Cover Page

STATISTICAL ANALYSIS PLAN
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A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis

STATISTICAL ANALYSIS PLAN

Protocol: EDP1815-201
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A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis

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1 Table of Contents

Table of Tables

Table of Figures

2 Abbreviations and Definitions

AE	Adverse event
BMI	Body mass index
BSA	Body surface area
BSFS	Bristol Stool Form Scale
CI	Confidence interval
CRF	Case report form
CrI	Credible interval
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
dp	Decimal place
DIC	Deviance information criterion
DLQI	Dermatology Life Quality Index
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EMICM	Expectation-maximisation iterative complex minorant
EOS	End of study
FUP	Functional uniform prior
GI	Gastrointestinal
HPD	Highest posterior density
IMP	Investigational medical product
IRT	Interactive response technology
ITT	Intention to treat
LDH	Lactate dehydrogenase
LS	Least squares
LSS	Lesion severity score
MCSE	Monte Carlo standard error
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
mNAPSI	Modified Nail Psoriasis Severity Index
NPMLE	Nonparametric maximum likelihood estimator
PASI	Psoriasis Area and Severity Index
PCI	Potentially clinically important
PGA	Physician’s Global Assessment
PIC	Powder in capsule
PSI	Psoriasis Symptom Inventory
PT	Preferred term
SAE	Serious adverse event
SF-36	36-Item Short Form Survey Instrument
SOC	System organ class
SAP	Statistical analysis plan
SD	Standard deviation

SE	Standard error
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

3 Introduction

The purpose of this SAP is to provide all information that is necessary to perform the required statistical analyses of study EDP1815-201. It also defines the summary TFLs to be included in the final clinical study report according to the protocol. The SAP is based upon, and assumes familiarity, with the study protocol, version 5.0, dated 17--Nov-2020.

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 evaluate the safety and efficacy of 3 different doses of EDP1815 for the treatment of psoriasis following daily dosing for 16 weeks.

The secondary objectives of the study are

- To evaluate the efficacy dose response of EDP1815 at Week 16.
- To evaluate the maximal clinical benefit of EDP1815 at Week 16.
- To evaluate the optimal dose of EDP1815 based on efficacy and safety up to Week 16.
- To evaluate the safety and tolerability of EDP1815 (all dose levels) throughout the study.
- To evaluate relapse and rebound of plaque psoriasis after cessation of EDP1815.

The exploratory objectives of the study are:

- To evaluate the time to onset of clinical response to EDP1815.
- To evaluate the effect of EDP1815 treatment on patient-reported outcomes including quality of life and pain.
- To evaluate the effect of EDP1815 treatment on biomarkers in blood.
- To evaluate the effect of EDP1815 treatment on biomarkers in skin plaques.
- To evaluate the effect of EDP1815 treatment on faecal microbiome composition.
- To evaluate the duration of remission, treatment success, and therapeutic effect of EDP1815.

4.2 Endpoints

The primary efficacy endpoint for the study is:

- Percentage change in PASI score from baseline at Week 16.

The secondary efficacy endpoints for the study are:

- Percentage change in PASI score from baseline at Weeks 4, 8 and 12.
- Absolute change from baseline in PASI score at Weeks 4, 8, 12 and 16.
- Achievement of PASI-50 at Weeks 4, 8, 12 and 16.
- Time to first achievement of PASI-50.
- Achievement of PASI-75, PASI-90 and PASI-100 at Week 16.
- Achievement of PGA of 0 or 1 with a ≥2-point improvement from baseline at Week 16.
- Achievement of PGA of 0 at Week 16.
- Percentage change from baseline in PGA*BSA at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in PGA*BSA at Weeks 4, 8, 12, and 16.
- Percentage change from baseline in LSS at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in LSS at Weeks 4, 8, 12, and 16.
- Percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16.
- Percentage change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16.
- Cumulative incidence of partial relapse at Weeks 20, 24, 28, and 40.
- Cumulative incidence of complete relapse at Weeks 20, 24, 28, and 40.
- Cumulative incidence of rebound at Weeks 20, 24, 28, and 40.

Exploratory efficacy endpoints are:

- Achievement of PASI-50, PASI-75, PASI-90, and PASI-100 at Weeks 4, 8, and 12.
- Achievement of PGA of 0 or 1 with a ≥2-point improvement at Weeks 4, 8, and 12.
- Achievement of PGA of 0 at Weeks 4, 8, and 12.
- Achievement of PGA of 0 or 1 at Weeks 4, 8, 12, and 16.
- Percentage change from baseline in BSA at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in BSA at Weeks 4, 8, 12, and 16.
- Achievement of BSA<3% and BSA-75 at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in PSI quality of life total and itch scores at Weeks 12 and 16.
- Percentage change from baseline in PSI quality of life total and itch scores at Weeks 12 and 16.
- Absolute change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16.
- Percentage change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16.
- Absolute change from baseline in fasting blood glucose and fasting lipid panel at Weeks 8 and 16.
- Mean duration of remission in participants who achieve PASI-100.
- Mean duration of treatment success in participants who achieve PASI-50.
- Mean duration of therapeutic effect in participants after cessation of study treatment.

Other exploratory endpoints are:

- Histological assessment of skin plaque biopsies (including epidermal thickness, basal mitotic counts and immune cell infiltrates) at Week 16 versus baseline.
- mRNA transcription analysis on skin plaque biopsies at Week 16 versus baseline.
- Blood cytokine and chemokine levels at Week 16 versus baseline.
- Microbiome composition (in faeces) at Week 16 and Week 20 versus baseline.

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

5 Study Methods

5.1 General Study Design and Plan

This is a multicentre, randomised double-blind, placebo-controlled, parallel cohort dose ranging study of participants with mild to moderate plaque psoriasis.

After eligibility is confirmed during the screening period (Protocol Section 4.1), participants will be randomly assigned in a 1:1:1 ratio to 1 of the following 3 parallel cohorts:

- Cohort 1: 0.8×10^{11} cells of EDP1815 or matching placebo administered as 1 PIC, once daily.
- Cohort 2: 3.2×10^{11} cells of EDP1815 or matching placebo administered as 4 PICs, once daily.
- Cohort 3: 8.0×10^{11} cells of EDP1815 or matching placebo administered as 10 PICs, once daily.

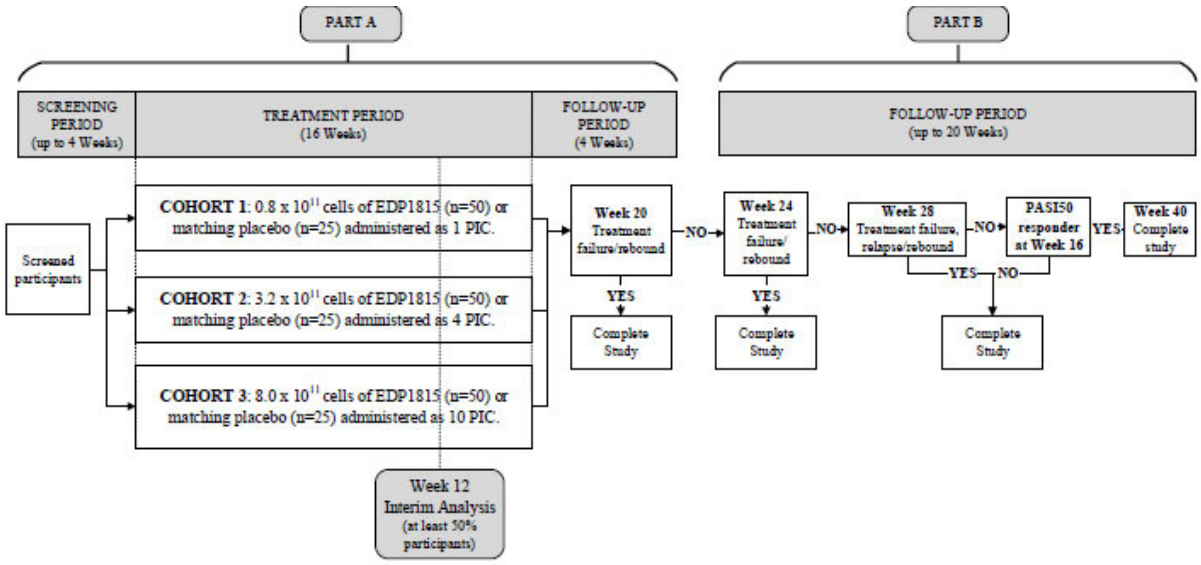
In each cohort, approximately 75 participants will be randomly assigned in a 2:1 ratio to receive either EDP1815 or matching placebo once daily for 16 weeks.

As shown in Figure 1, Part A of the study comprises a screening period of up to 4 weeks, a baseline visit, a treatment period of 16 weeks, and a follow-up visit at Week 20, making 11 scheduled study visits in total. On completion of Part A, the primary analysis will be performed.

Part B of the study is designed to assess the durability of treatment response and incidence of rebound of psoriasis following cessation of dosing. All participants will attend for skin assessments at Weeks 24 and 28, unless they have previously experienced treatment failure and/or had rebound of disease. A final visit at Week 40 will also be performed for those participants who experienced treatment response at Week 16 but have not yet met the definition of complete relapse. Part B therefore comprises a maximum of 3 additional scheduled study visits with a follow-up of up to 40 weeks (24 weeks after cessation of dosing). On completion of Part B, the final analysis will be performed.

'Treatment failure' is synonymous with 'starting a new psoriasis treatment' which is an oral agent, biological, or intermediate or high-potency dose topical therapy for plaque psoriasis. Starting topical unmedicated emollients and low-potency topical steroids which were not taken at baseline does not count as starting a new psoriasis treatment.

Figure 1 Study Schema



Note: PIC=Powder in capsule (formulation). All dosing is once daily.
Note: Since this figure was produced for the protocol, the Interim Analysis has been moved from Week 12 to when the last participant has received their last dose (Week 16).

An interim analysis will be performed after the last participant was scheduled to receive their last dose (Week 16).

Participants who withdraw from treatment in the first four weeks after randomisation may be replaced. Replacement participants will be assigned to the same cohort as the withdrawn participant but will be randomly assigned to treatment within that cohort.

5.2 Randomisation and Blinding

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 2:1 allocation ratio to receive either EDP1815 or matching placebo treatment.

Interactive response technology (IRT) will be used to administer the randomization schedule centrally. Successfully screened participants will be assigned to the next cohort randomisation number available at the time of their baseline visit to determine their cohort and then to the next treatment randomisation number available within that cohort.

Note that if a participant has withdrawn from treatment within 4 weeks of randomisation and is to be replaced, the next participant to be randomised will automatically be assigned to the same cohort as the participant who was withdrawn instead of being randomly assigned to a cohort. Within the cohort, the replacement participant will be randomly assigned to treatment group with the next within-cohort treatment randomisation number.

The allocation to cohort is not blinded as it is distinguishable to participants and study staff by the number of capsules administered per once-daily dose. The 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 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, any data collected after the unblinding occurred will be excluded from per-protocol analyses.

For the interim analysis, unblinded aggregate results will be produced by the unblinded team within [redacted] and reviewed by Evelo personnel for strategic planning use. These results will not be shared with study site staff, participants, or clinical monitors who will be involved in the collection and review of individual study data.

The data will be unblinded and the primary analysis will be performed once all participants have completed 4 weeks of post-treatment follow-up at Visit 11 (Week 20; at the end of Part A). Study site staff, participants, and clinical monitors who will be involved in the collection and review of individual study data will remain blinded until Part B is completed.

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 study 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. If data is collected on Day 1 without an associated time being provided, it will be assumed to be pre-dose. Efficacy data collected using the electronic clinical outcome assessment (eCOA) device on the same day as the first dose of study medication will also be assumed to be pre-dose data and can be used for the baseline assessment, regardless of whether the time indicates if it was before or after the time of first dose.

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/m^2
- <30 kg/m^2

5.3.2.1 Time since Diagnosis

Time since diagnosis in years at first dose will be calculated as:

Time since diagnosis (years) = (Date of first dose – Date of diagnosis)/365.25

Time since diagnosis will also be categorised as:

- <2 years
- ≥2 years

5.3.2.2 Treatment Compliance

Participants will be expected to dose once daily with 1, 4 or 10 capsules per dose respectively for cohorts 1, 2 and 3.

Compliance will be calculated in 8-week intervals (Weeks 1-8, and Weeks 9-16) as well as across the whole treatment period.

Start and end dates of each treatment period are shown in Table 1.

Expected capsules for each treatment period will be calculated as:

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

Actual capsules taken will be calculated from the dosing log using entries between the start and end days inclusively.

Table 1 Start and End Dates of Treatment Periods for Compliance Calculations

Treatment Period	Start Date	End Date[1]
Weeks 1-8	Day 1	Date of Week 8 visit - 1
Weeks 9-16	Date of Week 8 visit	Date of the last dose of study drug
Whole Treatment Period	Day 1	Date of the last dose of study drug

[1] If a participant prematurely discontinues treatment before the specified end date, the date of last dose will be used for the end date of that treatment period.

Treatment compliance will be calculated as:

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

Treatment compliance in each period will also be categorised within each treatment period as:

- <80%
- ≥80%

5.3.2.3 Prohibited Concomitant Medications

The following medications are not allowed during the course of the study:

- Systemic immunosuppressive therapy (MTX, apremilast, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus).
- Phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3and analogues (protocol versions 4.0 and earlier only, permitted after reconsent to protocol version 5.0), psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives).
- Lithium, antimalarials, IM gold, or leflunomide.
- Topical medications/treatments that could affect psoriasis or PGA evaluation (including [but not limited to] high- and mid-potency corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, and tacrolimus) within 2 weeks of the first administration of study drug.
- Live or live-attenuated vaccination.

- Treatment with another investigational drug, biological agent, or device.

Topical unmedicated emollients and low-potency topical steroids are permitted if participants were already using them as part of their care prior to study entry. The participant should not however start new medications or change the dose or frequency of this type during the course of the study.

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

5.3.3 Efficacy

5.3.3.1 General

Participants who discontinue treatment but do not withdraw from the study should only have efficacy data collected after discontinuation of treatment included in the supportive estimand for the primary endpoint. For all other analyses, data collected after withdrawal of treatment should be considered as missing.

5.3.3.2 Psoriasis Area and Severity Index

PASI score will be calculated within the eCOA system and taken directly from the supplied data. Further information on the scoring of the PASI is provided in Section 16.

PASI-50, PASI-75, PASI-90 and PASI-100 responses are defined respectively by at least a 50%, 75%, 90% and 100% reduction from Baseline in the PASI score.

Response at Week 16 is defined as achieving PASI-50 or greater at the Week 16 visit.

Partial relapse is defined, after the Week 16 visit, as loss of PASI-50 response after cessation of study treatment, or the participant begins a new treatment for psoriasis.

Relapse is defined, after the week 16 visit, as an increase in PASI score to the baseline value or greater, or the participant begins a new treatment for psoriasis.
Rebound is defined as an increase in PASI score to 125% of baseline value or above, or onset of new pustular/erythrodermic psoriasis, within 3 months of cessation of study treatment.

5.3.3.3 Time to First Achievement of PASI-50

As the PASI score is only collected at each study visit, the time to first occurrence of PASI-50 should be considered as interval-censored data. It is only known that the participant achieved PASI-50 at some point at or before the assessment at which it was first observed and after the previous assessment.

For participants who meet the criteria for PASI-50, the interval start and stop day for first achievement of PASI-50 will be defined as:

Interval start day = Study day of last PASI assessment before PASI-50 was first achieved +1

Interval end day = Study day of PASI assessment at which PASI-50 was first achieved

Participants who do not meet the criteria for PASI-50 during the Part A of the study will be right-censored at the last PASI assessment within 4 days of treatment discontinuation (for participants who did not complete the 16-week treatment period) or the last PASI assessment in Part A (for participants who did complete the 16-week treatment period). For the purposes of the analysis data set, the interval start and stop dates will be defined as:

Interval start day = Study day of last PASI assessment+1
Interval end day = missing

5.3.3.4 Duration Endpoints

The following duration endpoints will be defined:

Duration of remission is defined as time from first achievement of PASI-100 to loss of PASI-100 or start of a new psoriasis treatment whichever occurs first.

Duration of treatment success is defined as time from first achievement of PASI-50 to loss of PASI-50 or start of a new psoriasis treatment whichever occurs first.

Duration of therapeutic effect is defined as time from cessation of study treatment until increase of PASI to 50% of maximum improvement from baseline or start of a new psoriasis treatment whichever occurs first. Maximum improvement from baseline is a participant's lowest post-baseline PASI score. Increase of PASI to 50% of maximum improvement from baseline can only occur at a visit after the visit where maximum improvement from baseline occurred. Any participant who showed no improvement in PASI score from baseline up to end of treatment will not have duration of therapeutic effect calculated. Any participant who showed an improvement prior to end of treatment and whose end of treatment PASI score had already gone above 50% of maximum improvement from baseline will have duration of therapeutic effect equal to zero.

As the PASI score is only collected at each study visit, the duration endpoints should be considered as interval-censored data. Although an exact date of start of new psoriasis treatment will be collected, it is only known that the participant achieved and lost PASI-100/50 status, or achieved an increase of PASI to 50% of maximum improvement from baseline, at some point at or before the assessment at which it was first observed and after the previous assessment.

Duration should be calculated as:
Duration = End Day - Start Day

For duration of remission and duration of treatment success:
Start Day = Study day of PASI assessment at which PASI-100 or PASI-50, respectively, was first achieved
End Day = Study day of PASI assessment at which PASI-100 or PASI-50, respectively, was first lost, or start of new psoriasis treatment whichever occurs first

For duration of therapeutic effect, duration should be calculated as:
Start Day = Study day of end of study treatment
End Day = Study day of PASI assessment at which increase of PASI to 50% of maximum improvement from baseline first occurred, or start of new psoriasis treatment, whichever occurs first

If a participant does not meet the Start Day criteria relevant to a particular duration endpoint at any time during the study the endpoint will not be calculated.

If a participant has not met the End Day criteria relevant to a particular duration endpoint by the final study visit the last PASI assessment in Part A or Part B will be used as the End Day in the calculations above.

5.3.3.5 Physician Global Assessment

The physician will give a score on the participant's psoriasis disease for each of induration (thickness), erythema (redness) and scaling on a scale of 0 to 5. Further information on the PGA is provided in Section 17.

The PGA score will be calculated as the average of the three scores, rounded to the closest whole number.

PGA score will be calculated within the eCOA system and taken directly from the supplied data prior to the rounding being applied.

The rounded PGA value will be used in the calculation of the PGA*BSA variable and will also be used in any summaries and listings of the PGA data.

5.3.3.6 Percent of Body Surface Area Involvement

The percent of BSA involvement will be estimated for each participant, where 1% is approximately the area of the participant's handprint.

BSA-75 response is defined by at least a 75% reduction from Baseline in the BSA.

5.3.3.7 Lesion Severity Score

The lesion of interest, selected at the screening visit, will be scored for redness, induration (thickness) and scaling using a five-point scale:

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

The LSS is the sum of the redness, induration and scaling scores at each visit. The LSS will not be calculated unless all three sub-scores are non-missing.

All assessments must be performed throughout the study on the same lesion of interest as identified at Screening. If a different lesion is scored, compared to the Screening visit, then the LSS will be considered missing.

5.3.3.8 Dermatology Life Quality Index

The DLQI is a 10-item questionnaire with each item scored from 0 to 3. Further information on the scoring of the DLQI is provided in Section 18.

The DLQI score is the sum of the 10 individual items.

During the course of the study it was found that question 7 of the DLQI had been asked incorrectly. Therefore the following action will be taken: DLQI questionnaires of all participants at all visits (including Baseline) will be assigned a score of 0 for question 7. This concurs with the questionnaire's instructions on how to handle a question with a missing response. Up to one question can have a missing response and the total DLQI score is still considered valid. In the event that any questionnaire contains a missing response to another question, the DLQI score will be set to missing.

Once the error was found it was decided not to correct the asking of the question going forward, since this would result in comparing a slightly different questionnaire at baseline to later time points for the majority of participants and therefore complicate interpretation of change from baseline.

In order to investigate any potential effect of this error on conclusions drawn, sensitivity analyses of the DLQI will be carried out using the following scoring for question 7, based on the first part of the question:

Answer to first part of question 7	**Score assigned**
Yes	3
No	1.5 (median of the possible scores 0, 1, 2 and 3)
Not relevant	0

The second part of the question will not be used as this was where the error occurred.

5.3.3.9 Modified Nail Psoriasis Severity Index

The mNAPSI will only be collected in participants with psoriatic nail involvement.

The mNAPSI is assessed for each of the participant's 10 fingernails as detailed in Section 19. The mNAPSI score is the sum of the 10 scores for the individual nails.

If the investigator indicates at a visit that there is no nail disease, a score of zero will be assigned.

5.3.3.10 Psoriasis Symptom Inventory

The PSI will be completed daily by participants for the 7 days prior to each visit as detailed in Section 20.

For each of the 8 symptoms, the daily scores will be averaged to give a weekly symptom score for that visit. Data must be provided for at least 5 of the 7 days prior to the visit for a weekly symptom score to be calculated.

The PSI total score at the visit will be the sum of the 8 weekly symptom scores.

5.3.3.11 SF-36 Bodily Pain and Vitality Scores

The SF-36 bodily pain and vitality scores will be calculated using the algorithms provided by the RAND corporation as detailed in Section 21.

The SF-36 bodily pain score will be the average of the two question scores for pain and will be calculated if at least one of the two questions have been answered.

The SF-36 vitality score will be the average of the four question scores for vitality/energy and will be calculated if at least two of the two questions have been answered.

5.3.3.12 Pain and Fatigue Visual Analogue Scales

The pain VAS will ask the question: How severe is your pain today?
Participants will score this by marking a point on a line which goes from 0=no pain to 100=very severe pain

The fatigue VAS will ask the question: How much of a problem has fatigue or tiredness been for you in the past week?
Participants will score this by marking a point on a line which goes from 0=fatigue is no problem to 100=fatigue is a major problem.

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 randomized study treatment
- Treatment Phase: All AEs with onset date/time at the time of or after the first dose of randomized 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 Day 112 and the Follow-up Phase will be from Day 113 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.

For the primary analysis which considers only data collected in Part A, only events which start on or prior to the end of Part A date will be included in the adverse event summaries.

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

For the final analysis, only treatment related events which start in Part B will be included in the adverse event summaries.

Only treatment related events which start in Part B and any Part A AEs which change in Part B will be included in the relevant data listings.

6 Sample Size

The sample size of 225 participants in total, has been chosen to explore the tolerability and safety of EDP1815. Although the study will use a model-based probability inference approach in a Bayesian framework, the following power calculation was also performed (using a basic frequentist approach) in order to give confidence that enough participants are available to find a clinically meaningful difference between active dose and placebo if the below assumptions are met.

The primary efficacy endpoint is the percent change from baseline in the PASI score at Week 16. Percent change from baseline relative to placebo will be estimated within the model (Section 9.4.3) as (percent change in active) - (percent change in placebo), with a negative value indicating a greater improvement for active than placebo. A percent change from baseline relative to placebo of at least 20% will be considered clinically meaningful. The pooled standard deviation across all doses is assumed to be 25%.

Participants in the placebo arm of each cohort will be pooled for the statistical analysis in order to compare active and control arms resulting in 75 participants randomized to the pooled placebo group and 50 participants randomized to each active treatment group (EDP1815 0.8 × 1011 cells, EDP1815 3.2 × 1011 cells, and EDP1815 8.0 × 1011 cells). Assuming that no more than 15% of

participants will discontinue treatment before the Week 16 visit, at least 42 active and 21 placebo participants in each of the 3 cohorts are expected to provide data through the Week 16 visit.

Each pairwise comparison between pooled placebo and active dose would be expected to have more than 95% power to detect a difference between the treatment groups at the 5% significance level under the assumption that pooling the placebo groups is a valid strategy. If the 3 placebo cohorts are considered too heterogeneous for pooling into a single reference group (Section 9.1), the power to detect a difference in each within-cohort pairwise comparison between active and placebo doses would be greater than 80%.

As the statistical inference for this study will focus on estimation rather than testing a formal hypothesis, no multiplicity adjustments of the different comparisons between groups in order to control the study-wise type I error rate will be performed.

Similarly, as there is no intention to use any interim analyses to stop the study early for efficacy (Section 7.4), no adjustments for multiplicity will be made to account for any analyses performed as part of the interim analyses.

7 General Considerations

7.1 Analysis Populations

7.1.1 Enrolled Population

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

7.1.2 Modified Intention to Treat Population

The modified intention to treat (mITT) population will consist of all participants who were randomised to treatment and who received at least one dose of study treatment. Participants who withdraw from the study before the end of Week 4 and are replaced will be included in this analysis set.

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

7.1.3 Per-protocol Population

The per-protocol (PP) population will consist of all participants in the mITT population who had a duration of treatment exposure of at least 28 days (criteria for replacement) and who do not have a protocol deviation that may impact efficacy with a start date for the deviation before initiation of study treatment.

Note that in the case of participants who have a protocol deviation with a potential impact on efficacy which occurs after initiation of treatment, the participant will remain in the PP population but all data collected after the protocol deviation occurred will be excluded from any analyses performed using the per-protocol population.

Deviations that may affect efficacy are shown in Table 2.

Table 2 Protocol Deviations with a Potential Impact on Efficacy

Description	Evaluation Period	Impact on per-protocol analyses
Not meeting inclusion criteria 3, 4, or 6 or meeting any of exclusion criteria 1-12 or 27	Baseline	Exclude participant from the PP population.
Use of any prohibited medication (Section 5.3.2.3)	Throughout study	If start date of prohibited medication is before date of first dose of study drug then exclude participant from PP population. Otherwise, include participant in PP population but exclude all data collected on or after start date of prohibited medication.
Compliance with study drug <80%	Evaluated in 8-week periods (Weeks 1-8 and 9-16)	If participant is non-compliant within Week 1-8 treatment period, then exclude from PPS. If participant is non-compliant only within the Week 9-16 treatment period then include in the PPS but exclude all data collected after the Week 8 visit date.
>7 consecutive days with no study medication without participant being permanently withdrawn from study medication	Throughout study	Participant will not be excluded from the PP population, but all data collected after the 8th consecutive day with no study medication will be excluded.
>14 total days with no study medication (does not need to be continuous)	Throughout study	If a participant's dosing log shows >14 days in total with no treatment taken then they will be excluded from the PP population.
Incorrect study treatment taken	Throughout study	Participants will not be excluded from the PP population. If a participant received a study drug other than that received at the start of the study, then exclude all data collected on or after the date at which the treatment change occurred.

Description	Evaluation Period	Impact on per-protocol analyses
Study treatment blind broken	Throughout study	If participant's blind is broken prior to first dose of study drug then exclude from PP population. Otherwise, include participant in PP population but exclude all data collected on or after the date on which the blind was broken.

All analyses using the PP population will group participants according to treatment received at the start of the study.

7.1.4 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.

7.1.5 Week 16 Responders Population

The Week 16 responders population will consist of all mITT participants who achieved a PASI-50 response at Week 16.

7.1.6 Part B Population

The Part B population will consist of all participants who entered Part B of the study.

7.2 Covariates and Subgroups

If the placebo groups from the 3 cohorts are found to be too heterogeneous to be pooled (see Section 9.1), the primary and secondary analyses will be performed using within-cohort comparisons of active and placebo treatments, and summary tables will also be produced by cohort.

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

- Using baseline PASI score (<10, ≥10)
- Using baseline PGA score (2, 3)
- Using baseline BMI (<30 kg/m^2, ≥30 kg/m^2)

For the exploratory analysis indirectly comparing the results from this study to those in the UNVEIL study (Section 9.6.2) the following subgroup of participants will be used:

- Baseline PGA=3 and Baseline BSA 5-10%

For the inferential models defined in Section 9, in addition to the 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)
- Country (UK, Poland, Hungary, USA)
- Time since diagnosis (<2 years, ≥2 years)

7.3 Missing Data

Missing efficacy data such as individual item scores will be dealt with as detailed in Section 5.3.3. Otherwise, no imputation of missing efficacy data will be performed, and the use of mixed models will account for missing data.

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 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.

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 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.

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

The interim analysis will be to aid in the planning of future studies and for a better understanding of the benefit/risk profile of EDP1815.

No decisions regarding study conduct will be made based on the interim results and the study will not be stopped if superior efficacy is found.

7.4.2 Planned Schedule of Interim Analyses

The interim analysis will be performed after the last participant has received their last dose (scheduled for the end of Week 16). All Part A data collected at the time of the data cut will be included in the analysis, so some participants may have data from beyond the Week 16 visit.

7.4.3 Endpoints to be Included in the Interim Analysis

The following endpoints will be included in the interim analysis. Description of the analyses for these endpoints is described in Sections 8, 9 and 10. The list of outputs which will be provided as part of the interim analysis is provided in Section 15.

- Study disposition status
- Treatment disposition status
- Demography
- Baseline disease status
- Exposure to treatment
- Percentage change from baseline in PASI (primary estimand only) main analytical approach (MMRM) and sensitivity analysis (dose response model)
- Change from baseline in PASI - main analytical approach
- Achievement of PASI-50 – main analytical approach
- Achievement of PASI-75, PASI-90 and PASI-100 (summary only)
- Achievement of PGA of 0 or 1 with a ≥2 point improvement (summary only)
- Achievement of PGA of 0 (summary only)
- Percentage change from baseline in PGA*BSA (summary only)
- Incidence of adverse events

7.4.4 Adjustment of Confidence Intervals and p-values

As the study will not be stopped if superior efficacy is demonstrated at the interim analysis, there will be no adjustments for alpha-spending.

7.4.5 Practical Measures to Minimise Bias

Outputs featuring unblinded treatment assignments will be created by the unblinded analysis group within [redacted] and shared with selective Evelo personnel who are not directly involved in the conduct of the study.

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.

Aggregate data from the unblinded results may be more widely shared, including into the public domain, but no data which may have the potential to unblind will be released beyond the unblinded personnel and DMC. Data with the potential to unblind include:

- Efficacy or safety event data where only participants from one treatment group have experienced the event
- Categorical data where one or more categories contains only participants from one treatment group
- Minimum and maximum values for continuous data
- Time to event data where events at single timepoint occurred in only one treatment group

7.4.6 Documentation of Interim Analyses

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 database lock.

7.5 Multi-centre Studies

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

7.6 Multiple Testing

The statistical analysis for this study will focus on estimation rather than in testing a formal hypothesis. Therefore, no adjustments will be made to control the study-wise type I error rate.

7.7 Visit Windows

All data will be reported according to nominal visits, except for subjects who complete the follow-up Week 20 assessments due to withdrawing from the study before the Week 16 visit. 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.

Subjects who withdraw prematurely from the study should complete the assessments required for the follow-up visit (Week 20). However, this data will only be included in tables and figures which are produced **by visit** for subjects who completed the 16-week treatment period and provided Week 16 data prior to the Week 20/follow-up data being collected. Tables and figures which do not show summaries by visit and all listings will include all collected Week 20/follow-up data regardless of whether the subject completed the 16-week treatment period.

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 will not be included in summary or analysis tables, unless they are baseline measurements or provide data towards a safety endpoint which looks at worst-case post-baseline.

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 randomized treatment (Placebo, EDP1815), cohort (1, 2, 3), 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:

- Placebo 1 capsule
- EDP1815 1 capsule
- Placebo 4 capsules
- EDP1815 4 capsules
- Placebo 10 capsules
- EDP1815 10 capsules
- All Placebo
- All EDP1815
- Total

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

- All Placebo
- EDP1815 1 capsule
- EDP1815 4 capsules
- EDP1815 10 capsules
- All EDP1815 (concomitant medication and safety only)

For the efficacy analyses, if the 3 cohorts of placebo participants are found to be too heterogeneous for pooling, selected efficacy tables will also be presented by treatment within cohort, in which case columns will be ordered and labelled as:

- Placebo 1 capsule
- EDP1815 1 capsule
- Placebo 4 capsules
- EDP1815 4 capsules
- Placebo 10 capsules
- EDP1815 10 capsules

For the primary 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, the safety population will be used.

- For all other summaries and analyses the mITT population will be used, with selected efficacy outputs reproduced using the per-protocol population.

For the final analysis:

- For partial relapse and complete relapse endpoints analysis Week 16 Responders population will be used.

- For duration endpoints and rebound analysis mITT population will be used.

- For or all other summaries and analyses the Part B 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 (Part A for the primary analysis and Part B for the final analysis)
- Number and percentage of participants withdrawn from the study and the reported reason for withdrawal (Part A for the primary analysis and Part B for the final analysis)
- 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 (primary analysis)
- Number and percentage of participants who discontinued treatment early and reason for discontinuation (primary analysis)

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 country and within each 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 will be summarised.

Missed visits and assessments due to COVID-19 will also be summarised and listed.

8.2 Protocol Deviations

The number and percentage of participants in the mITT population with at least one protocol deviation with a potential impact on efficacy in each category specified in Table 2 will be summarised.

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 disease characteristics of time (years) since diagnosis and any current psoriasis treatment at the time of the Screening visit will be summarised.

8.4 Medical History

Medical history and concurrent illnesses will be captured and coded using the v23.0 of the Medical Dictionary for Regulatory Activities (MedDRA®).

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 9) 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) Version dated 01Mar2020. 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.

In the primary analysis 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.

In the final analysis concomitant medications started during Phase B and medications from Phase A which changed during Phase B will be listed.

8.6 Treatment Compliance

Treatment compliance will be summarised for each 8-week treatment period and 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 5.3.2.2. Percentages will use the number of participants who started the relevant treatment period as the denominator.

Data from the dosing log and the calculated treatment compliance in each treatment period will also be listed.

9 Efficacy Analyses

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 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 time to 25% and 50% (median) of participants with event . Kaplan-Meier curves of time to event will also be presented.

9.1 Pooling of Placebo Cohorts

The assumption that the 3 cohorts of placebo participants can be pooled into a single placebo group to be used as a control for all active doses will be examined using mean (±SD) and box plots of percent change in PASI score against time. In addition, a mixed model for repeated measures (MMRM) model will be used to compare the 3 cohorts of placebo participants. The model will include parameters for cohort, visit and baseline PASI score together with cohort*visit and baseline PASI score*visit interactions. LS mean (95% CI) estimates for each placebo cohort will be plotted by visit.

A decision will be made by the Evelo study team, based on examination of the above figures and model, on whether the pooling strategy is appropriate.

If any placebo cohort is considered too different from the other placebo cohorts then no pooling will be used. The pooling of 2 cohorts only will not be considered.

If the pooling strategy is considered appropriate, then the placebo cohorts will be pooled into a single 'all placebo' group for all efficacy analyses and will be used as a common control group for each active EDP1815 treatment group.

If the assumption of similarity across the placebo groups is found to be unreasonable, each placebo dose will be included in the model as a separate dose level and pairwise comparisons between each active EDP1815 dose and placebo will be performed using only the matching placebo dose data from the same cohort.

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

9.2 Selection of Additional Covariates

The covariates described in Section 7.2 will be considered and included in the primary efficacy model described in Section 9.4.3 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 treatment*visit and baseline PASI score*visit interactions have already been fitted.

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

9.3 Part B Analysis

For the Part B endpoints other than those relating to relapse, rebound and duration of effects, a principal strata estimand will be used including all participants in the Part B population with all data included regardless of other intercurrent events.

These endpoints will be summarised at each visit in Parts A and B. Mean (+/- SD) values over time will also be plotted in a figure.

9.4 Primary Efficacy Analysis

9.4.1 Primary Efficacy Estimand

The primary efficacy estimand will be the effect of EDP1815 compared to placebo on the percentage change from baseline to Week 16 in PASI score. The population summary measure of interest will be the difference in mean percentage change from baseline in PASI score at Week 16.

Intercurrent events will be accounted for in the following manner:

Table 3 Intercurrent Event Strategies for the Primary Estimand

Intercurrent event	Strategy to account for intercurrent event
Protocol deviation with potential to impact efficacy	Treatment policy PASI scores will be used as collected regardless of whether a protocol deviation occurred
Treatment discontinuation for any reason *	While on treatment PASI scores collected more than 4 days after treatment discontinuation will be considered as missing for all timepoints up to Week 16. For the Week 20/follow-up visit, PASI scores will be considered as missing for subjects who did not complete treatment up to Week 16.

* This includes participants who completed the 16-week treatment period but have their Week 16 visit more than 4 days after the end of treatment.

9.4.2 Supportive Estimands for the Primary Endpoint

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

Table 4 Supportive Estimands for the Primary Endpoint

Estimand	Purpose	Population	Intercurrent Event Strategy
Primary Supportive Estimand 1	Assess the impact of protocol deviations which may impact efficacy	PP	Protocol deviation with potential to impact efficacy While on treatment (PASI scores collected after the occurrence of the protocol deviation will be considered missing) Treatment discontinuation for any reason before Week 16 While on treatment (as per Primary estimand)

Estimand	Purpose	Population	Intercurrent Event Strategy
Primary Supportive Estimand 2	Assess the impact of treatment discontinuation for any reason	mITT	Protocol deviation with potential to impact efficacy Treatment policy (as per Primary estimand) Treatment discontinuation for any reason before Week 16 Treatment policy (PASI scores collected more than 4 days after treatment discontinuation will be included). Note that Week 20/follow-up data will still only be included for subjects who completed treatment.
Primary Supportive Estimand 3	Assess the impact of treatment discontinuation due to requirement for alternative therapy	mITT	Protocol deviation with potential to impact efficacy Treatment policy (as per Primary estimand) Treatment discontinuation due to requirement for alternative therapy before Week 16 Composite (highest recorded on-treatment PASI score carried forward to all scheduled visits after treatment discontinuation) Treatment discontinuation for any other reason before Week 16 While on treatment (as per Primary estimand)

9.4.3 Main Analytical Approach

Percentage change from baseline in PASI score at each visit will be summarised. Mean (+/- SD) percentage change from Baseline over time will be plotted in a figure. Also, waterfall plots will be created to show the ranked individual percentage change from Baseline at Week 16.

The primary analysis will be performed using a Bayesian mixed model for repeated measures (MMRM). The model will include parameters for treatment*visit and baseline PASI score*visit interactions and will not include an intercept.

Treatment will consist of 4 levels (all placebo, EDP1815 1 capsule, EDP1815 4 capsules and EDP1815 10 capsules) if the placebo pooling strategy is considered appropriate or 6 levels (Placebo 1 capsule, Placebo 4 capsules, Placebo 10 capsules, EDP1815 1 capsule, EDP1815 4 capsules, and EDP1815 10

capsules) if the placebo pooling strategy is not considered appropriate. Visit will consist of 7 levels (Weeks 1, 2, 4, 8, 12,16 and 20).

As described in Section 9.2 additional covariates for baseline factors will be assessed using this model for inclusion in all efficacy models.

The priors for all parameters in the model will be non-informative and follow a normal distribution with mean 0 and SD 1000. The prior for the variance-covariance matrix will follow an inverted Wishart distribution with degrees of freedom equal to the number of visits and an identity scale matrix. The choice of Wishart distribution is based on it being the conjugate prior of the inverse-covariance matrix of a multivariate-normal random vector.

The model will be blocked so that the MCMC procedure samples from the treatment*visit parameters first, then the baseline*visit parameters, then any additional fitted covariates and finally the variance-covariance matrix.

100,000 MCMC samples will be generated with a thin of 20 to leave 5000 retained samples after a burn-in of 10,000 samples. The number of samples or thin may be increased to reduce the ratio of the Monte Carlo standard error (MCSE) to the posterior SD, as deemed necessary.

If the assumption of similarity between the 3 placebo cohorts is considered appropriate, the placebo cohorts will be pooled, and a common all placebo control group will be used for the pairwise differences or each active dose to placebo. If the placebo pooling strategy is not considered appropriate, each placebo dose will be included in the model as a separate dose level and pairwise comparisons between each active EDP1815 dose and its matching placebo dose will be used.

The adjusted mean percentage change from baseline and the associated 95% highest posterior density (HPD) credible interval (CrI) for each treatment group at Week 16 will be reported, together with the adjusted mean difference from placebo and the associated 95% HPD CrI for each active dose at Week 16 and the probability that each active treatment difference is less than 0%, -20%, -30% and -50%.

At all other visits (Weeks 1, 2, 4, 8, 12 and 20) the adjusted mean percentage change from baseline and the associated 95% highest posterior density (HPD) credible interval (CrI) for each treatment group will be reported, together with the adjusted mean difference from placebo and the associated 95% HPD CrI for each active dose and the probability that each active treatment difference is less than 0%.

Posterior mean (with 95% HPD CrI) percentage change from baseline in PASI score will be plotted against time.

Model checking and diagnostic plots, including posterior density plots of the posterior samples for all parameters in the model will be produced. The assumption that data are missing at random will be evaluated by plotting the mean percentage change in PASI score against visit by treatment group for

the subgroups of participants who completed 16 weeks of study drug compared with those who discontinued study drug before Week 16.

If model checking and diagnostic plots show a violation of the assumptions underlying the analysis, alternative statistical methods will be considered, appropriate to the type of violation observed. This may include removing additional covariates even if they are found to be statistically significant if their inclusion causes issues with model inclusion, using an appropriate transformation (e.g. logarithmic) on the endpoint or changing the modelling strategy from MMRM. Requirements for alternative methods will be data driven and cannot be fully assessed until after the study has been unblinded and this document finalised. Any changes to the modelling strategy will be fully described in a SAP addendum.

The primary analysis approach will be repeated using the 3 supportive estimands described in Section 9.4.2.

9.4.4 Sensitivity Analyses

If the assumption of similarity between the placebo cohorts is supported and placebo cohorts can be pooled, a sensitivity analysis will be performed on the percent change from baseline to Week 16 in PASI score using a Bayesian Emax dose response model on the pooled cohorts in the following form:

Response = E0 + Emax*f(dose)

Three possible models will be considered for the f(dose):

- Log-linear: f(dose) = log(dose+0.01), where 0.01 is an offset to allow the model to fit for zero dose (placebo)
- 3-parameter model: f(dose) = dose/(dose+ED50)
- 4-parameter model: f(dose) = $dose^{slope}/(dose^{slope} + ED50^{slope})$

Where:

- Response = Percentage change from baseline in PASI at Week 16
- E0 = the response at dose = 0 (placebo)
- Emax = the maximal response over placebo
- ED50 = the dose that yields 50% of the maximal response
- slope = the dose-response slope parameter

Dose will be fitted as a continuous variable with values of 0, 1, 4 and 10 used to denote the number of active capsules taken by each of the treatment groups.

An inverse gamma prior with shape of 0.001 and scale of 0.001 will be used for the residual variance. Normal, non-informative priors will be used for the E0 and Emax parameters with mean 0 and SD 1000. A functional uniform prior (FUP) will be used, when required, for the ED50 and slope parameters where the prior density of the FUP is based on all the parameters in the model. For the FUP, the density will be calculated for values of dose from 0.01 to 10.01 in steps of 1. The use of a FUP shrinks the dose response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relationship compared to maximum likelihood (Bornkamp 2014).

Parameters will be blocked so that the MCMC procedure samples from E0 and Emax first, then the ED50 and slope parameters and finally the residual variance parameter.

100,000 MCMC samples will be generated with a thin of 20 to leave 5000 retained samples after a burn-in of 10,000 samples. The number of samples or thin may be increased to reduce the ratio of the MCSE to the posterior SD, as deemed necessary.

The best-fitting (lowest DIC) of the three models will be selected and based on the selected model, the posterior mean with associated 95% HPD CrI while be displayed for the percentage change from baseline in PASI score at Week 16 and the pairwise treatment differences between each active dose and the pooled placebo group. Posterior probabilities will also be presented for the pairwise treatment differences between each active dose and placebo being less than 0%, -20%, -30% and -50%.

A figure will be presented of the fitted mean dose response model with the 95% HPD CrI for all possible doses (0 to 10 in steps of 0.5) in the dose range, overlaid with the Week 16 posterior means and 95% HPD CrI for the MMRM model specified in Section 9.4.3.

If any of the results of the analyses using the supportive estimands are found to differ substantially from the primary estimand for the main analytical approach using the MMRM, this sensitivity analysis will be repeated using the supportive estimands.

9.4.5 Subgroup Analyses

The analyses described in Section 9.4.3 will be repeated on the primary estimand only using the subgroups defined in Section 7.2 for baseline disease severity and obesity. There will be no figures for the subgroup analyses.

9.5 Secondary Efficacy Analyses

The primary estimand approach will be applied to these endpoints, with the exception of the partial relapse, relapse and rebound endpoints, in the same manner as described in Section 9.4.1. No additional supportive or sensitivity analyses will be applied to these endpoints, with the exception of PASI-50 response which has a supportive estimand and DLQI score which has a supportive analysis.

There will be no waterfall plots for the secondary endpoints, with the exception of absolute change from Baseline in PASI score at Week 16.

9.5.1 Percentage Change from Baseline in PASI score at Weeks 4, 8 and 12

Mean percentage change from baseline in PASI score at Weeks 4, 8 and 12 will be analysed as part of the MMRM for the primary estimand. The same statistics produced for the Week 16 time point will also be produced at Weeks 4, 8 and 12.

9.5.2 Other Continuous Secondary Endpoints

The following secondary endpoints will be analysed in the same manner as described for the main analytical approach for the primary analysis (Section 9.4.30):

- Mean absolute change from baseline in PASI score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in LSS at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in LSS at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in PGA*BSA at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in PGA*BSA at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16 (main and sensitivity analysis)
- Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16 (main and sensitivity analysis)
- Mean percentage change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16

For the secondary endpoints the probability of each active treatment difference to placebo being less than 0 only will be presented.

Note that for the mNAPSI, only participants with psoriatic nail involvement (mNAPSI score>0) will be included in the summaries and analyses for this endpoint.

Similarly, 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.

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.

9.5.3 Response Endpoints with Inferential Analysis

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

- Achievement of PASI-50 at Weeks 4, 8, 12 and 16
- Achievement of PGA of 0 or 1 with a ≥2 point improvement from baseline at Week 16
- Achievement of PGA of 0 at Week 16

9.5.3.1 Estimands

The population summary measure of interest will be the odds ratio between each active dose and placebo for the achievement of response at the relevant time point.

9.5.3.2 Main Analytical Approach

A generalised linear mixed effects model with a logit link function will be fitted using data from all visits. Treatment, visit and baseline score terms will be included in the model as fixed effects

together with treatment*visit and baseline score*visit interactions, where the baseline score of PASI or PGA is used as appropriate to the endpoint.

Treatment will consist of 4 levels (all placebo, EDP1815 1 capsule, EDP1815 4 capsules and EDP1815 10 capsules) if the placebo pooling strategy is considered appropriate or 6 levels (Placebo 1 capsule, Placebo 4 capsules, Placebo 10 capsules, EDP1815 1 capsule, EDP1815 4 capsules, and EDP1815 10 capsules) if the placebo pooling strategy is not considered appropriate. Visit will consist of 5 levels (Weeks 4, 8, 12,16 and 20).

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 the assumption of similarity between the 3 placebo cohorts is considered appropriate, the placebo cohorts will be pooled, and a common all placebo control group will be used for the pairwise differences or each active dose to placebo. If the placebo pooling strategy is not considered appropriate, each placebo dose will be included in the model as a separate dose level and pairwise comparisons between each active EDP1815 dose and its matching placebo dose will be used.

If responder numbers are low and there are visits 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 and/or the Week 20 visit to ensure model convergence. Alternatively, the mixed effects model may be replaced with an individual logistic regression models at Week 16 or the baseline*visit interaction may be replaced by a fixed baseline effect only if either of these approaches appear 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 together with 95% CI for the percentage of responders, calculated using the exact method for binomial proportions. At each visit, the adjusted odds ratio, with 95% confidence interval (CI) associated p-value will also be presented. If the analysis is changed to exclude visits, 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 which were excluded from the model. Table footnotes will be added as appropriate to detail any changes to the planned analysis.

The adjusted odds ratios (with 95% CI) will be plotted by visit for the 3 active doses compared to placebo.

In addition, for the PASI-50 response endpoint only, a supportive analysis will be performed using the following supportive estimand. The estimand will differ only in the intercurrent event strategy.

Table 5 Intercurrent Event Strategy for Secondary Supportive Estimand for PASI-50

Estimand	Purpose	Population	Intercurrent Event Strategy
Secondary Supportive Estimand 1	Assess the impact of treatment discontinuation due to requirement for alternative therapy	mITT	Protocol deviation with potential to impact efficacy Treatment policy (as per Secondary estimand) Treatment discontinuation due to requirement for alternative therapy before Week 16 Composite (PASI-50 will be considered as not achieved at all scheduled visits after treatment discontinuation) Treatment discontinuation for any other reason before Week 16 While on treatment (as per Primary estimand)

9.5.3.3 Sensitivity Analyses

For the PASI-50, individually at each of Weeks 4, 8, 12, 16 and 20, and for the two endpoints for PGA score at Week 16, a Bayesian logistic regression will be performed. The model will include parameters for treatment and baseline PASI score.

Treatment will consist of 4 levels or 6 levels based on the appropriateness of the placebo pooling strategy as per the main analytical approach. 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.

The priors for all parameters in the model will be non-informative and follow a normal distribution with mean 0 and SD 1000.

100,000 MCMC samples will be generated with a thin of 20 to leave 5000 retained samples after a burn-in of 10,000 samples. The number of samples or thin may be increased to reduce the ratio of the Monte Carlo standard error (MCSE) to the posterior SD, as deemed necessary.

The posterior mean odds-ratios for each pairwise comparison of an active EDP1815 dose and placebo with associated 95% HPD CrI will be presented together with the posterior probability that the true odds ratio >1.

9.5.4 PASI-75, PASI-90 and PASI-100 at Week 16

The number and percentage of participants who achieve PASI-75 will be summarised by visit. Exact 95% CIs for the percentage of participants will also be displayed at each visit.

PASI-90 and PASI-100 will be summarised in the same manner.

9.5.5 Time to First Achievement of PASI-50

The time to first achievement of the PASI-50 will be analysed using a nonparametric survival analysis for interval-censored data. The expectation-maximisation iterative complex minorant (EMICM) method for iterative computation of the nonparametric maximum likelihood estimator for the survival function (Wellner and Zhan 1997) will be used.

Treatment will consist of 4 levels or 6 levels based on the appropriateness of the placebo pooling strategy as per the main analytical approach for the primary analysis.

The number and proportion of participants who meet the PASI-50 at least once during the study will be presented. Where calculable, the time to 25% and 50% of participants with PASI-50 will be displayed with its 95% confidence interval. A generalised log-rank test will be used to compare each active dose with placebo and the p-value for treatment difference will also be presented.

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

9.5.6 Partial Relapse, Relapse and Rebound

The following endpoints will be summarised by treatment group and visit in the

- Week 16 responders population:
  - Cumulative incidence of partial relapse at Weeks 20, 24, 28, and 40
  - Cumulative incidence of complete relapse at Weeks 20, 24, 28, and 40
- mITT population:
  - Cumulative incidence of rebound at Weeks 20, 24, 28, and 40

These summary tables will include the number of participants meeting the criteria for the endpoint, and the number of participants 'at risk' of meeting the criteria (the denominator for the cumulative incidence i.e. excluding any participants with a missing status for that endpoint).

For each endpoint, the cumulative incidences for each treatment group will be plotted against time (Week 20 to Week 40) as bars (with an 'error bar' for the corresponding 95% CI).
No inferential analysis of relapse or rebound will be carried out.

Table 6 Intercurrent Event Strategies for Partial Relapse, Relapse and Rebound Endpoints

Endpoint	Intercurrent event	Strategy to account for intercurrent event
Partial Relapse and (Complete) Relapse	Starting a new psoriasis treatment	Composite Starting a new psoriasis treatment is part of the endpoint definition

Endpoint	Intercurrent event	Strategy to account for intercurrent event
Rebound	Starting a new psoriasis treatment	While in the period following cessation of study treatment, without taking a new psoriasis treatment (analogous to While on treatment) Rebound status will be considered missing from 4 days after the day a new psoriasis treatment is started, onwards, and will not be counted in the denominator during calculation of cumulative incidences

Note that, according to the study design, starting a new psoriasis treatment (synonymous with study treatment failure) should result in a subject completing a PASI questionnaire at an unscheduled Follow-up (Part A)/Early Withdrawal (Part B) visit within 72 hours and then being withdrawn from the study. The above strategies for dealing with the intercurrent event of starting a new psoriasis treatment are included to cover the possibility of a protocol deviation occurring whereby a participant is not withdrawn from the study within 72 hours following the start of a new psoriasis treatment, and to clarify the estimand for rebound.

Once a participant has met the criteria for partial relapse, relapse or rebound (see Section 5.3.3.2) they will be counted as having met those criteria at the current (if a PASI criterion at Week 20 or later) or next, and all subsequent, scheduled visits where these endpoints are analysed (Week 20, 24, 28, and 40).

9.6 Exploratory Efficacy Analyses

9.6.1 Exploratory Efficacy Endpoints

The following exploratory endpoints will be summarised using statistics appropriate to the endpoint as described in Section 9:

- Percentage of participants achieving PASI-50, PASI-75, PASI-90, and PASI-100 at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 or 1 at Weeks 4, 8, 12, and 16.
- Mean percentage change from baseline in BSA at Weeks 4, 8, 12, and 16.
- Mean change from baseline in BSA at Weeks 4, 8, 12, and 16.
- Percentage of participants achieving BSA<3% and BSA-75 at Weeks 4, 8, 12, and 16.
- Mean change from baseline in PSI quality of life total and itch scores at Weeks 12 and 16

- Mean percentage change from baseline in PSI quality of life total and itch scores at Weeks 12 and 16
- Mean change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16
- Mean change from baseline in fasting blood glucose and fasting lipid panel at Weeks 8 and 16
- Mean duration of remission in participants who achieve PASI-100
- Mean duration of treatment success in participants who achieve PASI-50
- Mean duration of therapeutic effect in participants after cessation of study treatment

Note that if a participant has a zero score for any of the continuous measures (PSI score, Pain/Fatigue VAS or Bodily pain/Vitality SF-36 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.

In addition to the summary statistics as described in Section 9, response endpoints will also have 95% CIs presented for percentage of participants responding.

9.6.2 Indirect Comparisons with Apremilast

Adjusted indirect comparisons, pivoted around placebo, will be made with the Week 16 results and those from two studies in Apremilast in mild/moderate or moderate participants.

Only efficacy endpoints which were specified as primary or secondary endpoints in both this study and the comparator study will be assessed.

All indirect comparisons and their confidence intervals will be considered descriptive only. No p-values will be calculated.

Each active dose of EDP1815 will be independently compared to Ampremilast.

All data for the comparator studies will be taken from the published results for the study available on the clinicaltrials.gov website.

9.6.2.1 Binary (Response) Endpoints

For binary endpoints (e.g. PASI-50), the indirect comparison will be based on the unadjusted relative risk (RR) statistics re-calculated from the number of participants in each treatment/trial with the relevant endpoint at Week 16. Participants with missing data at Week 16 will have their last observed value before Week 16 carried forward.

N_A = number of participants evaluated on active treatment
N_P = number of participants evaluated on placebo treatment
n_A = number of participants with event on active treatment
n_P = number of participants with event on placebo treatment

Relative risk (RR) = $\frac{n_A/N_A}{n_P/N_p}$

SE(log RR) = $\sqrt{\left(\frac{1-n_A}{n_A N_A} + \frac{1-n_P}{n_P N_P}\right)}$

RR for Indirect Comparison ($RR_{Indirect}$) = $\frac{RR_{EDP1815}}{RR_{Apremilast}}$

SE (log RR) for indirect comparison = $\sqrt{\left[SE(\log RR_{EDP1815})^2 + SE\left(\log RR_{Apremilast}\right)^2\right]}$

95% CI for RR for indirect Comparison = $\exp\left(\log RR_{Indirect} \pm 1.96 \times SE(\log RR_{Indirect})\right)$

9.6.2.2 Continuous Endpoints

The indirect comparisons will use LS mean differences and their standard errors.
In order to provide LS means similar in methodology to those seen in the UNVEIL study, the LS mean differences will be taken from simple ANOVA models at Week 16 with only treatment group and country included in the model. Participants with missing data at Week 16 will have their last observed value before Week 16 carried forward.

For comparison with ADVANCE study, the LS mean differences will be taken from a Bayesian mixed model for repeated measures as described for the main analytical approach for the primary analysis. No additional imputation will be done for this analysis.

$LSMD_{EDP1815}$ = LS mean difference from placebo for EDP1815
$LSMD_{Apremilast}$ = LS mean difference from placebo for Apremilast
$SE_{EDP1815}$ = SE of $LSMD_{EDP1815}$
$SE_{Apreimlast}$ = SE of $LSMD_{Apremilast}$

LSMD for Indirect Comparison ($LSMD_{Indirect}$) = $LSMD_{EDP1815}$ - $LSMD_{Apremilast}$

SE for Indirect Comparison($SE_{Indirect}$) = $SE_{Indirect}$ = $\sqrt{\left[SE_{EDP1815}{}^2 + SE_{Apremilast})^2\right]}$

95% CI for LSMD for Indirect Comparison = $LSMD_{Indirect}$ ± 1.96 x $SE_{Indirect}$

9.6.2.3 Apremilast UNVEIL study (NCT02425826)

The UNVEIL study was performed on a population of moderate participants. The population of interest was defined as those with baseline PGA=3 and baseline BSA 5-10%. For the indirect comparisons with data from this study, the subgroup of participants which match those criteria will be used.

The following endpoints will be compared at Week 16:

- Achievement of PASI-50 (binary)

- Achievement of PASI-75 (binary)
- Achievement of PGA score of 0 or 1 (binary) – note that all participants achieving this must also have ≥2 point reduction from baseline as all participants in this analysis have PGA=3.
- Percentage change from baseline in PGA*BSA (continuous)

9.6.2.4 Apremilast ADVANCE study (NCT03721172)

The ADVANCE study was performed in a population of mild/moderate participants. The criteria specified for PGA, BSA or PASI for recruitment into this study were broadly similar to those for this study, therefore the results from the full mITT population will be used for comparison.

The following endpoints will be compared at Week 16:

- Achievement of PGA score of 0 or 1 with ≥2 point reduction from baseline (binary)
- Change from baseline in PASI score (continuous)

It should be noted that at the time of writing this SAP, the results were not yet available on clinicaltrials.gov for this study. This analysis will only be performed if these results are published prior to DB lock for this study.

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 for 28 days after cessation of dosing. 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.

In the primary analysis at the end of Part A, only adverse events which started on or before date of the end of Part A will be included in the summaries.

In the final analysis at the end of Part B, only adverse events which started during Part B will be included in the summaries. Treatment related events which start in Part B and any Part A AEs which change in Part B will be included in the relevant data listings.

All AEs will be coded using version 23.0 of MedDRA. 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 (Part A)
- Any TEAE of CTCAE grade 2 or above (Part A)
- Any TEAE of CTCAE grade 3 or above (Part A)
- Any TEAE of CTCAE grade 4 or above (Part A)
- Any fatal TEAE (Part A)
- Any serious TEAE (Part A)
- Any TEAE leading to permanent discontinuation of study drug (Part A)
- Any TEAE leading to withdrawal from the study (Part A)
- Any related TEAE (Part A and Part B)
- Any related TEAE of CTCAE grade 2 or above (Part A and Part B)
- Any related TEAE of CTCAE grade 3 or above (Part A and Part B)
- Any related TEAE of CTCAE grade 4 or above (Part A and Part B)
- Any related fatal TEAE (Part A and Part B)
- Any related serious TEAE (Part A and Part B)
- Any related TEAE leading to permanent discontinuation of study drug (Part A and Part B)
- Any related TEAE leading to withdrawal from the study (Part A and Part B)

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 9) and decreasing incidence of preferred term within SOC in the EDP1815 column.

In the primary analysis the above summary will be repeated for treatment phase TEAEs and follow-up phase TEAEs.

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 reported by at least 5% of participants in any treatment group will also be summarised by SOC and PT.

In the final analysis only related TEAEs will be summarized by SOC and PT in the same manner as described above.

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 10 (Section 23) 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 10 (Section 23). 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 7.

Table 7 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

Physical examination data will be listed.

10.6.3.1 Bristol Stool Form Scale

The data collected in the participant stool diary during the screening period, including the BSFS classification will be listed only.

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/credible 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/credible intervals of percentage change variables will be reported to 2 decimal places, standard errors will be reported to 3 decimal places
- Estimated odds ratios and 95% confidence/credible 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] (eCOA data). The analysis datasets will be produced using a similar structure to those described for ADaM but will be not be fully validated with respect to ADaM structure.

The datasets for the final analysis will follow analysis dataset model (ADaM) data specifications and will used 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).

For the Bayesian analyses, the production and quality control (QC) programmers will select different seeds and there is no expectation of an exact match between the production and QC programming. The statistical outputs will be confirmed as having passed QC as long as the differences between production and QC data is within the following tolerance limits:

- Estimates and 95% Credible Intervals for percentage change from baseline (all scales) – QC data points must be within 5% (relative difference) or within 2 (absolute difference) of the relevant production data point.
- Estimates and 95% Credible Intervals for change from baseline (all scales) – QC data points must be within 5% (relative difference) or within 0.5 (absolute difference) of the relevant production data point.
- Odds ratios and 95% Credible Intervals for response data - QC data points must be within 5% (relative difference) or 0.1 (absolute difference) of the relevant production data point.
- Probabilities - QC data points must be within 5% (relative difference) or 0.025 (absolute difference) of the relevant production data point.

Note that tolerance limits for either the relative difference or the absolute difference must be met. It is not required to meet both.

13 Summary of Changes from the Protocol

The following changes to the protocol defined analysis have been included in this SAP

Table 8 Changes to the Protocol Specified Analysis

Change	Rationale
Movement of interim analysis from Week 12 to when the last participant has received their last dose (Week 16)	It was decided to increase the amount of data available at the interim and slightly reduce the time available for planning future studies.
Addition of sensitivity analyses for DLQI score	To assess the impact of an error in the asking of question 7, and hence consider all responses to that question as missing in the main DLQI analyses.
Expansion to definition of partial relapse to include 'or the participant begins a new treatment for psoriasis'	Ensures that a participant cannot have a full relapse without having a partial relapse.
Addition of the Part B analysis set/population	Required for some Part B outputs.

The above changes may be updated in the protocol as part of a future protocol amendment.

14 References

Bornkamp, Bjorn. 2014. "Practical considerations for using functional uniform prior distributions for dose-response estaimation in clinical trials." *Biometrical Journal* 56 (6): 947-962.

Spiegelhalter, David, Keith Abrams, and Jonathan Myles. 2004. "Montitory using predictions: interim power." In *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*, 211-220. John Wiley and Sons Ltd.

Wellner, Jon A, and Yihui Zhan. 1997. "A Hybrid Algorithm for Computation of the Nonparametric Maximum Likelihood Estimator From Censored Data." *Journal of the American Statistical Association* 92 (439): 945-959.

15 Appendix 1: List of Tables, Figures and Listings

All outputs detailed in the following sections will be produced for the final analysis. In addition, those which will be produced for the interim analysis are flagged in the 'Interim' column.

15.1 Study Population

15.1.1 Tables

Number	Title	Population	Interim	Programming notes
14.1.1.1	Summary of Disposition	mITT	Y	
14.1.1.2	Summary of Screening Status	Enrolled		
14.1.1.3	Summary of Participants by Country and Site	mITT		
14.1.1.4	Summary of Attendance at Each Visit in Part A	mITT	Y	
14.1.1.5	Summary of Missed Visits Due to COVID-19 in Part A	mITT		
14.1.1.6	Summary of Protocol Deviations with A Potential Impact on Efficacy	mITT		
14.1.1.7	Summary of Populations	Enrolled		
14.1.2.1	Summary of Demography	mITT	Y	
14.1.2.2	Summary of Baseline Disease Characteristics	mITT	Y	
14.1.3.1	Summary of Past Medical History	mITT		
14.1.3.2	Summary of Current Medical History	mITT		
14.1.4.1	Summary of Prior Medications	mITT		
14.1.4.2	Summary of All Concomitant Medications	mITT		
14.1.4.3	Summary of Concomitant Medications Started Pre-treatment	mITT		
14.1.4.4	Summary of Concomitant Medications Started During the Treatment Period	mITT		
14.1.4.5	Summary of Concomitant Medications Started During the Follow-up Period	mITT		
14.1.5	Summary of Treatment Compliance	mITT		
14.1.6	Summary of Treatment Exposure	mITT	Y	

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	Interim	Programming notes
14.2.1.1.1	Summary of Percentage Change from Baseline in PASI Score Placebo Participants Only	mITT	Y	Format unchanged regardless of placebo pooling results
14.2.1.1.2	Analysis of Percentage Change from Baseline in PASI Score Placebo Participants Only	mITT	Y	Format unchanged regardless of placebo pooling results
14.2.1.2.1	Summary of Percentage Change from Baseline in PASI Score Primary Estimand	mITT	Y	
14.2.1.2.2	Summary of Percentage Change from Baseline in PASI Score Supportive Estimand 1	PP		
14.2.1.2.3	Summary of Percentage Change from Baseline in PASI Score Supportive Estimand 2	mITT		
14.2.1.2.4	Summary of Percentage Change from Baseline in PASI Score Supportive Estimand 3	mITT		
14.2.1.3.1	Analysis of Percentage Change from Baseline in PASI Score - Bayesian MMRM Primary Estimand	mITT	Y	
14.2.1.3.2	Analysis of Percentage Change from Baseline in PASI Score - Bayesian MMRM Supportive Estimand 1	PP		

Number	Title	Population	Interim	Programming notes
14.2.1.3.3	Analysis of Percentage Change from Baseline in PASI Score - Bayesian MMRM Supportive Estimand 2	mITT		
14.2.1.3.4	Analysis of Percentage Change from Baseline in PASI Score - Bayesian MMRM Supportive Estimand 3	mITT		
14.2.1.4.1	Analysis of Percentage Change from Baseline in PASI Score at Week 16 - Bayesian Dose Response Primary Estimand	mITT	Y	Only produced if placebo can be pooled.
14.2.1.4.2	Analysis of Percentage Change from Baseline in PASI Score at Week 16 - Bayesian Dose Response Supportive Estimand 1	PP		Only produced if placebo can be pooled and results of corresponding MMRM supplemental analysis are substantially difference from MMRM primary analysis
14.2.1.4.3	Analysis of Percentage Change from Baseline in PASI Score at Week 16 - Bayesian Dose Response Supportive Estimand 2	mITT		Only produced if placebo can be pooled and results of corresponding MMRM supplemental analysis are substantially difference from MMRM primary analysis
14.2.1.4.4	Analysis of Percentage Change from Baseline in PASI Score at Week 16 - Bayesian Dose Response Supportive Estimand 3	mITT		Only produced if placebo can be pooled and results of corresponding MMRM supplemental analysis are substantially difference from MMRM primary analysis
14.2.1.5.1	Summary of Percentage Change from Baseline in PASI Score by Baseline PASI Category Primary Estimand	mITT		

Number	Title	Population	Interim	Programming notes
14.2.1.5.2	Summary of Percentage Change from Baseline in PASI Score by Baseline PGA Category Primary Estimand	mITT		
14.2.1.5.3	Summary of Percentage Change from Baseline in PASI Score by Baseline BMI Category Primary Estimand	mITT		
14.2.1.6.1	Analysis of Percentage Change from Baseline in PASI Score by Baseline PASI Category - Bayesian MMRM Primary Estimand	mITT		
14.2.1.6.2	Analysis of Percentage Change from Baseline in PASI Score by Baseline PGA Category - Bayesian MMRM Primary Estimand	mITT		
14.2.1.6.3	Analysis of Percentage Change from Baseline in PASI Score by Baseline BMI Category - Bayesian MMRM Primary Estimand	mITT		
14.2.2.1	Summary of Change from Baseline in PASI Score	mITT	Y	
14.2.2.2	Analysis of Change from Baseline in PASI Score - Bayesian MMRM	mITT	Y	
14.2.3.1.1	Summary and Analysis of PASI-50 Response - GLMM	mITT	Y	
14.2.3.1.2	Summary and Analysis of PASI-50 Response - GLMM Secondary Supportive Estimand 1	mITT		
14.2.3.2	Analysis of PASI-50 Response - Bayesian Logistic by Visit	mITT		
14.2.4	Summary and Analysis of Time to First Achievement of PASI-50	mITT		
14.2.5	Summary of PASI-75 Response	mITT	Y	
14.2.6	Summary of PASI-90 Response	mITT	Y	
14.2.7	Summary of PASI-100 Response	mITT	Y	
14.2.8.1	Summary and Analysis of PGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - GLMM	mITT	Y	

Number	Title	Population	Interim	Programming notes
14.2.8.2	Analysis of PGA of 0 or 1 With a >=2 Point Improvement from Baseline Response - Bayesian Logistic at Week 16	mITT		
14.2.9.1	Summary and Analysis of PGA of 0 Response - GLMM	mITT	Y	
14.2.9.2	Analysis of PGA of 0 Response - Bayesian Logistic at Week 16	mITT		
14.2.9.3	Summary of PGA of 0 or 1 Response	mITT		
14.2.10.1	Summary of Percentage Change from Baseline in PGA*BSA	mITT	Y	
14.2.10.2	Analysis of Percentage Change from Baseline in PGA*BSA - Bayesian MMRM	mITT		
14.2.11.1	Summary of Change from Baseline in PGA*BSA	mITT	Y	
14.2.11.2	Analysis of Change from Baseline in PGA*BSA - Bayesian MMRM	mITT		
14.2.12.1	Summary of Percentage Change from Baseline in LSS	mITT		
14.2.12.2	Analysis of Percentage Change from Baseline in LSS - Bayesian MMRM	mITT		
14.2.13.1	Summary of Change from Baseline in LSS	mITT		
14.2.13.2	Analysis of Change from Baseline in LSS - Bayesian MMRM	mITT		
14.2.14.1.1	Summary of Percentage Change from Baseline in DLQI Score Main Analysis	mITT		
14.2.14.1.2	Summary of Percentage Change from Baseline in DLQI Score Sensitivity Analysis	mITT		
14.2.14.2.1	Analysis of Percentage Change from Baseline in DLQI Score - Bayesian MMRM Main Analysis	mITT		
14.2.14.2.2	Analysis of Percentage Change from Baseline in DLQI Score - Bayesian MMRM Sensitivity Analysis	mITT		
14.2.15.1.1	Summary of Change from Baseline in DLQI Score Main Analysis	mITT		
14.2.15.1.2	Summary of Change from Baseline in DLQI Score Sensitivity Analysis	mITT		

Number	Title	Population	Interim	Programming notes
14.2.15.2.1	Analysis of Change from Baseline in DLQI Score - Bayesian MMRM Main Analysis	mITT		
14.2.15.2.2	Analysis of Change from Baseline in DLQI Score - Bayesian MMRM Sensitivity Analysis	mITT		
14.2.16.1	Summary of Percentage Change from Baseline in mNAPSI Total Score for Participants with Psoriatic Nail Involvement at Baseline	mITT		
14.2.16.2	Analysis of Percentage Change from Baseline in mNAPSI Total Score for Participants with Psoriatic Nail Involvement at Baseline - Bayesian MMRM	mITT		
14.2.17.1	Summary of Change from Baseline in mNAPSI Total Score for Participants with Psoriatic Nail Involvement at Baseline	mITT		
14.2.17.2	Analysis of Change from Baseline in mNAPSI Total Score for Participants with Psoriatic Nail Involvement at Baseline - Bayesian MMRM	mITT		
14.2.18	Summary of Percentage Change from Baseline in PSI Total Score	mITT		
14.2.19	Summary of Change from Baseline in PSI Total Score	mITT		
14.2.20	Summary of Percentage Change from Baseline in PSI Itch Score	mITT		
14.2.21	Summary of Change from Baseline in PSI Itch Score	mITT		
14.2.22	Summary of Percentage Change from Baseline in SF-36 Bodily Pain Score	mITT		
14.2.23	Summary of Change from Baseline in SF-36 Bodily Pain Score	mITT		
14.2.24	Summary of Percentage Change from Baseline in Pain VAS Scale Score	mITT		
14.2.25	Summary of Change from Baseline in Pain VAS Scale Score	mITT		
14.2.26	Summary of Percentage Change from Baseline in SF-36 Vitality Score	mITT		
14.2.27	Summary of Change from Baseline in SF-36 Vitality Score	mITT		
14.2.28	Summary of Percentage Change from Baseline in Fatigue VAS Scale Score	mITT		
14.2.29	Summary of Change from Baseline in Fatigue VAS Scale Score	mITT		

Number	Title	Population	Interim	Programming notes
14.2.30	Summary of Change from Baseline in Fasting Glucose and Fasting Lipid Panel	mITT		
14.2.31	Summary of Percentage Change from Baseline in BSA	mITT		
14.2.32	Summary of Change from Baseline in BSA	mITT		
14.2.33	Summary of BSA<3% Response	mITT		
14.2.34	Summary of BSA-75 Response	mITT		
14.2.35.1.1	Indirect Comparison with Apremilast UNVEIL Study for Achievement of PASI-50 at Week 16	mITT		
14.2.35.1.2	Indirect Comparison with Apremilast UNVEIL Study for Achievement of PASI-75 at Week 16	mITT		
14.2.35.1.3	Indirect Comparison with Apremilast UNVEIL Study for Achievement of PGA of 0 or 1 at Week 16	mITT		
14.2.35.1.4	Indirect Comparison with Apremilast UNVEIL Study for Percentage Change from Baseline in PGA*BSA at Week 16	mITT		
14.2.35.2.1	Indirect Comparison with Apremilast ADVANCE Study for Achievement of PGA of 0 or 1 With >=2 Point Reduction from Baseline at Week 16	mITT		
14.2.35.2.2	Indirect Comparison with Apremilast ADVANCE Study for Change from Baseline in PASI Score at Week 16	mITT		

15.2.2 Figures

Number	Title	Population	Interim	Programming notes
14.2.1.1.1	Mean (+/-SD) Percentage Change in PASI Score Over Time by Cohort Placebo Participants Only	mITT	Y	Format unchanged regardless of placebo pooling results
14.2.1.1.2	Box plots over Time for Percentage Change in PASI Score by Cohort Placebo Participants Only	mITT	Y	Format unchanged regardless of placebo pooling results

Number	Title	Population	Interim	Programming notes
14.2.1.1.3	LS Mean (95% CI) Percentage Change in PASI Score Over Time by Cohort Placebo Participants Only	mITT	Y	Format unchanged regardless of placebo pooling results
14.2.1.2.1	Mean (+/-SD) Percentage Change in PASI Score Over Time Primary Estimand	mITT	Y	
14.2.1.2.2	Mean (+/-SD) Percentage Change in PASI Score Over Time Supportive Estimand 1	mITT		
14.2.1.2.3	Mean (+/-SD) Percentage Change in PASI Score Over Time Supportive Estimand 2	mITT		
14.2.1.2.4	Mean (+/-SD) Percentage Change in PASI Score Over Time Supportive Estimand 3	mITT		
14.2.1.3.1	Posterior Mean (95% CrI) Percentage Change from Baseline in PASI Score over Time Primary Estimand	mITT	Y	
14.2.1.3.2	Posterior Mean (95% CrI) Percentage Change from Baseline in PASI Score over Time Supportive Estimand 1	mITT		
14.2.1.3.3	Posterior Mean (95% CrI) Percentage Change from Baseline in PASI Score over Time Supportive Estimand 2	mITT		
14.2.1.3.4	Posterior Mean (95% CrI) Percentage Change from Baseline in PASI Score over Time Supportive Estimand 3	mITT		
14.2.1.4.1	Bayesian Dose Response Model for Percentage Change from Baseline in PASI Score at Week 16 Primary Supportive Estimand	mITT	Y	Only produced if placebo can be pooled

Number	Title	Population	Interim	Programming notes
14.2.1.4.2	Bayesian Dose Response Model for Percentage Change from Baseline in PASI Score at Week 16 Supportive Estimand 1	mITT		Only produced if placebo can be pooled and results of corresponding MMRM supplemental analysis are substantially difference from MMRM primary analysis
14.2.1.4.3	Bayesian Dose Response Model for Percentage Change from Baseline in PASI Score at Week 16 Supportive Estimand 2	mITT		Only produced if placebo can be pooled and results of corresponding MMRM supplemental analysis are substantially difference from MMRM primary analysis
14.2.1.4.4	Bayesian Dose Response Model for Percentage Change from Baseline in PASI Score at Week 16 Supportive Estimand 3	mITT		Only produced if placebo can be pooled and results of corresponding MMRM supplemental analysis are substantially difference from MMRM primary analysis
14.2.1.5	Mean Percentage Change from Baseline in PASI Score Over Time by Treatment Completion Status Primary Estimand	mITT	Y	
14.2.1.6	Waterfall plot of Percentage Change from Baseline in PASI Score at Week 16	mITT		
14.2.2.1	Mean (+/-SD) Change in PASI Score Over Time	mITT	Y	
14.2.2.2	Posterior Mean (95% CrI) Change from Baseline in PASI Score over Time	mITT	Y	
14.2.2.3	Waterfall plot of Change from Baseline in PASI Score at Week 16	mITT		
14.2.3.1.1	Proportion (95% CI) of Participants Achieving PASI-50 At Week 16	mITT	Y	
14.2.3.1.2	Proportion (95% CI) of Participants Achieving PASI-50 At Week 16 Secondary Supportive Estimand 1	mITT		
14.2.3.2.1	Adjusted Odds Ratio (95% CI) for Achievement of PASI-50 Over Time	mITT	Y	

Number	Title	Population	Interim	Programming notes
14.2.3.2.2	Adjusted Odds Ratio (95% CI) for Achievement of PASI-50 Over Time Secondary Supportive Estimand 1	mITT		
14.2.4	Estimated Survival Function Curve for Time to First Achievement of PASI-50	mITT		
14.2.5	Proportion (95% CI) of Participants Achieving PASI-75 At Week 16	mITT	Y	
14.2.6	Proportion (95% CI) of Participants Achieving PASI-90 At Week 16	mITT	Y	
14.2.7	Proportion (95% CI) of Participants Achieving PASI-100 At Week 16	mITT	Y	
14.2.8.1	Proportion (95% CI) of Participants Achieving PGA of 0 or 1 With a >=2 Point Improvement from Baseline At Week 16	mITT	Y	
14.2.8.2	Adjusted Odds Ratio (95% CI) for Achievement of PGA of 0 or 1 With a >=2 Point Improvement from Baseline at Week 16	mITT	Y	
14.2.9.1	Proportion (95% CI) of Participants Achieving PGA of 0 At Week 16	mITT	Y	
14.2.9.2	Adjusted Odds Ratio (95% CI) for Achievement of PGA of 0 at Week 16	mITT	Y	
14.2.9.3	Proportion (95% CI) of Participants Achieving PGA of 0 or 1 at Week 16	mITT		
14.2.10.1	Mean (+/-SD) Percentage Change in PGA*BSA Over Time	mITT	Y	
14.2.10.2	Posterior Mean (95% CrI) Percentage Change from Baseline in PGA*BSA over Time	mITT		
14.2.11.1	Mean (+/-SD) Change in PGA*BSA Over Time	mITT	Y	
14.2.11.2	Posterior Mean (95% CrI) Change from Baseline in PGA*BSA over Time	mITT		
14.2.12.1	Mean (+/-SD) Percentage Change in LSS Over Time	mITT		
14.2.12.2	Posterior Mean (95% CrI) Percentage Change from Baseline in LSS over Time	mITT		
14.2.13.1	Mean (+/-SD) Change in LSS Over Time	mITT		
14.2.13.2	Posterior Mean (95% CrI) Change from Baseline in LSS over Time	mITT		
14.2.14.1.1	Mean (+/-SD) Percentage Change in DLQI Score Over Time – Main Analysis	mITT		

Number	Title	Population	Interim	Programming notes
14.2.14.1.2	Mean (+/-SD) Percentage Change in DLQI Score Over Time – Sensitivity Analysis	mITT		
14.2.14.2.1	Posterior Mean (95% CrI) Percentage Change from Baseline in DLQI Score over Time – Main Analysis	mITT		
14.2.14.2.2	Posterior Mean (95% CrI) Percentage Change from Baseline in DLQI Score over Time – Sensitivity Analysis	mITT		
14.2.15.1.1	Mean (+/-SD) Change in DLQI Score Over Time – Main Analysis	mITT		
14.2.15.1.2	Mean (+/-SD) Change in DLQI Score Over Time – Sensitivity Analysis	mITT		
14.2.15.2.1	Posterior Mean (95% CrI) Change from Baseline in DLQI Score over Time – Main Analysis	mITT		
14.2.15.2.2	Posterior Mean (95% CrI) Change from Baseline in DLQI Score over Time – Sensitivity Analysis	mITT		
14.2.16.1	Mean (+/-SD) Percentage Change in mNAPSI Total Score Over Time for Participants with Psoriatic Nail Involvement at Baseline	mITT		
14.2.16.2	Posterior Mean (95% CrI) Percentage Change from Baseline in mNAPSI Total Score over Time	mITT		
14.2.17.1	Mean (+/-SD) Change in mNAPSI Total Score Over Time for Participants with Psoriatic Nail Involvement at Baseline	mITT		
14.2.17.2	Posterior Mean (95% CrI) Change from Baseline in mNAPSI Total Score over Time for Participants with Psoriatic Nail Involvement at Baseline	mITT		

15.3 Safety

15.3.1 Tables

Number	Title	Population	Interim	Programming notes
14.3.1.1.1	Overview of TEAEs	Safety	Y	
14.3.1.1.2	Summary of TEAEs by System Organ Class and Preferred Term	Safety	Y	

Number	Title	Population	Interim	Programming notes
14.3.1.1.3	Summary of Treatment Phase TEAEs by System Organ Class and Preferred Term	Safety		
14.3.1.1.4	Summary of Follow-up Phase TEAEs by System Organ Class and Preferred Term	Safety		
14.3.1.2	Summary of Related TEAEs by System Organ Class and Preferred Term	Safety		
14.3.1.3	Summary of TEAEs of CTCAE Grade 3 or Above by System Organ Class and Preferred Term	Safety	Y	
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		
14.3.1.5	Summary of Serious TEAEs by System Organ Class and Preferred Term	Safety	Y	
14.3.1.6	Summary of Fatal TEAEs by System Organ Class and Preferred Term	Safety		
14.3.1.7	Summary of TEAEs Leading to Permanent Discontinuation from Study Drug by System Organ Class and Preferred Term	Safety	Y	
14.3.1.8	Summary of TEAEs Leading to Withdrawal from the Study by System Organ Class and Preferred Term	Safety	Y	
14.3.4.1.1	Summary of Haematology Parameters	Safety		
14.3.4.1.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the Normal Range for Haematology Parameters	Safety		
14.3.4.1.3	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria for Haematology Parameters	Safety		
14.3.4.2.1	Summary of Chemistry Parameters	Safety		
14.3.4.2.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the Normal Range for Chemistry Parameters	Safety		
14.3.4.2.3	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria for Chemistry Parameters	Safety		
14.3.5.1	Summary of ECG Parameters	Safety		

Number	Title	Population	Interim	Programming notes
14.3.5.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criterion for QTcF	Safety		
14.3.6.1	Summary of Vital Signs	Safety		
14.3.6.2	Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criterion for Vital Signs	Safety		

15.4 Data Listings

Number	Title	Population	Interim	Programming notes
16.2.1.1	Inclusion/Exclusion criteria failed	Enrolled		
16.2.1.2	End of Treatment Disposition	mITT		
16.2.1.3	End of Part A Disposition	mITT		
16.2.1.4	Participants for Whom the Blind Was Broken	mITT		
16.2.1.5	Planned and Actual Treatments	mITT		
16.2.1.6	Visits Missed Due to COVID-19	mITT		
16.2.2	Protocol Deviations	mITT		
16.2.3	Participants Excluded from Any Population	Enrolled		
16.2.4.1	Demographics	mITT		
16.2.4.2	Baseline Disease Characteristics	mITT		
16.2.4.3	Past and Current Psoriasis Treatment	mITT		
16.2.4.4	Medical History	mITT		
16.2.4.5	Prior Medications	mITT		
16.2.4.6	Concomitant Medications	mITT		
16.2.5.1	Exposure to Study Drug	mITT		
16.2.5.2	Study Drug Compliance	mITT		
16.2.6.1	Individual Components of the PASI Questionnaire	mITT		
16.2.6.2	PASI Endpoints	mITT		
16.2.6.3	Time to Event Endpoints for PASI	mITT		

Number	Title	Population	Interim	Programming notes
16.2.6.4	PGA Score	mITT		
16.2.6.5	BSA and PGA*BSA	mITT		
16.2.6.6	LSS Items and Score	mITT		
16.2.6.7	DLQI Items and Score	mITT		
16.2.6.8	mNAPSI Items and Score	mITT		
16.2.6.9	PSI Items and Total Score	mITT		
16.2.6.10	SF-36 Pain Score: Individual Items and Scores	mITT		
16.2.6.11	SF-36 Vitality Score: Individual Items and Scores	mITT		
16.2.6.12	Pain and Fatigue VAS Scores	mITT		
16.2.7.1.1	Adverse Events	Enrolled		
16.2.7.1.2	Serious Adverse Events	Enrolled		
16.2.7.1.3	Fatal Adverse Events	Safety		
16.2.7.1.4	Adverse Events Leading to Permanent Discontinuation from Study Drug	Safety		
16.2.7.2.1	Haematology Parameters	Safety		
16.2.7.2.2	Haematology Parameters for Participants with at Least One PCI Value	Safety		
16.2.7.2.3	Clinical Chemistry Parameters	Safety		
16.2.7.2.4	Clinical Chemistry Parameters for Participants with at Least One PCI Value	Safety		
16.2.7.2.5	Urinalysis Parameters	Safety		
16.2.7.3.1	ECG Parameters	Safety		
16.2.7.3.2	ECG Parameters for Participants with at Least One PCI Value	Safety		
16.2.7.4.1	Vitals Signs	Safety		
16.2.7.4.2	Vitals Signs for Participants with at Least One PCI Value	Safety		
16.2.7.5	Physical Examination	Safety		
16.2.7.6	Female Fertility Status and Pregnancy Test Results	Safety		
16.2.7.7	Bristol Stool Scale	Safety		

15.5 Part B Outputs

15.5.1 Tables

Number	Title	Population	Programming notes
14.4.1.1	Summary of Disposition in Part B	Part B	
14.4.1.2	Summary of Attendance at Each Visit in Part B	Part B	
14.4.1.3	Summary of Missed Visits Due to COVID-19 in Part B	Part B	
14.4.1.4	Summary of Populations	Part B	
14.4.1.5	Summary of Demography	Part B	
14.4.1.6	Summary of Baseline Disease Characteristics	Part B	
14.4.1.7	Summary of Concomitant Medications Used in Part B	Part B	
14.4.2.1	Summary of Percentage Change from Baseline in PASI Score	Part B	
14.4.2.2	Summary of Change from Baseline in PASI Score	Part B	
14.4.2.3	Summary of Percentage Change from Baseline in PGA*BSA	Part B	
14.4.2.4	Summary of Change from Baseline in PGA*BSA	Part B	
14.4.2.5	Summary of Percentage Change from Baseline in LSS	Part B	
14.4.2.6	Summary of Change from Baseline in LSS	Part B	
14.4.2.7.1	Summary of Percentage Change from Baseline in DLQI Score - Main Analysis	Part B	
14.4.2.7.2	Summary of Percentage Change from Baseline in DLQI Score – Sensitivity Analysis	Part B	
14.4.2.8.1	Summary of Change from Baseline in DLQI Score - Main Analysis	Part B	
14.4.2.8.2	Summary of Change from Baseline in DLQI Score - Sensitivity Analysis	Part B	
14.4.2.9	Summary of Percentage Change from Baseline in mNAPSI Total Score for Participants with Psoriatic Nail Involvement at Baseline	Part B	
14.4.2.10	Summary of Change from Baseline in mNAPSI Total Score for Participants with Psoriatic Nail Involvement at Baseline	Part B	
14.4.2.11	Summary of Percentage Change from Baseline in PSI Total Score	Part B	

Number	Title	Population	Programming notes
14.4.2.12	Summary of Change from Baseline in PSI Total Score	Part B	
14.4.2.13	Summary of Percentage Change from Baseline in PSI Itch Score	Part B	
14.4.2.14	Summary of Change from Baseline in PSI Itch Score	Part B	
14.4.2.15	Cumulative Incidence of Partial Relapse	Week 16 Responders	
14.2.2.16	Cumulative Incidence of Relapse	Week 16 Responders	
14.4.2.17	Cumulative Incidence of Rebound	mITT	
14.4.2.18	Summary of Duration of Remission	mITT	
14.2.2.20	Summary of Duration of Treatment Success	mITT	
14.4.2.21	Summary of Duration of Therapeutic Effect	mITT	
14.4.3.1	Overview of Related TEAEs Starting in Part B	Part B	
14.4.3.2	Summary of Related TEAEs by System Organ Class and Preferred Term Starting in Part B	Part B	

15.5.2 Figures

Number	Title	Population	Programming notes
14.4.2.1	Mean (+/-SD) Percentage Change in PASI Score Over Time	Part B	
14.4.2.2	Mean (+/-SD) Change in PASI Score Over Time	Part B	
14.4.2.3	Mean (+/-SD) Percentage Change in PGA*BSA Over Time	Part B	
14.4.2.4	Mean (+/-SD) Change in PGA*BSA Over Time	Part B	
14.4.2.5	Mean (+/-SD) Percentage Change in LSS Over Time	Part B	
14.4.2.6	Mean (+/-SD) Change in LSS Over Time	Part B	
14.4.2.7.1	Mean (+/-SD) Percentage Change in DLQI Score Over Time – Main Analysis	Part B	
14.4.2.7.2	Mean (+/-SD) Percentage Change in DLQI Score Over Time – Sensitivity Analysis	Part B	

Number	Title	Population	Programming notes
14.2.2.8.1	Mean (+/-SD) Change in DLQI Score Over Time – Main Analysis	Part B	
14.2.2.8.2	Mean (+/-SD) Change in DLQI Score Over Time – Sensitivity Analysis	Part B	
14.4.2.9	Mean (+/-SD) Percentage Change in mNAPSI Total Score Over Time for Participants with Psoriatic Nail Involvement at Baseline	Part B	
14.4.2.10	Mean (+/-SD) Change in mNAPSI Total Score Over Time for Participants with Psoriatic Nail Involvement at Baseline	Part B	
14.4.2.11	Mean (+/-SD) Percentage Change in PSI Total Score Over Time	Part B	
14.4.2.12	Mean (+/-SD) Change in PSI Total Score Over Time	Part B	
14.4.2.13	Mean (+/-SD) Percentage Change in PSI Itch Score Over Time	Part B	
14.4.2.14	Mean (+/-SD) Change in PSI Itch Score Over Time	Part B	
14.4.2.15	Cumulative Incidence (+/- 95% CI) of Partial Relapse	Week 16 Responders	
14.4.2.16	Cumulative Incidence (+/- 95% CI) of Relapse	Week 16 Responders	
14.4.2.17	Cumulative Incidence (+/- 95% CI) of Rebound	mITT	

15.5.3 Data Listings

Number	Title	Population	Programming notes
16.2.8.1.1	Reasons for Withdrawal from Part B	Part B	
16.2.8.1.2	Visits Missed Due to COVID-19 in Part B	Part B	
16.2.8.1.3	Concomitant Medications Started or Changed in Part B	Part B	
16.2.8.2.1	Individual Components of the PASI Questionnaire – Part B Visits	Part B	
16.2.8.2.2	PASI Endpoints– Part B Visits	Part B	
16.2.8.2.4	PGA Score– Part B Visits	Part B	
16.2.8.2.5	BSA and PGA*BSA – Part B Visits	Part B	
16.2.8.2.6	LSS Items and Score– Part B Visits	Part B	
16.2.8.2.7	DLQI Items and Score – Part B Visits	Part B	

Number	Title	Population	Programming notes
16.2.8.2.8	mNAPSI Items and Score – Part B Visits	Part B	
16.2.8.2.9	PSI Items and Total Score – Part B Visits	Part B	
16.2.8.3	Adverse Events Started or Changed in Part B	Part B	

16 Appendix 2: Psoriasis Area and Severity Index Score

Intensity

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

The intensity of erythema (redness), induration (thickness) and desquamation (scaling) of the psoriasis in each body region is scored as:

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

An intensity score is calculated for each body region as the sum of the three scores for erythema, induration and desquamation.

- A1 = Intensity score for head and neck
- A2 = Intensity score for upper limbs
- A3 = Intensity score for trunk
- A4 = Intensity score for lower limbs

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 = >0% - <10%
- 2 = 10% - <30%
- 3 = 30% - <50%
- 4 = 50% - <70%
- 5 = 70% - <90%
- 6 = 90% - 100%

PASI score calculation

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

The PASI score is the sum of the four area and intensity scores:

PASI score = C1 + C2 + C3 + C4.

17 Appendix 3: Physician Global Assessment

The physician will give a score on the participant's psoriasis disease activity, according to the following grades:

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

- 0 = no evidence of plaque elevation
- 1= minimal plaque elevation, =0.25mm
- 2 = mild plaque elevation, =0.5mm
- 3 = moderate plaque elevation, =0.75mm
- 4 = marked plaque elevation, =1mm
- 5 = severe plaque elevation, =1.25mm or more

Erythema (E) (averaged over all lesions)

- 0 = no evidence of erythema, hyperpigmentation may be present
- 1 = faint erythema
- 2 = light red coloration
- 3 = moderate red coloration
- 4 = bright red coloration
- 5 = dusky to deep red coloration

Scaling (S) (averaged over all lesions)

- 0 = no evidence of scaling
- 1 = minimal; occasional fine scale over less than 5% of the lesion
- 2 = mild, fine scale dominates
- 3 = moderate, course scale dominates
- 4 = marked, thick nontenacious scale dominates
- 5 = severe, very thick nontenacious scale dominates

The PGA score will be the average of the three scores and will be rounded to the nearest whole number.

18 Appendix 4: 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.

19 Appendix 5: Modified Nail Psoriasis Severity Index

The mNAPSI assesses each nail abnormality for each of the participant's 10 fingernails. If the rater is unsure which grade to give they should select the lower of the grades.

Three features or groups of features (pitting, onycholysis and oil-drop dyschromia, and crumbling) of each fingernail will be graded on a scale from zero to 3, according to the directions below. Four features (leukonychia, splinter haemorrhages, hyperkeratosis, and red spots in the lunula) will be graded as either present or absent for each fingernail.

Onycholysis and oil-drop dyschromia
Onycholysis: Separation of the nail plate from the nail bed. The separated part of the nail is opaque and can have white, yellow, or greenish tinge. If there is a piece of nail missing, estimate where the nail normally would have ended at the end of the nail bed, and count that missing part as involved in onycholysis.
Oil-drop (salmon patch) dyschromia: Reddish-brown discoloration under the nail plate.

Onycholysis and oil-drop dyschromia are considered together. When looking at the nail, combine the total percentage area of the nail that is affected by either and use that combined total to score the nail.

Score: Percent of nail with onycholysis or oil-drop dyschromia present

- 0 = No onycholysis or oil drop dyschromia present
- 1= 1–10% of the nail has onycholysis or oil-drop dyschromia
- 2 =11–30% of the nail has onycholysis or oil-drop dyschromia
- 3 = > 30% of the nail has onycholysis or oil-drop dyschromia

Pitting
Small, sharply defined depressions in the nail surface. Pits are discrete abnormalities ("ice-pick-like"). If there is nail plate crumbling that is confluent with pits, do not score for pits. If the pits are separate from crumbling, they may be scored regardless of whether crumbling is present or not.

Score: Number of pits

- 0 = 0
- 1 = 1–10
- 2 = 11–49
- 3 = > 50

Nail plate crumbling
Crumbling or fragmentation of friable nail plate which may be associated with confluent pitting. Crumbling involves alteration of the nail plate surface. Horizontal ridging of the nail, "wave-like" appearance, and horizontal lines are all features of crumbling.
Score: Percent of nail with crumbling present

- 0 = No crumbling
- 1 = 1–25% of the nail has crumbling
- 2 = 26–50% of the nail has crumbling
- 3 = > 50% of the nail has crumbling

Additional features

The next 4 abnormalities are scored only by their presence or absence. A score of 1 indicates present and a score of zero indicates not present.

- Leukonychia: White spots in the nail plate due to psoriasis in the mid matrix. Leukonychia are just color changes. If it appears that there is depression or irregularity to the nail surface, this may be pitting or crumbling, not leukonychia. If the leukonychia is adjacent to, or confluent with crumbling or pits, it is counted as part of the crumbling or pitting and not as a separate abnormality.
- Splinter hemorrhages: Small, longitudinal, linear, dark brown haemorrhage under the fingernail.
- Nail bed hyperkeratosis: Thickened keratin in the nail bed.
- Red spots in the lunula: Small pink or red macules in the lunula.

mNAPSI score

Each fingernail is scored as above to give a score of 0-13. The mNAPSI score is the total of the 10 individual fingernail scores.

20 Appendix 6: Psoriasis Symptom Inventory

The PSI is a patient reported outcome which assesses 8 symptoms of severity with a recall period of 24 hours. It will be completed daily by participants in the 7 days before attending the site for a visit.

The participant should answer each of the following questions every day:

Overall, during the last 24 hours:

- How severe was the itch from your psoriasis?
- How severe was the redness from your lesions?
- How severe was the scaling from your lesions?
- How severe was the burning from your lesions?
- How severe was the stinging from your lesions?
- How severe was the cracking from your lesions?
- How severe was the flaking from your lesions?
- How severe was the pain from your lesions?

Each question is scored on a 5-point scale as follows:

- 0 = Not at all
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Very Severe

If the participant has answered the symptom question on at least 5 of the 7 days, a weekly symptom score will be calculated as the average of the available daily scores for each symptom. If less than 5 daily answers are provided, the weekly symptom score will be considered as missing.

The PSI total score will be the sum of the 8 weekly symptom scores. It will only be calculated when all 8 weekly symptom scores are non-missing.

21 Appendix 7: SF-36 Pain and Vitality Scores

Pain score

The pain score will be calculated from questions 21 and 22 of the SF-36 questionnaire:

Q21: How much bodily pain have you had during the past 4 weeks?

- 1 = None
- 2 = Very mild
- 3 = Mild
- 4 = Moderate
- 5 = Severe
- 6 = Very severe

The Q21 score = 100*[(6-x)/5] where x=1-6 is the Q21 item value as above.

Q22: During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- 1 = Not at all
- 2 = A little bit
- 3 = Moderately
- 4 = Quite a bit
- 5 = Extremely

The Q22 score = 100*[(5-x)/4] where x=1-5 is the Q22 item value as above.

The SF-36 bodily pain score is the average of the Q21 and Q22 scores. If at least one of the two questions have been answered, the SF-36 bodily pain score will be calculated.

Vitality score

The vitality score will be calculated from questions 23, 27, 29 and 31 of the SF-36 questionnaire:

How much of the time during the past 4 weeks…
Q23: Did you feel full of pep?
Q27: Did you have a lot of energy?
Q29: Did you feel worn out?
Q31: Did you feel tired?

Each question has possible answers (x):

- 1 = All of the time
- 2 = Most of the time
- 3 = A good bit of the time
- 4 = Some of the time
- 5 = A little of the time
- 6 = None of the time

The Q23 score = 100*[(6-x)/5] where x=1-6 is the Q23 item value as above.
The Q27 score = 100*[(6-x)/5] where x=1-6 is the Q27 item value as above.
The Q29 score = 100*[x/5] where x=1-6 is the Q29 item value as above.
The Q31 score = 100*[x/5] where x=1-6 is the Q31 item value as above.

The SF-36 vitality score is the average of the Q23, Q27, Q29 and Q31 scores. If at least two of the four questions have been answered, the SF-36 bodily pain score will be calculated.

22 Appendix 8: 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 9.

Table 9 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

23 Appendix 9: Safety Laboratory Evaluations

Table 10 Safety Laboratory Parameters and Units

Category	Parameter	Conventional Unit	SI Units	PCI Criteria (SI units)	
				Low	High
Hematology	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	
	Platelets	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
	Direct bilirubin	mg/dL	mcmol/L		
	CRP	mg/L	nmol/L		
	Creatinine kinase	U/L	U/L		>2.5xULN
	Fasting glucose	mg/dL	mmol/L	<0.17	
	Total cholesterol	mg/dL	mmol/L		>7.77
	HDL cholesterol	mg/dL	mmol/L		
	LDL cholesterol	mg/dL	mmol/L		
	Triglycerides	mg/dL	mmol/L		>3.39

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.