by SOC and PT, however, PTs will be presented only in case of TEAEs reported by at least 5% of participants in any treatment group.

10.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Treatment emergent SAEs, TEAEs leading to discontinuation of study drug or withdrawal from the study will be summarized separately by treatment, SOC and preferred term.

Serious AEs, fatal AEs and AEs leading to discontinuation of study drug will each be listed separately by participant.

No specific adverse events are considered to be of special interest for EDP1815.

10.4 Pregnancies

Pregnancy test data will be listed only.

10.5 Clinical Laboratory Evaluations

Central laboratory data will be used for all safety laboratory evaluations. Table 6 (Section 25) shows the parameters which will be collected and the units in which they will be supplied. Lab data will be transformed as appropriate to the International System of Units (SI units) as part of the SDTM programming and SI units will be used for all summaries.

Haematology and chemistry parameters will be summarised by visit, including change from baseline for all post-baseline visits.

The number and percentage of participants showing shifts from baseline to worst-case post-baseline with respect to the normal ranges will also be summarised for each haematology and chemistry parameter. Categories will be:

- Low
- Normal
- High

Haematology and chemistry values will also be flagged for potentially clinically important (PCI) values if they meet any of the criteria for Grade 2 or higher events according to CTCAE V5.0. The PCI criteria are listed in Table 6 (Section 25). The number and percentage of participants showing shifts from baseline to worst-case baseline with respect to PCI criteria will be summarised for all parameters where PCI criteria have been defined. Categories will be:

- Low
- Within range
- High

For both the normal range and PCI summaries, the determination of worst-case post-baseline will consider both scheduled and unscheduled assessments which occur after the first dose of study treatment. Percentages will use the number of participants with at least one post-baseline assessment available as the denominator. If the baseline value is missing it will be assumed to be normal/within range. Worst-case can be either High or Low and if a participant has post-baseline values both above and below the normal range/PCI criteria then they will be counted in both relevant categories.

Haematology and chemistry data will be listed, including changes from baseline, normal ranges, flags for measurements outside the normal range, and flags for meeting PCI criteria. In addition, for participants who meet at least one PCI criteria, all values within the laboratory type (haematology or chemistry) will be listed separately.

Urinalysis data will be listed only.

10.6 Other Safety Measures

10.6.1 ECG

Ventricular rate, PR interval, RR interval, QRS duration, QT interval and QTcF interval will be summarised by visit, including change from baseline.

In addition, the QTcF interval will be flagged for PCI if it meets the CTCAE (v5.0) criteria for a Grade 3 or above event (>500 ms or a >60 ms increase from baseline).
The number and percentage of participants showing a shift from baseline to worst-case post-baseline with respect to the QTcF PCI criteria will be summarised. Categories will be:

- Within range
- High

The determination of worst-case post-baseline will consider all scheduled and unscheduled assessments which occur after the first dose of study treatment. Percentages will use the number of participants with at least one post-baseline assessment available. If the baseline value is missing it will be assumed to be normal for this summary.

All ECG data will be listed, including flags for values which meet the PCI criteria for QTcF. In addition, a separate listing of all ECG assessments for any participant who has at least one value meeting the QTcF PCI criteria will be produced.

10.6.2 Vital Signs

Systolic blood pressure (BP), diastolic BP, pulse rate, respiratory rate and temperature will be summarised by visit, including change from baseline.

In addition, vital signs data will be flagged as potentially clinically important (PCI) if they meet the CTCAE (v5.0) criteria for a Grade 3 or above event as shown in Table 3.

Table 3 PCI Criteria for Vital Signs

Parameter	Units	PCI Criteria
Systolic Blood Pressure	mmHg	≥ 160
Diastolic Blood Pressure	mmHg	≥ 100

The number and percentage of participants showing shifts from baseline to worst-case post-baseline with respect to the PCI criteria will also be summarized for each parameter. Categories will be:

- Within range
- High

The determination of worst-case post-baseline will consider all scheduled and unscheduled assessments which occur after the first dose of study treatment. Percentages will use the number of participants with at least one post-baseline assessment available. If the baseline value is missing it will be assumed to be within range for this summary.

All vital signs data will be listed, including flags for values which meet the PCI criteria. In addition, a separate listing of all vital signs assessments for any participant who meet has at least one value meeting the PCI criteria will be produced.

10.6.3 Physical Examination

All clinically significant abnormalities identified through physical examination should be recorded as an adverse events and listed with adverse events.

11 Reporting Conventions

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfil certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is 0, there will be no percentage presented at all
- All other percentage displays will use 1 decimal place

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean and median will use 1 decimal place more than the original data
- Standard deviation will use 2 decimal places more than then original data
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. However, if n<3, present the n, min and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only. The other descriptive statistics will be left blank

Where reporting estimated statistics from inferential tests and models, the following rules will apply in general:

- P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001".
- Estimated parameters and 95% confidence intervals on the same scale as raw observations will be reported to 1 decimal place more than the original data, standard errors will be reported to 2 decimal places more
- Estimated parameters and 95% confidence intervals of percentage change variables will be reported to 2 decimal places, standard errors will be reported to 3 decimal places
- Estimated odds ratios, rate ratios and associated 95% confidence intervals will be reported to 2 decimal places.
- Estimated parameters and 95% confidence intervals, not on the same scale as raw observations or for percentage change statistics (e.g. regression coefficients) will be reported to 3 decimal places, standard errors will be reported to one further decimal place.

12 Technical Details

Statistical evaluation will be performed by [redacted]

The datasets for the interim analysis will not use CDISC standards but will be programmed directly from the raw data supplied by [redacted] data management (eCRF data) and [redacted]

The datasets for the cohorts 1-3 and final analyses will follow analysis dataset model (ADaM) data specifications and will use standard data tabulation model (SDTM) data sets provided by [redacted] data management as the source data.

All analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA).

13 Summary of Changes from the Protocol

The SAP is based on the latest Protocol v5.0.

Table 44: Summary of Changes from the Protocol

Protocol Version	Summary of Change	Justification for change
V5.0	"Percentage of Participants developing skin infections requiring topical or systemic antibiotic treatment [Time Frame: Week 16]" endpoint changed to "Percentage of participants requiring topical antimicrobial or systemic antibiotic treatment for skin infections by Week 16"	Antimicrobials may be prescribed in order to prevent possible skin infections and these cases also needs to be considered
V5.0	Rescue therapy endpoints defined in the Protocol will only consider TCS/TCI rescue therapy	TCS/TCI rescue therapy is of interest. Exploratory endpoint to assess antimicrobial therapy modified to cover all antimicrobial rescue therapy
V5.0	Emollient compliance will be calculated through only Treatment Period (from Day 1 till the last dose of IMP) and not Follow-up. Previously the whole study period was considered.	Only compliance during treatment period is of interest and may affect efficacy
V5.0	Intercurrent event of TCS rescue therapy use will also include TCI rescue therapy	TCS/TCI rescue therapy is of interest.
V5.0	Prohibited medications intercurrent events (previously treated as Protocol Deviations events) are separated to type 1 and type 2. Type 1 prohibited medications are considered equivalent to TCS/TCI rescue therapy intercurrent event. Type 2 prohibited medications are considered equivalent to study withdrawal due to treatment related reason from the time of start of medication.	Prohibited medications have potential to affect efficacy and appropriate intercurrent event strategies should be used
V5.0	Other Protocol Deviations affecting efficacy added as possible intercurrent events	Not all Protocol Deviations affecting efficacy were listed initially
V5.0	Interim analysis goal changed from being a sample size recalculation to just checking for the balance between the treatment groups.	Evelo decided to not increase sample size.
V5.0	Endpoint "Proportion of participants not requiring TCS/TCI rescue therapy in Weeks 1-4, 5-8, 9-12 and 13-16 and for Weeks 1-16" changed to "Proportion of participants requiring TCS/TCI rescue therapy in Weeks 1-4, 5-8, 9-12 and 13-16 and for Weeks 1-16"	Evelo decided that modelling requirement for rescue therapy rather than not requirement is easier to interpret.
V5.0	Added SCORAD-35 Endpoint	Evelo decided to add SCORAD-35 at the time of Dry Run
V5.0	Removed endpoints for worst-case change from baseline with respect to values outside the normal ranges for vital signs and ECG parameters	Worst-case change from baseline with respect to values outside the normal ranges for vital signs, ECG parameters and clinical laboratory parameters for

Protocol Version	Summary of Change	Justification for change
		given as secondary safety endpoint but only changes with respect to normal ranges were summarized for the lab parameters. For ECG and vital signs, it was felt that only changes from PCI criteria were of specific interest.
V5.0	Added time to first achievement of EASI-75 Endpoint	Evelo decided to add endpoint at the time of Dry Run
V5.0	Added time to first achievement of vIGA of 0 or 1 Endpoint	Evelo decided to add endpoint at the time of Dry Run

14 Bibliography

15 Appendix 1: List of Tables, Figures and Listings

All outputs detailed in the following sections will be produced for the final analysis.
Cohort 4 specific efficacy analysis outputs are listed in SAP Addendum.

15.1 Study Population

15.1.1 Tables

Number	Title	Population	Data Point Set	Programming notes
14.1.1.1	Summary of Disposition	FAS	SDPS2	Include in TLR
14.1.1.2	Summary of Screening Status	Enrolled	SDPS2	
14.1.1.3	Summary of Participants by Region, Country, and Site	FAS	SDPS2	
14.1.1.4	Summary of Attendance at Each Visit	FAS	SDPS2	
14.1.1.5	Summary of Missed Visits Due to COVID-19	FAS	SDPS2	
14.1.1.6	Summary of Protocol Deviations	FAS	SDPS2	
14.1.1.7	Summary of Populations	Enrolled	SDPS2	
14.1.2.1	Summary of Demography	FAS	SDPS2	
14.1.2.2	Summary of Baseline Disease Characteristics	FAS	SDPS2	Include in TLR
14.1.3.1	Summary of Past Medical History	FAS	SDPS2	
14.1.3.2	Summary of Current Medical History	FAS	SDPS2	
14.1.4.1	Summary of Prior Medications	FAS	SDPS2	
14.1.4.2	Summary of All Concomitant Medications	FAS	SDPS2	
14.1.4.3	Summary of Concomitant Medications Started Pre-treatment	FAS	SDPS2	
14.1.4.4	Summary of Concomitant Medications Started During the Treatment Period	FAS	SDPS2	
14.1.4.5	Summary of Concomitant Medications Started During the Follow-up Period	FAS	SDPS2	

Number	Title	Population	Data Point Set	Programming notes
14.1.5	Summary of Treatment Compliance	FAS	SDPS2	
14.1.6	Summary of Emollient Compliance	FAS	SDPS2	
14.1.7	Summary of Treatment Exposure	SAS	SDPS2	

15.2 Efficacy

Apart from the table and figures on the subcategory of placebo participants only, the format of all tables and figures will be dependent on whether the placebo pooling strategy is considered appropriate or not as per Section 9.1. The titles of the table will remain unchanged regardless of which strategy is used.

15.2.1 Tables

Number	Title	Population	Data Point Set	Programming notes
14.2.1.1.1	Summary of EASI-50 Response	FAS	EDPS1	Include in TLR
14.2.1.1.2	Summary of EASI-50 Response	FAS	EDPS2	
14.2.1.1.3	Summary of EASI-50 Response	FAS	EDPS3	
14.2.1.1.4	Summary of EASI-50 Response	FAS	EDPS4	
14.2.1.1.5	Summary of EASI-50 Response	FAS	EDPS5	
14.2.1.1.6	Summary of EASI-50 Response	FAS	EDPS6	Include in TLR
14.2.1.2.1	Analysis of EASI-50 Response at Week 16 - Logistic Regression	FAS	EDPS1	Include in TLR
14.2.1.2.2	Analysis of EASI-50 Response at Week 16 - Logistic Regression	FAS	EDPS2	
14.2.1.2.3	Analysis of EASI-50 Response at Week 16 - Logistic Regression	FAS	EDPS3	
14.2.1.2.4	Analysis of EASI-50 Response at Week 16 - Logistic Regression	FAS	EDPS4	
14.2.1.2.5	Analysis of EASI-50 Response at Week 16 - Logistic Regression	FAS	EDPS5	
14.2.1.2.6	Analysis of EASI-50 Response at Week 16 - Logistic Regression	FAS	EDPS6	Include in TLR
14.2.1.3.1	Analysis of EASI-50 Response - GLMM	FAS	EDPS1	Include in TLR

Number	Title	Population	Data Point Set	Programming notes
14.2.1.3.2	Analysis of EASI-50 Response - GLMM	FAS	EDPS2	
14.2.1.3.3	Analysis of EASI-50 Response - GLMM	FAS	EDPS6	Include in TLR
14.2.1.4.1	Summary of EASI-50 Response by Baseline vIGA Score	FAS	EDPS1	
14.2.1.4.2	Analysis of EASI-50 Response at Week 16 by Baseline vIGA Score - Logistic Regression	FAS	EDPS1	
14.2.1.5	Summary of EASI-50 Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	
14.2.2.1	Summary and Analysis of EASI-75 Response - GLMM	FAS	EDPS1	Include in TLR
14.2.2.2	Summary and Analysis of EASI-75 Response - GLMM	FAS	EDPS2	
14.2.2.3	Summary and Analysis of EASI-75 Response - GLMM	FAS	EDPS6	Include in TLR
14.2.2.4	Summary of EASI-75 Response by Baseline vIGA Score	FAS	EDPS1	
14.2.2.5	Summary of EASI-75 Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	
14.2.3.1	Summary and Analysis of EASI-90 Response - GLMM	FAS	EDPS1	Include in TLR
14.2.3.2	Summary and Analysis of EASI-90 Response - GLMM	FAS	EDPS2	
14.2.3.3	Summary and Analysis of EASI-90 Response - GLMM	FAS	EDPS6	
14.2.3.4	Summary of EASI-90 Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	
14.2.4.1.1	Summary of Percentage Change from Baseline in EASI Score	FAS	EDPS1	
14.2.4.1.2	Summary of Percentage Change from Baseline in EASI Score	FAS	EDPS2	
14.2.4.2.1	Analysis of Percentage Change from Baseline in EASI Score - MMRM	FAS	EDPS1	
14.2.4.2.2	Analysis of Percentage Change from Baseline in EASI Score - MMRM	FAS	EDPS2	
14.2.5.1.1	Summary of Absolute Change from Baseline in EASI Score	FAS	EDPS1	
14.2.5.1.2	Summary of Absolute Change from Baseline in EASI Score	FAS	EDPS2	
14.2.5.2.1	Analysis of Absolute Change from Baseline in EASI Score - MMRM	FAS	EDPS1	
14.2.5.2.2	Analysis of Absolute Change from Baseline in EASI Score - MMRM	FAS	EDPS2	
14.2.6.1	Summary of vIGA Score	FAS	EDPS1	
14.2.6.2	Summary of vIGA Score	FAS	EDPS2	
14.2.7.1	Summary and Analysis of vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - GLMM	FAS	EDPS1	Include in TLR

Number	Title	Population	Data Point Set	Programming notes
14.2.7.2	Summary and Analysis of vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - GLMM	FAS	EDPS2	
14.2.7.3	Summary and Analysis of vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - GLMM	FAS	EDPS6	
14.2.7.4	Summary of vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	
14.2.8.1	Summary and Analysis of vIGA of 0 or 1 Response - GLMM	FAS	EDPS1	Include in TLR
14.2.8.2	Summary and Analysis of vIGA of 0 or 1 Response - GLMM	FAS	EDPS2	
14.2.8.3	Summary and Analysis of vIGA of 0 or 1 Response - GLMM	FAS	EDPS6	
14.2.8.4	Summary of vIGA of 0 or 1 Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	
14.2.9.1	Summary and Analysis of vIGA of 0 Response at Week 16 - GLMM	FAS	EDPS1	
14.2.9.2	Summary and Analysis of vIGA of 0 Response at Week 16 - GLMM	FAS	EDPS2	
14.2.9.3	Summary and Analysis of vIGA of 0 Response at Week 16 - GLMM	FAS	EDPS6	
14.2.10.1.1	Summary of Percentage Change from Baseline in vIGA*BSA	FAS	EDPS1	
14.2.10.1.2	Summary of Percentage Change from Baseline in vIGA*BSA	FAS	EDPS2	
14.2.10.2.1	Analysis of Percentage Change from Baseline in vIGA*BSA – MMRM	FAS	EDPS1	
14.2.10.2.2	Analysis of Percentage Change from Baseline in vIGA*BSA – MMRM	FAS	EDPS2	
14.2.11.1.1	Summary of Absolute Change from Baseline in vIGA*BSA	FAS	EDPS1	
14.2.11.1.2	Summary of Absolute Change from Baseline in vIGA*BSA	FAS	EDPS2	
14.2.11.2.1	Analysis of Absolute Change from Baseline in vIGA*BSA – MMRM	FAS	EDPS1	
14.2.11.2.2	Analysis of Absolute Change from Baseline in vIGA*BSA – MMRM	FAS	EDPS2	
14.2.12.1	Summary of Percentage Change from Baseline in BSA	FAS	EDPS1	
14.2.12.2	Analysis of Percentage Change from Baseline in BSA - MMRM	FAS	EDPS1	
14.2.13.1	Summary of Absolute Change from Baseline in BSA	FAS	EDPS1	
14.2.13.2	Analysis of Absolute Change from Baseline in BSA - MMRM	FAS	EDPS1	
14.2.14.1	Summary and Analysis of BSA-50 Response - GLMM	FAS	EDPS1	
14.2.14.2	Summary of BSA-50 Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	

Number	Title	Population	Data Point Set	Programming notes
14.2.15.1	Summary and Analysis of BSA-75 Response - GLMM	FAS	EDPS1	
14.2.15.2	Summary of BSA-75 Response at Week 16 by Rescue Therapy Use	FAS	EDPS7	
14.2.16	Summary and Analysis of BSA Reduction to <=3% - GLMM	FAS	EDPS1	
14.2.17.1	Summary of Percentage Change from Baseline in SCORAD Score	FAS	EDPS1	
14.2.17.2	Analysis of Percentage Change from Baseline in SCORAD Score - MMRM	FAS	EDPS1	
14.2.18.1	Summary of Absolute Change from Baseline in SCORAD Score	FAS	EDPS1	
14.2.18.2	Analysis of Absolute Change from Baseline in SCORAD Score - MMRM	FAS	EDPS1	
14.2.53	Summary and Analysis of SCORAD-35 Response - GLMM	FAS	EDPS1	
14.2.19	Summary and Analysis of SCORAD-50 Response - GLMM	FAS	EDPS1	
14.2.20	Summary and Analysis of SCORAD-75 Response - GLMM	FAS	EDPS1	
14.2.21.1	Summary of Percentage Change from Baseline in DLQI Score	FAS	EDPS1	
14.2.21.2	Analysis of Percentage Change from Baseline in DLQI Score - MMRM	FAS	EDPS1	
14.2.22.1	Summary of Absolute Change from Baseline in DLQI Score	FAS	EDPS1	
14.2.22.2	Analysis of Absolute Change from Baseline in DLQI Score - MMRM	FAS	EDPS1	
14.2.23	Summary and Analysis of DLQI With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS1	
14.2.24.1.1	Summary of Absolute Change from Baseline in PP-NRS Score	FAS	EDPS1	
14.2.24.1.2	Summary of Absolute Change from Baseline in PP-NRS Score	FAS	EDPS2	
14.2.24.2.1	Analysis of Absolute Change from Baseline in PP-NRS Score - MMRM	FAS	EDPS1	
14.2.24.2.2	Analysis of Absolute Change from Baseline in PP-NRS Score - MMRM	FAS	EDPS2	
14.2.25.1	Summary and Analysis of PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS1	
14.2.25.2	Summary and Analysis of PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS2	
14.2.25.3	Summary and Analysis of PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS6	

Number	Title	Population	Data Point Set	Programming notes
14.2.26.1	Summary and Analysis of PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS1	
14.2.26.2	Summary and Analysis of PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS2	
14.2.26.3	Summary and Analysis of PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS6	
14.2.27.1	Summary of Absolute Change from Baseline in SD-NRS Score	FAS	EDPS1	
14.2.27.2	Analysis of Absolute Change from Baseline in SD-NRS Score - MMRM	FAS	EDPS1	
14.2.28	Summary and Analysis of SD-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS1	
14.2.29.1	Summary of Percentage Change from Baseline in POEM Score	FAS	EDPS1	
14.2.29.2	Analysis of Percentage Change from Baseline in POEM Score - MMRM	FAS	EDPS1	
14.2.30.1	Summary of Absolute Change from Baseline in POEM Score	FAS	EDPS1	
14.2.30.2	Analysis of Absolute Change from Baseline in POEM Score - MMRM	FAS	EDPS1	
14.2.31	Summary and Analysis of POEM With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS1	Include in TLR
14.2.32.1	Summary of Number of Courses of Rescue Therapy	FAS	EDPS7	
14.2.32.2	Analysis of Number of Courses of Rescue Therapy – Poisson Regression	FAS	EDPS7	
14.2.33.1	Summary of Days with Rescue Therapy	FAS	EDPS7	
14.2.33.2	Analysis of Days with Rescue Therapy – Poisson Regression	FAS	EDPS7	
14.2.34	Summary and Analysis of Requirement for Rescue Therapy - GLMM	FAS	EDPS7	
14.2.35	Summary of Time to First Achievement of EASI-50 Response	FAS	EDPS1	
14.2.36	Summary of Time to First Achievement of Sustained EASI-50 Response	FAS	EDPS1	
14.2.54	Summary of Time to First Achievement of EASI-75 Response	FAS	EDPS1	
14.2.37	Summary of Time to First Achievement of vIGA of 0 or 1 with a >=2 Point Improvement from Baseline	FAS	EDPS1	
14.2.55	Summary of Time to First Achievement of vIGA of 0 or 1	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.38	Summary of Time to First Achievement of PP-NRS Score with a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.39	Summary of Time to First Achievement of PP-NRS Score with a >=2 Point Sustained Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.40	Summary of Time to First Achievement of PP-NRS Score with a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline	FAS	EDPS1	
14.2.41	Summary of Time to First Achievement of PP-NRS Score with a >=4 Point Sustained Improvement from Baseline for Participants with a Score of >=4 at Baseline	FAS	EDPS1	
14.2.42	Summary of Time to First Achievement of SD-NRS Score with a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.43	Summary of Time to First Achievement of SD-NRS Score with a >=2 Point Sustained Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.44	Summary of vIGA of 0 or 1 With a >=2 Point Improvement from Screening Response	FAS	EDPS1	
14.2.45	Summary of Percentage Change from Screening in EASI Score	FAS	EDPS1	
14.2.46	Summary of Absolute Change from Screening in EASI Score	FAS	EDPS1	
14.2.47	Summary of Topical Antimicrobial or Systemic Antibiotic Rescue Therapy Use on or before Week 16	FAS	EDPS1	
14.2.48	Summary of Absolute Change from Baseline in SF-12 MCS	FAS	EDPS1	
14.2.49	Summary of Absolute Change from Baseline in SF-12 PCS	FAS	EDPS1	
14.2.50	Summary of Absolute Change from Baseline in HADS Anxiety Score	FAS	EDPS1	
14.2.51	Summary of Absolute Change from Baseline in HADS Depression Score	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.52	Summary of Absolute Change from Baseline in ADCT Score	FAS	EDPS1	

15.2.2 Figures

Number	Title	Population	Data Point Set	Programming notes
14.2.1.2.1	Actual and Predicted Probability (95% CI) of EASI-50 Response At Week 16	FAS	EDPS1	Include in TLR
14.2.1.2.2	Actual and Predicted Probability (95% CI) of EASI-50 Response At Week 16	FAS	EDPS2	
14.2.1.2.3	Actual and Predicted Probability (95% CI) of EASI-50 Response At Week 16	FAS	EDPS3	
14.2.1.2.4	Actual and Predicted Probability (95% CI) of EASI-50 Response At Week 16	FAS	EDPS4	
14.2.1.2.5	Actual and Predicted Probability (95% CI) of EASI-50 Response At Week 16	FAS	EDPS5	
14.2.1.2.6	Actual and Predicted Probability (95% CI) of EASI-50 Response At Week 16	FAS	EDPS6	Include in TLR
14.2.1.3.1	Adjusted Odds Ratio (95% CI) for Achievement of EASI-50 Over Time - GLMM	FAS	EDPS1	Include in TLR
14.2.1.3.2	Adjusted Odds Ratio (95% CI) for Achievement of EASI-50 Over Time - GLMM	FAS	EDPS2	
14.2.1.3.3	Adjusted Odds Ratio (95% CI) for Achievement of EASI-50 Over Time - GLMM	FAS	EDPS6	Include in TLR
14.2.2.1.1	Proportion (95% CI) of Participants Achieving EASI-75 At Week 16	FAS	EDPS1	Include in TLR
14.2.2.1.3	Proportion (95% CI) of Participants Achieving EASI-75 At Week 16	FAS	EDPS6	
14.2.2.2.1	Adjusted Odds Ratio (95% CI) for Achievement of EASI-75 Over Time - GLMM	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.2.2.3	Adjusted Odds Ratio (95% CI) for Achievement of EASI-75 Over Time - GLMM	FAS	EDPS6	
14.2.3.1.1	Proportion (95% CI) of Participants Achieving EASI-90 At Week 16	FAS	EDPS1	Include in TLR
14.2.3.1.3	Proportion (95% CI) of Participants Achieving EASI-90 At Week 16	FAS	EDPS6	
14.2.3.2.1	Adjusted Odds Ratio (95% CI) for Achievement of EASI-90 Over Time - GLMM	FAS	EDPS1	
14.2.3.2.3	Adjusted Odds Ratio (95% CI) for Achievement of EASI-90 Over Time - GLMM	FAS	EDPS6	
14.2.4.1.1	Waterfall Plot of Percentage Change from Baseline in EASI Score at Week 16	FAS	EDPS1	Include in TLR
14.2.4.1.2	Waterfall plot of Percentage Change from Baseline in EASI Score at Weeks 4, 8 12 and 16 with Week 16 EASI-50 Responders Highlighted	FAS	EDPS1	
14.2.4.1.3	Waterfall plot of Percentage Change from Baseline in EASI Score at Weeks 4, 8 12 and 16 with Week 16 EASI-75 Responders Highlighted	FAS	EDPS1	
14.2.4.2.1	LS Mean (95% CI) Percentage Change in EASI Score Over Time - MMRM	FAS	EDPS1	
14.2.4.3.1	LS Mean Difference (95% CI) in Percentage Change from Baseline in EASI Score - MMRM	FAS	EDPS1	
14.2.5.1.1	Waterfall Plot of Absolute Change from Baseline in EASI Score at Week 16	FAS	EDPS1	
14.2.5.2.1	LS Mean (95% CI) Absolute Change in EASI Score Over Time – MMRM	FAS	EDPS1	
14.2.5.3.1	LS Mean Difference (95% CI) in Absolute Change from Baseline in EASI Score - MMRM	FAS	EDPS1	
14.2.7.1.1	Proportion (95% CI) of Participants Achieving vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response	FAS	EDPS1	Include in TLR
14.2.7.1.3	Proportion (95% CI) of Participants Achieving vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response	FAS	EDPS6	

Number	Title	Population	Data Point Set	Programming notes
14.2.7.2.1	Adjusted Odds Ratio (95% CI) for Achievement of vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - GLMM	FAS	EDPS1	
14.2.7.2.3	Adjusted Odds Ratio (95% CI) for Achievement of vIGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - GLMM	FAS	EDPS6	
14.2.8.1.1	Proportion (95% CI) of Participants Achieving vIGA of 0 or 1 Response	FAS	EDPS1	Include in TLR
14.2.8.1.3	Proportion (95% CI) of Participants Achieving vIGA of 0 or 1 Response	FAS	EDPS6	
14.2.8.2.1	Adjusted Odds Ratio (95% CI) for Achievement of vIGA of 0 or 1 Response - GLMM	FAS	EDPS1	
14.2.8.2.3	Adjusted Odds Ratio (95% CI) for Achievement of vIGA of 0 or 1 Response - GLMM	FAS	EDPS6	
14.2.9.1.1	Proportion (95% CI) of Participants Achieving vIGA of 0 Response at Week 16	FAS	EDPS1	
14.2.9.1.3	Proportion (95% CI) of Participants Achieving vIGA of 0 Response at Week 16	FAS	EDPS6	
14.2.9.2.1	Adjusted Odds Ratio (95% CI) for Achievement of vIGA of 0 Response - GLMM	FAS	EDPS1	
14.2.9.2.3	Adjusted Odds Ratio (95% CI) for Achievement of vIGA of 0 Response - GLMM	FAS	EDPS6	
14.2.10.1.1	Waterfall Plot of Percentage Change from Baseline in vIGA*BSA at Week 16	FAS	EDPS1	
14.2.10.2.1	LS Mean (95% CI) Percentage Change from Baseline in vIGA*BSA - MMRM	FAS	EDPS1	
14.2.10.3.1	LS Mean Difference (95% CI) in Percentage Change from Baseline in vIGA*BSA - MMRM	FAS	EDPS1	
14.2.12.1	Waterfall Plot of Percentage Change from Baseline in BSA at Week 16	FAS	EDPS1	
14.2.12.2	LS Mean (95% CI) Percentage Change from Baseline in BSA - MMRM	FAS	EDPS1	
14.2.12.3	LS Mean Difference (95% CI) in Percentage Change from Baseline in BSA - MMRM	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.13.1	Waterfall Plot of Absolute Change from Baseline in BSA at Week 16	FAS	EDPS1	
14.2.13.2	LS Mean (95% CI) Absolute Change from Baseline in BSA - MMRM	FAS	EDPS1	
14.2.13.3	LS Mean Difference (95% CI) in Absolute Change from Baseline in BSA - MMRM	FAS	EDPS1	
14.2.14.1	Proportion (95% CI) of Participants Achieving BSA-50 Response at Week 16	FAS	EDPS1	
14.2.14.2	Adjusted Odds Ratio (95% CI) for Achievement of BSA-50 Response - GLMM	FAS	EDPS1	
14.2.15.1	Proportion (95% CI) of Participants Achieving BSA-75 Response at Week 16	FAS	EDPS1	
14.2.15.2	Adjusted Odds Ratio (95% CI) for Achievement of BSA-75 Response – GLMM	FAS	EDPS1	
14.2.16.1	Proportion (95% CI) of Participants Achieving BSA Reduction to <=3% at Week 16	FAS	EDPS1	
14.2.16.2	Adjusted Odds Ratio (95% CI) for Achievement of BSA Reduction to <=3% - GLMM	FAS	EDPS1	
14.2.17.1	Waterfall Plot of Percentage Change from Baseline in SCORAD Score at Week 16	FAS	EDPS1	
14.2.17.2	LS Mean (95% CI) Percentage Change from Baseline in SCORAD Score - MMRM	FAS	EDPS1	
14.2.17.3	LS Mean Difference (95% CI) in Percentage Change from Baseline in SCORAD Score - MMRM	FAS	EDPS1	
14.2.18.1	Waterfall Plot of Absolute Change from Baseline in SCORAD Score at Week 16	FAS	EDPS1	
14.2.18.2	LS Mean (95% CI) Absolute Change from Baseline in SCORAD Score - MMRM	FAS	EDPS1	
14.2.18.3	LS Mean Difference (95% CI) in Absolute Change from Baseline in SCORAD Score - MMRM	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.53.1	Proportion (95% CI) of Participants Achieving SCORAD-35 Response at Week 16	FAS	EDPS1	
14.2.53.2	Adjusted Odds Ratio (95% CI) for Achievement of SCORAD-35 Response - GLMM	FAS	EDPS1	
14.2.19.1	Proportion (95% CI) of Participants Achieving SCORAD-50 Response at Week 16	FAS	EDPS1	
14.2.19.2	Adjusted Odds Ratio (95% CI) for Achievement of SCORAD-50 Response - GLMM	FAS	EDPS1	
14.2.20.1	Proportion (95% CI) of Participants Achieving SCORAD-75 Response at Week 16	FAS	EDPS1	
14.2.20.2	Adjusted Odds Ratio (95% CI) for Achievement of SCORAD-75 Response – GLMM	FAS	EDPS1	
14.2.22.1	Waterfall Plot of Absolute Change from Baseline in DLQI Score at Week 16	FAS	EDPS1	
14.2.22.2	LS Mean (95% CI) Absolute Change from Baseline in DLQI Score	FAS	EDPS1	
14.2.22.3	LS Mean Difference (95% CI) in Absolute Change from Baseline in DLQI Score - MMRM	FAS	EDPS1	
14.2.23.1	Proportion (95% CI) of Participants Achieving DLQI With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline at Week 16	FAS	EDPS1	
14.2.23.2	Adjusted Odds Ratio (95% CI) for Achievement of DLQI With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS1	
14.2.24.1.1	Waterfall Plot of Absolute Change from Baseline in PP-NRS Score at Week 16	FAS	EDPS1	
14.2.24.2.1	LS Mean (95% CI) Absolute Change from Baseline in PP-NRS Score - MMRM	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.24.3.1	LS Mean Difference (95% CI) in Absolute Change from Baseline in PP-NRS Score - MMRM	FAS	EDPS1	
14.2.25.1.1	Proportion (95% CI) of Participants Achieving PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline at Week 16	FAS	EDPS1	
14.2.25.1.3	Proportion (95% CI) of Participants Achieving PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline at Week 16	FAS	EDPS6	
14.2.25.2.1	Adjusted Odds Ratio (95% CI) for Achievement of PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS1	
14.2.25.2.3	Adjusted Odds Ratio (95% CI) for Achievement of PP-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS6	
14.2.26.1.1	Proportion (95% CI) of Participants Achieving PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline at Week 16	FAS	EDPS1	
14.2.26.1.3	Proportion (95% CI) of Participants Achieving PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline at Week 16	FAS	EDPS6	
14.2.26.2.1	Adjusted Odds Ratio (95% CI) for Achievement of PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS1	
14.2.26.2.3	Adjusted Odds Ratio (95% CI) for Achievement of PP-NRS With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - GLMM	FAS	EDPS6	
14.2.27.1	Waterfall Plot of Absolute Change from Baseline in SD-NRS Score at Week 16	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.27.2	LS Mean (95% CI) Absolute Change from Baseline in SD-NRS Score - MMRM	FAS	EDPS1	
14.2.27.3	LS Mean Difference (95% CI) in Absolute Change from Baseline in SD-NRS Score - MMRM	FAS	EDPS1	
14.2.28.1	Proportion (95% CI) of Participants Achieving SD-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline at Week 16	FAS	EDPS1	
14.2.28.2	Adjusted Odds Ratio (95% CI) for Achievement of SD-NRS With a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - GLMM	FAS	EDPS1	
14.2.30.1	Waterfall Plot of Absolute Change from Baseline in POEM Score at Week 16	FAS	EDPS1	
14.2.30.2	LS Mean (95% CI) Absolute Change from Baseline in POEM Score - MMRM	FAS	EDPS1	
14.2.30.3	LS Mean Difference (95% CI) in Absolute Change from Baseline in POEM Score - MMRM	FAS	EDPS1	
14.2.31.1	Proportion (95% CI) of Participants Achieving POEM With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline at Week 16	FAS	EDPS1	Include in TLR
14.2.31.2	Adjusted Odds Ratio (95% CI) for Achievement of POEM With a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline GLMM	FAS	EDPS1	
14.2.32	Histogram of Number of Courses of Rescue Therapy	FAS	EDPS7	
14.2.34.1	Proportion (95% CI) of Participants Not Requiring for Rescue Therapy on or before Week 16	FAS	EDPS7	
14.2.34.2	Adjusted Odds Ratio (95% CI) for Not Requiring for Rescue Therapy - GLMM	FAS	EDPS7	
14.2.35	Cumulative Incidence (95% CI) of EASI-50	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.36	Cumulative Incidence (95% CI) of Sustained EASI-50	FAS	EDPS1	
14.2.54	Cumulative Incidence (95% CI) of EASI-75	FAS	EDPS1	
14.2.37	Cumulative Incidence (95% CI) of IGA of 0 or 1 with a >=2 Point Improvement from Baseline	FAS	EDPS1	
14.2.55	Cumulative Incidence (95% CI) of IGA of 0 or 1	FAS	EDPS1	
14.2.38	Kaplan-Meier Survival Curve for Time to First Achievement of PP-NRS Score with a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.39	Kaplan-Meier Survival Curve for Time to First Achievement of PP-NRS Score with a >=2 Point Sustained Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.40	Kaplan-Meier Survival Curve for Time to First Achievement of PP-NRS Score with a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline	FAS	EDPS1	
14.2.41	Kaplan-Meier Survival Curve for Time to First Achievement of PP-NRS Score with a >=4 Point Sustained Improvement from Baseline for Participants with a Score of >=4 at Baseline	FAS	EDPS1	
14.2.42	Kaplan-Meier Survival Curve for Time to First Achievement of SD-NRS Score with a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.43	Kaplan-Meier Survival Curve for Time to First Achievement of SD-NRS Score with a >=2 Point Sustained Improvement from Baseline for Participants with a Score of >=2 at Baseline	FAS	EDPS1	
14.2.44	Proportion (95% CI) of Participants Achieving vIGA of 0 or 1 With a >=2 Point Improvement from Screening Response	FAS	EDPS1	
14.2.45.1	Waterfall Plot of Percentage Change from Screening in EASI Score at Week 16	FAS	EDPS1	
14.2.45.2	Mean (SD) Percentage Change from Screening in EASI Score	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.46.1	Waterfall Plot of Absolute Change from Screening in EASI Score at Week 16	FAS	EDPS1	
14.2.46.2	Mean (SD) Absolute Change from Screening in EASI Score	FAS	EDPS1	
14.2.47	Histogram of Number of Courses of Topical Antimicrobial or Systemic Antibiotic Rescue Therapy on or before Week 16	FAS	EDPS1	
14.2.48.1	Waterfall Plot of Absolute Change from Baseline in SF-12 MCS at Week 16	FAS	EDPS1	
14.2.48.2	Mean (SD) Absolute Change from Baseline in SF-12 MCS	FAS	EDPS1	
14.2.49.1	Waterfall Plot of Absolute Change from Baseline in SF-12 PCS at Week 16	FAS	EDPS1	
14.2.49.2	Mean (SD) Absolute Change from Baseline in SF-12 PCS	FAS	EDPS1	
14.2.50.1	Waterfall Plot of Absolute Change from Baseline in HADS Anxiety Score at Week 16	FAS	EDPS1	
14.2.50.2	Mean (SD) Absolute Change from Baseline in HADS Anxiety Score	FAS	EDPS1	
14.2.51.1	Waterfall Plot of Absolute Change from Baseline in HADS Depression Score at Week 16	FAS	EDPS1	
14.2.51.2	Mean (SD) Absolute Change from Baseline in HADS Depression Score	FAS	EDPS1	
14.2.52.1	Waterfall Plot of Absolute Change from Baseline in ADCT Score at Week 16	FAS	EDPS1	
14.2.52.2	Mean (SD) Absolute Change from Baseline in ADCT Score	FAS	EDPS1	
14.2.56	Mean Absolute Change from Baseline in PP-NRS Score - Daily	FAS	EDPS1	
14.2.57	Proportion of Participants Achieving PP-NRS Score with a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - Daily	FAS	EDPS1	
14.2.58	Proportion of Participants Achieving PP-NRS Score with a >=4 Point Improvement from Baseline for Participants with a Score of >=4 at Baseline - Daily	FAS	EDPS1	
14.2.59	Mean Absolute Change from Baseline in SD-NRS Score - Daily	FAS	EDPS1	

Number	Title	Population	Data Point Set	Programming notes
14.2.60	Proportion of Participants Achieving SD-NRS Score with a >=2 Point Improvement from Baseline for Participants with a Score of >=2 at Baseline - Daily	FAS	EDPS1	

15.3 Safety

15.3.1 Tables

Number	Title	Population	Data Point Set	Programming notes
14.3.1.1.1	Overview of TEAEs	Safety	SDPS2	Include in TLR
14.3.1.1.2	Summary of TEAEs by System Organ Class and Preferred Term	Safety	SDPS2	Include in TLR
14.3.1.2	Summary of Related TEAEs by System Organ Class and Preferred Term	Safety	SDPS2	Include in TLR
14.3.1.3	Summary of TEAEs of CTCAE Grade 3 or Above by System Organ Class and Preferred Term	Safety	SDPS2	
14.3.1.4	Summary of Non-serious TEAEs Reported by at Least 5% of Participants in Any Treatment Group by System Organ Class and Preferred Term	Safety	SDPS2	
14.3.1.5	Summary of Serious TEAEs by System Organ Class and Preferred Term	Safety	SDPS2	
14.3.1.6	Summary of Fatal TEAEs by System Organ Class and Preferred Term	Safety	SDPS2	
14.3.1.7	Summary of TEAEs Leading to Permanent Discontinuation from Study Treatment by System Organ Class and Preferred Term	Safety	SDPS2	
14.3.4.1.1	Summary of Haematology Parameters	Safety	SDPS1	
14.3.4.1.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the Normal Range for Haematology Parameters	Safety	SDPS2	
14.3.4.1.3	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria for Haematology Parameters	Safety	SDPS2	
14.3.4.2.1	Summary of Haematology Parameters	Safety	SDPS1	
14.3.4.2.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the Normal Range for Chemistry Parameters	Safety	SDPS2	

Number	Title	Population	Data Point Set	Programming notes
14.3.4.2.3	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria for Chemistry Parameters	Safety	SDPS2	
14.3.5.1	Summary of ECG Parameters	Safety	SDPS1	
14.3.5.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criterion for QTcF	Safety	SDPS2	
14.3.6.1	Summary of Vital Signs	Safety	SDPS1	
14.3.6.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criterion for Vital Signs	Safety	SDPS2	

15.4 Data Listings

Number	Title	Population	Data Point Set	Programming notes
16.2.1.1	Reasons for Screen Failure	Enrolled	SDPS2	
16.2.1.2	End of Treatment Disposition	FAS	SDPS2	
16.2.1.3	End of Study Disposition	FAS	SDPS2	
16.2.1.4	Participants for Whom the Blind Was Broken	FAS	SDPS2	
16.2.1.5	Planned and Actual Treatments	FAS	SDPS2	
16.2.1.6	Visits Missed Due to COVID-19	FAS	SDPS2	
16.2.2.1	Protocol Deviations	FAS	SDPS2	
16.2.2.2	Participants Not Meeting Inclusion and Exclusion Criteria	FAS	SDPS2	
16.2.3	Participants Excluded from Any Population	Enrolled	SDPS2	
16.2.4.1	Demographics	FAS	SDPS2	
16.2.4.2	Smoking Status	FAS	SDPS2	
16.2.4.3	Baseline Disease Characteristics	FAS	SDPS2	
16.2.4.4.1	Past Atopic Dermatitis Treatment	FAS	SDPS2	
16.2.4.4.2	Current Atopic Dermatitis Treatment	FAS	SDPS2	
16.2.4.5	Medical History	FAS	SDPS2	
16.2.4.6	Prior Medications	FAS	SDPS2	

Number	Title	Population	Data Point Set	Programming notes
16.2.4.7	Concomitant Medications	FAS	SDPS2	
16.2.5.1	Participant Dosing Diary	FAS	SDPS2	
16.2.5.2	Study Drug Compliance	FAS	SDPS2	
16.2.5.3	Exposure to Emollient	FAS	SDPS2	
16.2.5.4	Emollient Compliance	FAS	SDPS2	
16.2.6.1	Individual Components of the EASI Questionnaire	FAS	EDPS7	
16.2.6.2	EASI Endpoints	FAS	EDPS7	
16.2.6.3	vIGA Score	FAS	EDPS7	
16.2.6.4.1	BSA and vIGA*BSA	FAS	EDPS7	
16.2.6.4.2	vIGA and BSA Response Endpoints	FAS	EDPS7	
16.2.6.5	Individual Components of the SCORAD Questionnaire	FAS	EDPS7	
16.2.6.6	SCORAD Endpoints	FAS	EDPS7	
16.2.6.7	DLQI Items and Score	FAS	EDPS7	
16.2.6.8	PP-NRS and SD-NRS Scores	FAS	EDPS7	
16.2.6.9	POEM Items and Score	FAS	EDPS7	
16.2.6.10	Topical Corticosteroid or Calcineurin Inhibitors	FAS	EDPS7	
16.2.6.11	Topical Antimicrobial or Systemic Antibiotic Rescue Therapy	FAS	EDPS7	
16.2.6.12	Rescue Therapy Endpoints	FAS	EDPS7	
16.2.6.13	PP-NRS and SD-NRS Time to Event Endpoints	FAS	EDPS1	
16.2.6.14	SF-12 Individual Components and Scores	FAS	EDPS7	
16.2.6.15	HADS Individual Components and Scores	FAS	EDPS7	
16.2.6.16	ADCT Individual Components and Scores	FAS	EDPS7	
16.2.7	Inclusion/Exclusion of Participants Data from Analysis	FAS	EDPS7	
16.2.7.1.1	Adverse Events	Safety	SDPS2	
16.2.7.1.2	Serious Adverse Events	Safety	SDPS2	
16.2.7.1.3	Fatal Adverse Events	Safety	SDPS2	
16.2.7.1.4	Adverse Events Leading to Treatment Discontinuation or Early Termination of the Study	Safety	SDPS2	

Number	Title	Population	Data Point Set	Programming notes
16.2.7.2.1	Haematology parameters	Safety	SDPS2	
16.2.7.2.2	Haematology parameters PCI	Safety	SDPS2	
16.2.7.2.3	Chemistry parameters	Safety	SDPS2	
16.2.7.2.4	Chemistry parameters PCI	Safety	SDPS2	
16.2.7.2.5	Urinalysis	Safety	SDPS2	
16.2.7.3.1	ECG Data	Safety	SDPS2	
16.2.7.3.2	ECG PCI	Safety	SDPS2	
16.2.7.4.1	Vital Signs	Safety	SDPS2	
16.2.7.4.2	Vital Signs PCI	Safety	SDPS2	
16.2.7.5	Female Fertility Status and Pregnancy Test Results	Safety	SDPS2	

16 Appendix 2: Eczema Area and Severity Index

Intensity

A representative area of psoriasis is selected for each body region (head and neck, upper limbs, trunk, lower limbs).

The average severity of each of four signs (erythema/redness, edema/papulation, excoriation, lichenification) in each body region is scored as:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild.

A severity score is calculated for each body region as the sum of the four scores for erythema/redness, edema/papulation, excoriation and lichenification.

- A1 = A severity score for head and neck
- A2 = A severity score for upper extremities
- A3 = A severity score for trunk
- A4 = A severity score for lower extremities

Each subtotal is multiplied by the body surface area represented by that region as follows:

- B1 = 0.1 x A1
- B2 = 0.2 x A2
- B3 = 0.3 x A3
- B4 = 0.4 x A4

Percentage area affected

The percentage area affected by psoriasis is evaluated in each of the four body regions. In each body region the area is expressed as:

- 0 = not affected at all
- 1 = 1 – 9%
- 2 = 10-29%
- 3 = 30-49%
- 4 = 50%-69%
- 5 = 70-89%
- 6 = 90-100%

EASI score calculation

Each of the body area scores is multiplied by the severity score for the relevant body region (B1-B4) to gives four area intensity scores (C1-C4).

The EASI score is the sum of the four area intensity scores:

EASI score = C1 + C2 + C3 + C4.

EASI score ranges from 0 to 72.

17 Appendix 3: Validated Investigator Global Assessment

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

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

The vIGA score ranges from 0 to 4.

18 Appendix 4: Severity Scoring of Atopic Dermatitis

Investigator-rated area score

Extent

The rule of 9 is used to calculate the affected area (A) as a percentage of the whole body.

In each affected area the area involved is assessed:

	Front	Back
Head and Neck	0 to 4.5	0 to 4.5
Upper limbs (left)	0 to 4.5	0 to 4.5
Upper limbs (right)	0 to 4.5	0 to 4.5
Palms	0, 1, 2	
Trunk	0 to 18	0 to 18
Genitals	0, 0.5, 1	
Lower limbs (left)	0 to 9	0 to 9
Lower limbs (right)	0 to 9	0 to 9

The scores for each area are added together to give 'A'. It should be noted that this gives a theoretical maximum of 102% BSA.

Intensity

An intensity of each of six signs (erythema/redness, edema/papulation, oozing/crust, excoriation, lichenification, dryness) in each body region is scored as:

- 0 = Absence
- 1 = Mild
- 2 = Moderate
- 3 = Severe

The intensity scores are added together to give 'B' (maximum 18).

Subjective symptoms component

- Pruritus is measured on visual analogue scale and ranges from 0 to 10.
- Sleep loss is measured on visual analogue scale and ranges from 0 to 10.

The subjective symptoms scores are added together to give 'C' (maximum 20).

SCORAD calculation

The SCORAD score is defined as:

$$\text{SCORAD score} = A/5 + 7B/2 + C.$$

SCORAD score ranges from 0 to 103.

19 Appendix 5: Patient Oriented Eczema Measure

The POEM consists of 7 questions:

1. Over the last week, on how many days has your skin been itchy because of the eczema?
2. Over the last week, on how many nights has your sleep been disturbed because of the eczema?
3. Over the last week, on how many days has your skin been bleeding because of the eczema?
4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of the eczema?
5. Over the last week, on how many days has your skin been cracked because of the eczema?
6. Over the last week, on how many days has your skin been flaking off because of the eczema?
7. Over the last week, on how many days has your skin felt dry or rough because of the eczema?

Each question is scored as:

- 0 = No days
- 1 = 1-2 days
- 2 = 3-4 days
- 3 = 5-6 days
- 4 = Every day

If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28.
If two or more questions are left unanswered the questionnaire is not scored.

The POEM score is the sum of the 7 item scores and ranges from 0 to 28.

20 Appendix 6: Dermatology Quality of Life Index

The DLQI consists of 10 questions:

1. Over the last week, how itchy, sore, painful or stinging has your skin been?
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?
4. Over the last week, how much has your skin influences the clothes you wear?
5. Over the last week, how much has your skin affected any social or leisure activities?
6. Over the last week, how much has your skin made it difficult for you to do any sport?
7. Over the last week, has your skin prevented you from working or studying?
   If "No", over the last week how much has your skin been a problem at work or studying?
8. Over the last week, how much has your skin created problems for your partner or any of your close friends or relatives?
9. Over the last week, how much has your skin caused any sexual difficulties?
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or taking up time?

Questions 1 and 2 is scored on a four-point Likert scale:

- 3 = Very much
- 2 = A lot
- 1 = A little
- 0 = Not at all

Questions 3-6 and 8-10 also have an option of not relevant and are scored as:

- 3 = Very much
- 2 = A lot
- 1 = A little
- 0 = Not at all
- 0 = Not relevant

Question 7 is a 2-part question and is scored as:

- 3 = Yes
- 3 = No; Very much
- 2 = No; A lot
- 1 = No; A little
- 0 = No; Not at all
- 0 = Not relevant

Any unanswered question is scored as 0.
The DLQI score is the sum of the 10 item scores.

21 Appendix 7: 12-Item Short Form Health Survey

The SF-12 consists of 12 questions:

1. In general, would you say your health is
2. Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?
3. Does your health now limit you in climbing several flights of stairs? If so, how much?
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of your physical health
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Were limited in the kind of work or other activities as a result of your physical health
6. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)
7. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
9. How much of the time during the past 4 weeks have you felt calm and peaceful?
10. How much of the time during the past 4 weeks did you have a lot of energy?
11. How much of the time during the past 4 weeks have you felt downhearted and depressed?
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

Questions 1 is scored as:

- Excellent
- Very good
- Good
- Fair
- Poor

Questions 2 and 3 are scored as:

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

Questions 4-7 and 9-12 are scored as:

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Question 8 is scored as:

- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely

PCS component is based on questions 1-5 and 8. MCS component is based on questions 6-7 and 9-12.

SF-12 MCS and PCS are calculated using Optum's PRO CoRE software and ranges from 0 to 100.

22 Appendix 8: Hospital Anxiety and Depression Scale

The HADS consists of 14 questions (7 anxiety and 7 depression):

1. I feel tense or "wound up" *(anxiety)*
2. I enjoy the things I used to enjoy *(depression)*
3. I get a sort of frightened feeling as if something awful is about to happen *(anxiety)*
4. I can laugh and see the funny side of things *(depression)*
5. Worrying thoughts go through my mind *(anxiety)*
6. I feel cheerful *(depression)*
7. I can sit at ease and feel relaxed *(anxiety)*
8. I feel as if I am slowed down *(depression)*
9. I get a sort of anxious feeling like 'butterflies' in the stomach *(anxiety)*
10. I have lost interest in my appearance *(depression)*
11. I feel restless as I have to be on the move *(anxiety)*
12. I look forward with enjoyment to things *(depression)*
13. I get sudden feelings of panic *(anxiety)*
14. I can enjoy a good book, radio or television program *(depression)*

Each question is scored on a four-point Likert scale:

Question 1:

- 3 = Most of the time
- 2 = A lot of the time
- 1 = From time to time, occasionally
- 0 = Never

Question 2:

- 0 = Definitely
- 1 = Not quite so much
- 2 = Only a little
- 3 = Hardly at all

Question 3:

- 3 = Very definitely and fairly badly
- 2 = Yes, but not too badly
- 1 = Sometimes, but it doesn't worry me
- 0 = Never

Question 4:

- 0 = As much as I always could
- 1 = Not quite so much now

- 2 = Definitely not so much now
- 3 = Not at all

Question 5:

- 3 = A great deal of the time
- 2 = A lot of the time
- 1 = From time to time, but not too often
- 0 = Only occasionally

Question 6:

- 3 = Not at all
- 2 = Not often
- 1 = Sometimes
- 0 = Most of the time

Question 7:

- 0 = Definitely
- 1 = Usually
- 2 = Not often
- 3 = Not at all

Question 8:

- 3 = Nearly all the time
- 2 = Very often
- 1 = Sometimes
- 0 = Not at all

Question 9:

- 0 = Not at all
- 1 = Occasionally
- 2 = Quite Often
- 3 = Very Often

Question 10:

- 3 = Definitely
- 2 = I don't take as much care as I should
- 1 = I may not take quite as much care
- 0 = I take just as much care as ever

Question 11:

- 3 = Very much indeed
- 2 = Quite a lot
- 1 = Not very much

- 0 = Not at all

Question 12:

- 0 = As much as I ever did
- 1 = Rather less than I used to
- 2 = Definitely less than I used to
- 3 = Hardly at all

Question 13:

- 3 = Very often indeed
- 2 = Quite often
- 1 = Not very often
- 0 = Not at all

Question 14:

- 0 = Often
- 1 = Sometimes
- 2 = Not often
- 3 = Very seldom

HADS Anxiety and Depression Total Scores

The HADS anxiety total score is the sum of the 7 anxiety scores. The HADS depression total score is the sum of the 7 depression scores.

Total scores for anxiety and depression ranges from 0 to 21 and classifies as:

- 8-10 = Mild
- 11-14 = Moderate
- 15-21 = Severe

23 Appendix 9: Atopic Dermatitis Control Tool

The ADCT consists of 6 questions:

1. Over the last week, how would you rate your eczema-related symptoms (for example, itching, dry skin, skin rash)?
2. Over the last week, how many days did you have intense episodes of itching because of your eczema?
3. Over the last week, how bothered have you been by your eczema?
4. Over the last week, how many nights did you have trouble falling or staying asleep because of your eczema?
5. Over the last week, how much did your eczema affect your daily activities?
6. Over the last week, how much did your eczema affect your mood or emotions?

Questions 1 is scored as:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Very severe

Question 2 is scored as:

- 3 = Not at all
- 2 = 1-2 days
- 1 = 3-4 days
- 0 = 5-6 days
- 0 = Every day

Question 3 is scored as:

- 0 = Not at all
- 1 = A little
- 2 = Moderately
- 3 = Very
- 4 = Extremely

Question 4 are scored as:

- 3 = No nights
- 2 = 1-2 nights
- 1 = 3-4 nights
- 0 = 5-6 nights
- 0 = Every night

Questions 5 and 6 are scored as:

- 0 = Not at all
- 1 = A little
- 2 = Moderately
- 3 = A lot
- 4 = Extremely

The ADCT total score is the sum of the 6 ADCT questions and ranges from 0 to 24.

24 Appendix 10: MedDRA Internationally Agreed Order for System Organ Class

The internationally agreed SOC order to be used for medical history and AE summary tables is provided in Table 5.

Table 5 MedDRA Internationally Agreed SOC Order

Order Number	System Organ Class
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

25 Appendix 11: Safety Laboratory Evaluations

Table 6 Safety Laboratory Parameters and Units

Category	Parameter	Conventional Unit	SI Units	PCI Criteria (SI units)	
				Low	High
Haematology	Hemoglobin	g/dL	g/L	<100 ≥20 decrease from BL	>20 increase from BL
	Hematocrit	%	L/L		
	Red blood cell count	10^6/uL	10^12/L		
	White blood cell count	10^3/uL	10^9/L	<3	
	Platelet count	10^3/uL	10^9/L	<75	
	Mean corpuscular volume	fL	fL		
	Mean corpuscular hemoglobin	pg	pg		
	Mean corpuscular hemoglobin concentration	g/dL	g/L		
	Absolute neutrophils	10^3/uL	10^9/L	<1.5	
	Absolute lymphocytes	10^3/uL	10^9/L	<0.8	>4
	Absolute monocytes	10^3/uL	10^9/L		
	Absolute eosinophils	10^3/uL	10^9/L		
	Relative neutrophils	%	%		
	Relative lymphocytes	%	%		
	Relative monocytes	%	%		
	Relative eosinophils	%	%		
	Relative reticulocytes	%	%		

Category	Parameter	Conventional Unit	SI Units	PCI Criteria (SI units)	
				Low	High
Chemistry	Aspartate aminotransferase	U/L	U/L		>3xULN if BL did not exceed ULN, >3xBL if BL was above ULN
	Alanine aminotransferase	U/L	U/L		>3xULN if BL did not exceed ULN, >3xBL if BL was above ULN
	Creatinine	mg/dL	mcmol/L		>1.5xULN if did not exceed ULN, >1.5xBL if BL was above ULN
	Potassium	mEq/L	mmol/L		>5.5
	Sodium	mEq/L	mmol/L	<125	>150
	Blood urea nitrogen	mg/dL	mmol/L		
	Total bilirubin	mg/dL	mcmol/L		>1.5xULN if BL did not exceed ULN, >1.5xBL if BL was above ULN
	CRP	mg/L	nmol/L		
	Gamma-glutamyl transpeptidase	U/L	U/L		

Category	Parameter	Conventional Unit	SI Units	PCI Criteria (SI units)	
				Low	High
Urinalysis	Protein	mg/dL	mg/dL		
	Blood				
	Glucose	mg/dL	mg/dL		
	Ketones	mg/dL	mg/dL		
	Bilirubin				
	pH	pH	pH		
	Nitrites				
	Specific gravity				

BL=Baseline, PCI = potentially clinically important, ULN = Upper limit of normal range.

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STATISTICAL ANALYSIS PLAN
Cohort 4 Addendum

Protocol: EDP1815-207
Protocol Version: V5.0 25APR2022

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple-Cohort Study Investigating the Effect of EDP1815 in Participants for the Treatment of Mild, Moderate and Severe Atopic Dermatitis

SAP/Amendment Number	Date
Final SAP C4 Addendum v1.0	14 March 2023

Prepared for: Evelo Biosciences Inc.

Prepared by: [redacted]

Approved by	Signature	Date
[redacted] Clinical Lead, Evelo Biosciences Inc.	[redacted]	
[redacted] Director of Statistics, Evelo Biosciences Inc.		

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Senior Statistician,

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1 Table of Contents

Table of Tables

2 Abbreviations and Definitions

BSA	Body Surface Area
BMI	Body Mass Index
CI	Confidence Intervals
DPS	Data Point Set
EASI	Eczema Area and Severity Index
FAS	Full Analysis Set
PS	Propensity Score
SD	Standard Deviation
SAP	Statistical Analysis Plan
vIGA	Validated Investigator Global Assessment

3 Introduction

The purpose of this SAP Cohort 4 Addendum is to provide information that, together with the main SAP, is necessary to perform the required cohort 4 specific statistical analyses of study EDP1815-207. It also defines the cohort 4 specific TFLs to be included in the final clinical study report according to the protocol. The SAP addendum is based upon, and assumes familiarity, with the study protocol, version 5.0, dated 25-Apr-2022.
Only additional information specific to cohort 4 analyses or different from what was stated in the main SAP is included in this SAP addendum. The main study SAP should be referred to for all derivations, estimand definitions and model specifications.

Changes to the analyses described in the protocol or the main SAP other than those already listed in the main SAP are summarised in Section 0.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP Addendum will be amended accordingly. The content of this SAP Addendum is compatible with the ICH E9 Guidance document.

4 Efficacy Analyses

4.1 Pooling of Placebo Cohorts

For cohort 4 efficacy analyses, cohort 4 placebo group and set of 35 matched placebo participants from cohorts 1-3 will be pooled into a single ‘cohort 4 matched placebo’ group and will be used as a common control group for the cohort 4 EDP1815 treatment group.

As a sensitivity analysis, the cohort 4 EDP1815 treatment group will also be compared to the cohort 4 placebo group in all relevant analyses.

4.1.1 Selection of Matched Placebo

Selection of matched placebo participants will be made separately by the unblinded team before cohort 4 DBL but close enough to ensure that data needed for analysis is cleaned and will not change for all cohort 4 participants.
Only pre-treatment data (covariates from screening or baseline) of cohorts 1-3 placebo participants and cohort 4 participants and treatment assignments of cohort 4 participants will be provided to the unblinded team for analysis.
The process management details and team responsibilities are described in an interim analysis process plan.

35 placebo participants will be selected from cohorts 1-3. The group will include 5 to 7 participants with mild vIGA score and 3 to 5 participants with severe vIGA score to match cohort 4 vIGA frequencies.

Propensity scores

Propensity scores (PS) will be estimated by a logistic regression model. The treatment assignment (binary: 0 for placebo and 1 for active) is regressed through covariates.
The following covariates will be selected for initial model:

- Categorical: vIGA, sex, region (North America, rest of the world)
- Continuous: BMI, BSA, EASI score

Covariates will come from the last pre-treatment assessment which can be screening, baseline or unscheduled visit. To ensure the fit of the model sex or region may be excluded from covariates list.

Main matching algorithm

Each patient in active treatment group of cohort 4 will be matched with one placebo patient from cohort 1-3 using optimal matching to minimize overall calliper distance of matched pairs (Austin 2011). Initially calliper distance will be set to 0.25 (SD of logit(PS)) and may be increased to get more matches and ensure better balance of covariates.
From all matched pairs, only pairs with loose* vIGA match will be selected.
From the loose matched pairs, 5 pairs with lowest logit(PS) difference where cohort 4 matched subject has mild vIGA score and 3 pairs with lowest logit(PS) difference where cohort 4 matched subject has severe vIGA score will be selected to ensure minimum requested frequency of mild and severe vIGA. Another 27 pairs will be selected from the remaining loose matched pairs with the least logit(PS) difference to ensure that best matched candidates are chosen.
If more than 7 pairs with mild vIGA cohort 4 matched subjects or 5 pairs with severe vIGA cohort 4 matched subjects will be selected, excess pairs with highest logit(PS) difference will replaced by pairs with moderate vIGA cohort 4 matched subjects (chosen from remaining pairs with lowest logit(PS) difference).

Placebo participants from these pairs will be considered as matched group from cohorts 1-3 and included in the cohort 4 matched placebo group in addition to cohort 4 placebo participants.

* Loose match keeps mild – moderate and moderate – severe matches in addition to exact matches and only discards the matches between mild and severe in either group.

Balance diagnostics

After selection is complete, balance diagnostics will be performed. Balance of all covariates will be compared for before matching and after matching scenarios.
Graphics will be presented for:

- continuous covariates - side by side box plot
- binary/categorical covariates - grouped bar-plot to compare frequencies

Also, standardized differences will be calculated:

- continuous covariates:

$$d = \frac{\bar{x}_{TRT} - \bar{x}_{CON}}{\sqrt[2]{\frac{S^2_{TRT} + S^2_{CON}}{2}}},$$

here $\bar{x}_{TRT}, S^2_{TRT}$ is sample mean and sample variance of treatment group.

- binary/categorical covariates:

$$d = \frac{\hat{p}_{TRT} - \hat{p}_{CON}}{\sqrt[2]{\frac{\hat{p}_{TRT}(1-\hat{p}_{TRT}) + \hat{p}_{CON}(1-\hat{p}_{CON})}{2}}},$$

here $\hat{p}_{TRT}$ is response rate in treated group. For variables (e.g. region) with multiple categories, "d" will be measured for each category.

PS matching will be assessed against pre and post matching balance diagnostics. The calliper distance may be modified accordingly until an acceptable balance is achieved across the covariates or some covariates may be excluded.

In case of the main algorithm failure the alternative algorithm will be used.

Alternative matching algorithm

Perform optimal fixed ratio matching for cohort 4 placebo participants with cohort 4 EDP1815 participants. Exact matching for vIGA covariate should be considered.
Remaining unmatched 35 EDP1815 participants from cohort 4 will be matched (using similar fixed ratio optimal matching) with 35 placebos from cohorts 1-3. Placebo participants from these pairs will be considered as matched group and analysed in the cohort 4 matched placebo group.

4.2 Selection of Additional Covariates

The covariates selected for cohorts 1-3 primary model will be used in all cohort 4 analytical models.

4.3 Primary Efficacy Analysis

For all estimands intercurrent events will be accounted for as described in the main SAP.

4.3.1 Primary Efficacy Estimand

The primary efficacy estimand will be the effect of cohort 4 EDP1815 compared to the cohort 4 matched placebo group on the percentage of participants achieving EASI-50 at Week 16. The population summary measure of interest will be the odds ratio between active EDP1815 treatment group and matched placebo.

4.3.2 Main Analytical Approach

The primary analysis will be performed using a logistic regression model as described in the main SAP.

Treatment will consist of 4 levels (cohort 4 placebo, matched placebo from cohorts 1-3, cohort 4 EDP1815 and cohort 1 EDP1815). Baseline vIGA will consist of 3 levels (2, 3 and 4).

The following treatment differences will be of estimated:

- Cohort 4 EDP1815 vs Cohort 4 matched placebo
- Cohort 4 EDP1815 vs Cohort 1 EDP1815*
- Cohort 4 EDP1815 vs Cohort 4 placebo**

* Comparisons between cohort 4 EDP1815 and cohort 1 EDP1815 will be considered as exploratory analysis.
** Comparisons between cohort 4 EDP1815 and cohort 4 placebo will be considered as sensitivity analysis.

P-values will be only displayed for the comparison of active treatment vs placebo groups.

4.3.3 Cohort 4 Specific Sensitivity Analyses

4.3.3.1 Within Cohort 4 Analysis

Comparison between cohort 4 EDP1815 and cohort 4 placebo will be considered a sensitivity analysis for the primary endpoint. Primary analysis approach will be used.

4.3.3.2 Bayesian sensitivity analysis

A sensitivity analysis on the primary endpoint will be performed using Bayesian dynamic borrowing via robust mixture priors. The analysis will incorporate all Cohort 4 data and Cohort 1-3 placebo data.

Robust mixture priors utilize historical data (in this case, Cohort 1-3 placebo data) to supplement concurrent data (Cohort 4 placebo data). In contrast to other methods, this method is more robust due to the inclusion of a weakly informative component in the prior distribution. The inclusion of this component allows for dynamic borrowing, increasing borrowing from historical data which is similar to the concurrent data, and decreasing borrowing in the event of prior-data conflict (Heinz Schmidli 2014).

The analysis model will be constructed as follows. Let y_0, y_1, and y_2 be the number of EASI-50 responses at Week 16 observed in Cohorts 1-3 placebo, Cohort 4 placebo, and Cohort 4 EDP1815 groups. Similarly, denote N_0, N_1, and N_2 as the number of patients with a Week 16 observation, per the Primary Estimand definition. The likelihood functions for the Cohort 4 Active and Cohort 4 placebo groups are:

$$y_1 \sim Bin(N_1, \pi_1)$$
$$y_2 \sim Bin(N_2, \pi_2)$$

The prior distribution for the Cohort 4 EDP1815 response rate is the weakly informative prior:

$$\pi_2 \sim \text{Beta}(1,1)$$

The prior distribution for the Cohort 4 placebo group response rate is based on a robust mixture of an informative component, based on the data observed in Cohorts 1-3 placebo group, and a weakly informative component:

$$\pi_1 \sim (1-w)\text{Beta}(y_0, N_0 - y_0) + wBeta(1,1)$$

Here w is the a priori weight on the weakly informative component of the prior. Based on a simulation study, the weight will be set to .5 to adequately control Type 1 error and provide adequate power.

Posterior distributions will be calculated using the RBest package in R. The following summary statistics will be calculated based on the posterior distributions:

- Posterior means, standard deviations and 95% credible intervals for π_1, π_2, and $\pi_2 - \pi_1$
- Posterior probability $\Pr(\pi_2 - \pi_1 > 0)$
- Approximate number of Cohort 1-3 patients borrowed for the analysis

The approximate number of patients borrowed will be calculated based on the difference of ESS of the π_1 posterior and number patients in the Cohort 4 placebo group: $ESS - N_1$. ESS will be calculated based on the Elir method (Beat Neuenschwander 2020).

4.3.3.3 Subgroup sensitivity analysis

[redacted]

4.4 Secondary Efficacy Analyses

The following treatment differences will be estimated:

- Cohort 4 EDP1815 vs Cohort 4 matched placebo
- Cohort 4 EDP1815 vs Cohort 4 placebo
- Cohort 4 EDP1815 vs Cohort 1 EDP1815 *

* Comparisons between cohort 4 EDP1815 and cohort 1 EDP1815 will be considered as exploratory analysis.

Treatment will consist of 4 levels (cohort 4 placebo, matched placebo from cohorts 1-3, cohort 4 EDP1815 and cohort 1 EDP1815).

The comparison with pooled placebo groups (cohort 4 matched placebo) will be done using contrasts (LSMESTIMATE statement) within the relevant SAS procedures.

For other information see the main study SAP.

4.5 Exploratory Efficacy Analyses

The exploratory efficacy analyses described in the main SAP will also be produced for cohort 4.

5 Technical Details

In addition to the technical details of processes described in the main SAP where [redacted] team is involved, the Bayesian dynamic borrowing sensitivity analysis of the primary endpoint will be conducted by [redacted] utilizing RBest package in R.

6 Summary of Changes from the Protocol

The SAP Addendum is based on the latest Protocol v5.0.

Table 1: Summary of Changes from the Protocol and the main SAP

Protocol Version	Summary of Change	Justification for change
V5.0	Protocol states the sensitivity analysis for the primary endpoint of Cohort 4 will utilize a commensurate prior method to perform dynamic borrowing. The approach has been updated to utilize robust mixture priors to perform the dynamic borrowing sensitivity analysis	The robust mixture priors method is more robust due to the inclusion of a weakly informative component in the prior distribution
V5.0	Sensitivity analysis to compare cohort 4 EDP1815 to a cohort 4 placebo was added.	Due to the concerns in cohorts 1-3 placebo participants similarity to cohort 4 placebo, it was decided to add sensitivity analysis (within cohort 4 comparison). So in the case of different behaviour of cohort 4 placebo participants, sensitivity analysis vs. cohort 4 placebo still will be valid, however, with less power (as described in the Protocol).

7 Bibliography

Austin, Peter C. 2011. *Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies.* Pharm Stat. 2011 Mar; 10(2): 150–161. doi:10.1002/pst.433.

Beat Neuenschwander, Sebastian Weber,Heinz Schmidli,Anthony O'Hagan. 2020. *Predictively consistent prior effective sample sizes.* doi: https://doi.org/10.1111/biom.13252.

Heinz Schmidli, Sandro Gsteiger,Satrajit Roychoudhury,Anthony O'Hagan,David Spiegelhalter,Beat Neuenschwander. 2014. *Robust meta-analytic-predictive priors in clinical trials with historical control information.* doi: https://doi.org/10.1111/biom.12242.

8 Appendix 1: List of Tables, Figures and Listings

Only additional outputs not listed in the main SAP included in this section.

8.1 Efficacy

All efficacy outputs numbers will be displayed as 14.2.xx.xx.xxB to distinguish from cohorts 1-3 analysis outputs.

8.1.1 Tables

Number	Title	Population	Data Point Set	Programming notes
14.2.1.4.3	Summary of EASI-50 Response within Investigators Subgroup	FAS	EDPS1	Subgroup sensitivity analysis described in Section 4.3.3.3
14.2.1.4.4	Analysis of EASI-50 Response at Week 16 within Investigators Subgroup - Logistic Regression	FAS	EDPS1	Subgroup sensitivity analysis described in Section 4.3.3.3
14.2.1.6	Analysis of EASI-50 Response – Bayesian Sensitivity	FAS	EDPS1	Bayesian sensitivity analysis described in Section 4.3.3.2

8.1.2 Figures

Number	Title	Population	Data Point Set	Programming notes
14.2.1.4.1	Actual and Predicted Probability (95% CI) of EASI-50 Response within Investigators Subgroup at Week 16	FAS	EDPS1	Subgroup sensitivity analysis described in Section 4.3.3.3

9 Appendix 2: List of [redacted] patients

Participant Number
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DocuSign

Certificate Of Completion

Envelope Id: 6904C7F0924C4B3E9246F550D5E5C881
Status: Completed
Subject: Complete with DocuSign: EDP1815-207 SAP C4 Addendum V1.0 clean.pdf
Source Envelope:
Document Pages: 13
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC)

Record Tracking

Status: Original
3/15/2023 8:50:46 AM
Holder:
Location: DocuSign

Signer Events	Signature	Timestamp
Senior Statistician I Veramed Security Level: Email, Account Authentication (Required), Logged in	Signature Adoption: Uploaded Signature Image Signature ID: B5F84737-8784-4E0C-BEBC-5A7ECBE37658 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/15/2023 8:52:03 AM Viewed: 3/15/2023 8:52:19 AM Signed: 3/15/2023 8:52:33 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Security Level: Email, Account Authentication (Required)	Signature Adoption: Uploaded Signature Image Signature ID: 6FE28088-426D-4FE0-802F-CDAAE5551E4C With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/15/2023 8:52:03 AM Viewed: 3/15/2023 9:58:25 AM Signed: 3/15/2023 9:58:57 AM
Electronic Record and Signature Disclosure: Accepted: 6/23/2021 9:43:31 AM ID: 624ba298-fa6d-4264-857e-e8216fbf522c		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: BBCA57D2-D0F8-4BFD-A51F-97F66945B42E [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/15/2023 8:52:04 AM Viewed: 3/15/2023 10:49:39 AM Signed: 3/15/2023 10:49:59 AM
Electronic Record and Signature Disclosure: Accepted: 3/15/2023 10:49:39 AM ID: 77b810e9-cdbb-439d-be1f-6d197da6280a		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	3/15/2023 8:52:04 AM
Certified Delivered	Security Checked	3/15/2023 10:49:39 AM
Signing Complete	Security Checked	3/15/2023 10:49:59 AM
Completed	Security Checked	3/15/2023 10:49:59 AM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

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