Statistical Analysis Plan

Safety and Effect of LEO 90100 aerosol foam on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to < 17 Years) with Plaque Psoriasis

A phase 2 trial evaluating the safety and efficacy of once daily topical treatment with LEO 90100 aerosol foam in adolescent subjects with plaque psoriasis

An international, multi-centre, prospective, open-label, non-controlled, single-group, 4-week trial in adolescent subjects with plaque psoriasis
1 Statistical Analysis Plan Approval

1.1 Approval Statement

On behalf of LEO, the Biostatistics Lead and the Medical Lead, are authorised to approve the Statistical Analysis Plan.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan using electronic signatures as presented on the last page of this document.

PPD
Biostatistics Lead, Global Clinical Operations

PPD
Medical Lead, Medical Sciences and Safety

PPD
QC Statistician, Biostata Aps
2 Statistical Analysis Plan Statements

2.1 Compliance with Good Clinical Practice

This Statistical Analysis Plan is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3: Structure and Content of Clinical Study Reports, E6: Good Clinical Practice, and E9: Statistical Principles for Clinical Trials).
# Table of Contents

1 Statistical Analysis Plan Approval........................................................................... 2

1.1 Approval Statement................................................................................................. 2

2 Statistical Analysis Plan Statements........................................................................ 3

2.1 Compliance with Good Clinical Practice.............................................................. 3

Table of Contents ........................................................................................................... 4

3 List of Abbreviations ............................................................................................... 5

3.1 List of Abbreviations ............................................................................................ 5

4 Statistical Analysis Plan Authors............................................................................. 5

5 Introduction ............................................................................................................... 6

6 Statistical Analysis.................................................................................................... 6

6.1 Baseline Considerations ....................................................................................... 6

6.1.1 Compliance......................................................................................................... 7

6.2 Analysis of Efficacy ............................................................................................... 7

6.3 Analysis of Safety .................................................................................................. 9

6.3.1 Drug Accountability .......................................................................................... 9

6.3.2 Exposure............................................................................................................ 11

6.3.3 Adverse Events ................................................................................................ 11

6.3.4 Clinical Laboratory Evaluation ................................................................-------- 12

6.3.5 Other observations ........................................................................................... 13

6.4 General Principles ............................................................................................... 14

6.4.1 Pooling of Trial Sites ....................................................................................... 14

6.4.2 Handling of Drop-outs and Missing Values .................................................... 14

6.4.3 Treatment Labels ............................................................................................ 15

Appendix I .................................................................................................................... 16
3 List of Abbreviations

3.1 List of Abbreviations

ACTH   Adrenocorticotropic hormone
AE     Adverse Event
BSA    Body Surface Area
CDLQI  Children’s Dermatology Life Quality Index
CI     Confidence Interval
CRF    Case Report Form
CTR    Clinical Trial Report
FDLQI  Family’s Dermatology Life Quality Index
ICH    International Conference on Harmonisation
IGA    Investigator’s global assessment
LOCF   Last Observation Carried Forward
LLOQ   Lower Limit of Quantification
IMP    Investigational Medicinal Product
MedDRA Medical Dictionary for Regulatory Activities
PASI   Psoriasis Area and Severity Index
PGA    Physician’s Global Assessment
PK     Pharmacokinetics
PT     Preferred Term
SAP    Statistical Analysis Plan
SOC    System Organ Classification

4 Statistical Analysis Plan Authors

PPD , MSc, Senior Statistician, Biostatistics, LEO Pharma A/S, DK-2750, Ballerup,
Denmark, tel: +45 PPD, e-mail: PPD @leo-pharma.com

PPD , MSc, Statistician, Biostatistics, LEO Pharma A/S, DK-2750,
Ballerup, Denmark, tel: +45 PPD, e-mail: PPD @leo-pharma.com

PPD , PhD, Clinical Project Manager, Trial Management, LEO Pharma A/S, DK-2750,
Ballerup, Denmark, tel: +45 PPD, e-mail: PPD @leo-pharma.com

PPD , PhD, Senior Medical Writer, Medical Communication, LEO Pharma A/S, DK-
2750, Ballerup, Denmark, tel: +45 PPD, e-mail: PPD @leo-pharma.com
5 Introduction

The statistical analysis will be performed as outlined in the Consolidated Clinical Trial Protocol. This Statistical Analysis Plan, prepared after review of the data, contains a more technical and detailed elaboration of some points in the statistical analysis described in the protocol. Minor deviations from the planned data presentation and analysis are accounted for. The analysis sets which are to be used for the statistical analysis are presented in Analysis Set Definition Document.

No protocol amendments that are relevant to the statistical reporting have been made.

6 Statistical Analysis

The statistical analysis will be carried out as described in the Consolidated Clinical Trial Protocol with a few exceptions as described below.

Lists of planned tables, figures and individual subject data listings for the Clinical Trial Report are provided in Appendix 1.

6.1 Baseline Considerations

According to the protocol descriptive statistics of demographics and other baseline characteristics will be presented for all subjects assigned to treatment and separately for the per protocol analysis set.

Age, sex, ethnicity, race and baseline disease severity according to the PGA on the body and scalp will be given by country and not by centre as described in the protocol, due to too few number of subjects at most centres.

The age will be presented in three categories:

- Overall
- 12 to 14 years
- 15 to <17 years.
Tabulation of concomitant medication will be made for ACT Level 1 and ACT Level 4. The tabulation of the concurrent diagnoses will include SOC and PT, and will be made for Visit 1.

The baseline is defined as last assessment performed prior the first application of IMP.

### 6.1.1 Compliance

As described in the protocol, compliance with treatment instructions will be tabulated for all subjects assigned to treatment. Non-compliance is defined by number of missed days due to other reasons than cleared psoriasis in relation to treatment period. Treatment period is defined as the number of days from the treatment assignment at Visit 1 to either trial completion or early withdrawal.

The number and percentage of subjects who either did or did not comply with the trial treatment regimen will be summarized. The extent of non-compliance as categories of the percentage of applications missed will also be presented:

- No
- Yes: <=10% applications missed
- Yes: >10% to <=20% applications missed
- Yes: >20% to <=30% applications missed
- Yes: >30% to <=40% applications missed
- Yes: >40% to <=50% applications missed
- Yes: >50% applications missed
- Total

### 6.2 Analysis of Efficacy

The statistical analysis of efficacy will be based on the full analysis set.

‘Treatment success’ according to PGA on the body at week 4 and at end of treatment will be presented in a table by age group. The categories to be used are the same as defined in section 6.1, however the overall group will not be presented.

‘Treatment success’ according to PGA on the body at week 4 and at end of treatment will be presented in a table by country and not by centre as described in the protocol.

The following additional tables, not planned in the protocol, will be produced:
• Treatment success (PGA on the body and scalp) at week 4 and end of treatment by baseline extent of body psoriasis and scalp psoriasis: full analysis set

The total extent of psoriasis will be presented in following three categories:

• 2-10%
• >10-15%
• >15-30%

The categories of the extent of body psoriasis and scalp psoriasis will be defined later.

Baseline for the efficacy is defined as last observation collected prior the first application of IMP, and is defined as Visit 1 for all assessments.

Treatment success is defined as PGA score of ‘clear’ or ‘almost clear’ for subjects with at least a 2-step improvement from baseline i.e.:

‘clear’ or ‘almost clear’ for subjects with at least ‘moderate’ disease at baseline and ‘clear’ for subjects with ‘mild’ disease at baseline.

Treatment success for subject’s global assessment is defined as ‘clear’ or ‘very mild’.

The CDLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. For interpretation of incorrectly completed questionnaires following rules will be used:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If both question 7a and 7b are completed the higher of the two scores should be counted

The FDLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. For interpretation of incorrectly completed questionnaires following rules will be used:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If two or more response options are ticked, the response option with the highest score should be recorded.
4. If there is a response between two tick boxes, the lower of the two score options should be recorded.

6.3 Analysis of Safety

The analysis of safety will be based on the safety analysis set, except where otherwise stated. The analysis of the results from the ACTH-challenge test will be based on the per protocol analysis set.

According to the ACTH-challenge procedure described in the protocol, samples of venous blood were to be drawn exactly 30 min and 60 min after the CORTROSYN®/Synacthen® injection. However a time deviation of +/- 10 minutes is considered acceptable as the overall value of the test is to observe substantial increases in cortisol levels and identify adrenal insufficiency up to 1 hour after the initial injection, therefore the exact timing of the incremental time points (30 and 60 minutes) is of less importance. Samples outside the acceptable window will not be included in the analysis. No measurements outside the accepted window were observed.

The tabulation of following two analyses will not be made due to too few number of subjects:

- serum cortisol concentration at time 0 and at 30 and 60 minutes after ACTH challenge for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge
- change in serum cortisol concentration from time 0 to 30 and 60 minutes at baseline, week 4 and FU2 for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge

Instead the tabulation of individual data for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge will be presented.

Baseline for the safety analysis is defined as last observation collected prior the first application of IMP.

6.3.1 Drug Accountability

The amount of IMP used in grams and the average weekly amount used in grams will be tabulated for the safety analysis set and per protocol analysis set, and separately for three
different treatment periods (first two weeks, second two weeks, and the total treatment period).

Furthermore, a plot of the average weekly amount of IMP use over the total treatment period against baseline extent of the total BSA involvement will be presented for the safety analysis set and the per protocol analysis set.

The average weekly amount of IMP used, during the total treatment period, in defined usage categories, will be tabulated; this table was not planned in the protocol:

- <20 g/week
- 20 to <40 g/week
- 40 to <50 g/week
- 50 to <60 g/week
- >=60 g/week
- Total

The mean weight of full cans, including label of IMP, is presented in Table 1 for each batch and kit number. The label type is also given.

Table 1: Mean weight of full cans of IMP by batch number and kit number

<table>
<thead>
<tr>
<th>Batch number</th>
<th>Kit number</th>
<th>Weight of a full bottle + label (g)</th>
<th>Label Type</th>
</tr>
</thead>
</table>
| CCI          | CCI        | CCI                                 | Single panel
| CCI          | CCI        | CCI                                 | Booklet   |
| CCI          | CCI        | CCI                                 | Booklet   |
| CCI          | CCI        | CCI                                 | Single panel
| CCI          | CCI        | CCI                                 | Booklet   |

For each treatment period the following rules for calculating the amount of IMP used will apply:

For each subject the weight of IMP used for a particular treatment period will be determined by calculating the difference between the weight of a set of full cans dispensed and the weight of the returned cans.
If any subject received cans for a particular treatment period but did not return them all, then the amount of IMP used for that treatment period will not be calculated. If any cans are not dispensed, they will not contribute to the weight of IMP used for that treatment period. If any cans are returned with their seal unbroken, the weight of IMP used from that bottle will be assigned a value of zero. If a returned bottle weighs more than the estimated mean weight of a full bottle, it will be assumed that zero grams were used.

The average weekly amount of IMP used will be calculated for each subject as the amount of IMP used for a particular treatment period, divided by the duration (days) of the treatment period and then multiplied by 7.

6.3.2 Exposure

As described in the protocol, the duration of exposure (weeks) and extent of exposure (subject-treatment-weeks) to LEO 90100 will be summarized for the safety analysis set.

6.3.3 Adverse Events

The AEs will be presented for the safety analysis set as described in the protocol.

The AEs are coded in accordance with the MedDRA dictionary version 18.0.

The number of events will be presented in all adverse events tables where number of subjects is presented.

No subjects had any serious adverse events and no subject was withdrawn early from the trial due to an adverse event, therefore serious adverse events and adverse events leading to withdrawal will not be tabulated.

Additional tables, not planned in the protocol will be produced:

- Adverse events by age group, MedDRA, primary system organ class and preferred term
- Adverse events by sex, MedDRA primary system organ class and preferred term
- Adverse events by race, MedDRA primary system organ class and preferred term
- Adverse events by baseline PGA on the body, MedDRA primary system organ class and preferred term
- Adverse events by baseline PGA on the scalp, MedDRA primary system organ class and preferred term
• Adverse events by baseline total extent of body psoriasis, MedDRA primary system organ class and preferred term
• Adverse events by baseline total extent of scalp psoriasis, MedDRA primary system organ class and preferred term
• Adverse events by IMP usage, MedDRA primary system organ class and preferred term.

Adverse events will be presented separately for two categories of IMP usage, the categories will be defined later.

Following table will only be made for the subgroups 12 to 14 years and 15 to <17 years:

• Adverse events by age group, MedDRA primary system organ class and preferred term

6.3.4 Clinical Laboratory Evaluation

The laboratory data will be presented for the safety analysis set, except where otherwise stated.

The following approach will be used in case of repeated or missed laboratory measurements:

• if an initial measurement was normal but the measurement was still repeated then the initial measurement will be presented in the tables and both measurements will be included in the listing.
• if an initial measurement was repeated by mistake then the initial measurement will be presented in the tables and both measurements will be included in the listing.
• if an initial measurement was abnormal and the measurement was repeated due to a technical problem then the repeated measurement will be presented in the tables and both measurements will be included in the listing.
• if an initial measurement was missing but a measurement from an unscheduled visit is available and the unscheduled visit was performed within 5 days after the actual visit then the measurement from the unscheduled visit will be used.

The number of measurements outside the reference range will be presented in relevant laboratory tables. The number of measurements for other than primary and secondary endpoints that fall outside the limit for quantification will be presented in relevant laboratory tables.
The measurements below limit of quantification for primary or secondary endpoints will replaced by the limit of quantification.

### 6.3.5 Other observations

#### PK evaluation

The PK evaluation will be presented in a bioanalytical report.

Plasma concentrations will be presented in the listing.

#### Vital signs

For systolic and diastolic blood pressure, heart rate and temperature, the absolute value by visit and change from baseline to each visit will be summarized.

Clinically significant abnormalities in the vital signs at baseline and Week 4 will be presented. Any abnormalities at Week 4 that were not present at baseline will be presented in the listing.

The following approach will be used in case of repeated vital signs measurements:

- if an initial measurement was normal but the measurement was still repeated then the initial measurement will be presented in the tables
- if an initial measurement was abnormal and the measurement was repeated then the average of both measurements will be presented in the tables.

All measurements will be included in the listings (initial measurement and repeated measurements).

Baseline for vital signs is defined as last observation collected prior the first application of IMP (visit 1 and not screening visit 2 as written in the protocol).

#### Local Safety and Tolerability

Local safety and tolerability will be tabulated as described in the protocol.
6.4 General Principles

6.4.1 Pooling of Trial Sites

There will be no pooling of centres.

6.4.2 Handling of Drop-outs and Missing Values

An observed cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit), except for the tabulation of end of treatment. The end of treatment value for a particular parameter will be defined as the last value recorded for that parameter up to and including Visit 3 (Week 4). However, for laboratory parameters this will be the last value recorded after baseline (SV2) up to and including Visit 3.

The extent of missing values are described in Table 2 for some of the primary endpoints and secondary endpoints involving laboratory measurements:

Table 2: Number of observations/Total.\(^A\)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Test</th>
<th>(Number of observations/Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Screening Visit 2</td>
</tr>
<tr>
<td>Primary</td>
<td>Albumin corrected serum calcium(^B)</td>
<td>104/106</td>
</tr>
<tr>
<td>Primary</td>
<td>24-hours urinary calcium excretion(^C)</td>
<td>33/34</td>
</tr>
<tr>
<td>Primary</td>
<td>24-hours urinary calcium:creatinine ratio(^C)</td>
<td>32/34</td>
</tr>
<tr>
<td>Primary</td>
<td>Serum cortisol at time 0(^D)</td>
<td>33/33</td>
</tr>
<tr>
<td>Primary</td>
<td>Serum cortisol at time 30 min(^D)</td>
<td>33/33</td>
</tr>
<tr>
<td>Primary</td>
<td>Serum cortisol at time 60 min(^D)</td>
<td>33/33</td>
</tr>
<tr>
<td>Secondary</td>
<td>Urinary calcium:creatinine ratio in spot urine(^E)</td>
<td>58/72</td>
</tr>
</tbody>
</table>

A: Duplicates by subject, visit and numerical results are excluded. The table includes only subjects assigned to treatment
B: All subjects assigned to treatment.
C: Only for 24-hour urine HPA subjects.
D: Only for the per protocol analysis. Serum Cortisol at time 0 and 30 min and 60 min after ACTH challenge.
E: Only for spot urine non-HPA subjects.
6.4.3 Treatment Labels

The treatment label to be used in text and tables in the CTR and in the individual subject data listings is ‘LEO 90100’.
Appendix I
Tables, Figures and Listings
Tables and Figures, Baseline Characteristics and Investigational Product Data (Module 2)

Tables

Table 1-1 Subject enrolment and treatment assignment: Enrolled subjects and subjects assigned treatment.

Table 1-2 Reasons for withdrawal during the trial by last visit attended: full analysis set and per protocol analysis set

Table 1-3 Sex, ethnicity, race and skin type: full analysis set and per protocol analysis set.

Table 1-4 Age, BMI, height, weight and duration of plaque psoriasis: full analysis set and per protocol analysis set

Table 1-5 Physician’s global assessment (PGA) of disease severity on the body and scalp at baseline: full analysis set and per protocol analysis set

Table 1-6 Subject’s global assessment of disease severity on the body and scalp at baseline: full analysis set and per protocol analysis set

Table 1-7 Physician’s assessment of extent of psoriasis vulgaris (total involvement as % of BSA, on trunks and/or limbs as % of BSA, and scalp as % of scalp area) at baseline: full analysis set and per protocol analysis set

Table 1-8 PASI at baseline: full analysis set and per protocol analysis set

Table 1-9 Concomitant medication at baseline: full analysis set and per protocol analysis set

Table 1-10 Concurrent diagnoses at baseline by MedDRA primary system organ class and preferred term: full analysis set and per protocol analysis set

Note: The tabulation of the concurrent diagnoses will include SOC and PT, and will be made for Visit 1.

Table 1-11 Age by country: full analysis set and per protocol analysis set

Table 1-12 Sex by country: full analysis set and per protocol analysis set
Table 1-13 Ethnicity by country: full analysis set and per protocol analysis set

Table 1-14 Race by country: full analysis set and per protocol analysis set

Table 1-15 Physician’s global assessment of disease severity on the body and scalp at baseline by country: full analysis set and per protocol analysis set

Table 1-16 Compliance with treatment instructions: full analysis set and per protocol analysis set

Figures

Figure 1-1 Visit attendance: enrolled subjects

Figure 1-2 Trial analysis sets: enrolled subjects

Tables and Figures, Efficacy Data (Module 3)

Tables

Table 2-1 Physician’s global assessment of disease severity on the body and scalp by visit and at end of treatment: full analysis set

Table 2-2 Treatment success (PGA on the body and scalp) by visit and at end of treatment: full analysis set

Note: Calculate 95% CI based on a binomial distribution for the proportion of subjects with ‘treatment success’ at week 4 and end of treatment.

Table 2-3 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by age group: full analysis set

Table 2-4 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by sex: full analysis set

Table 2-5 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by ethnicity: full analysis set
Table 2-6 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by race: full analysis set

Table 2-7 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by baseline PGA on the body and scalp: full analysis set

Table 2-8 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by country: full analysis set

Table 2-9 Treatment success (PGA on the body and scalp) at week 4 and end of treatment by baseline extent of body psoriasis and scalp psoriasis: full analysis set

Table 2-10 PASI by visit and end of treatment: full analysis set

Table 2-11 Percentage change in PASI from baseline to each visit and end of treatment: full analysis set

*Note: Calculate 95% CI for mean change in PASI based on a normal distribution for week 4 and end of treatment.*

Table 2-12 Physician’s assessment of extent of psoriasis (total involvement as % of BSA, on body as % of BSA and scalp as % of scalp area) by visit and at end of treatment: full analysis set

Table 2-13 Treatment success (subject’s global assessment of disease severity on the body and scalp) by visit and at end of treatment: full analysis set

*Note: Calculate 95% CI based on a binomial distribution for the proportion of subjects with ‘treatment success’ at week 4 and end of treatment.*

Table 2-14 Subject’s global assessment of disease severity on the body and scalp by visit and at end of treatment: full analysis set

Table 2-15 Subject’s assessment of itch by visit and end of treatment: full analysis set

Table 2-16 Change in itch from baseline to each visit and end of treatment: full analysis set

*Note: Calculate 95% CI for mean change in itch based on a normal distribution for week 4 and end of treatment.*
Table 2-17 Subject’s assessment of itch-related sleep loss by visit and end of treatment: full analysis set

Table 2-18 Change in itch-related sleep loss from baseline to each visit and end of treatment: full analysis set

Table 2-19 CDLQI total score by visit and end of treatment: full analysis set.

Table 2-20 Change in CDLQI total score from baseline to each visit and end of treatment: full analysis set.

Table 2-21 Subjects with CDLQI scores of 0 or 1 by visit and at end of treatment: full analysis set.

Note: Only for subjects with baseline score >1.

Table 2-22 Subjects with ≥ 5 points improvement in CDLQI score from baseline by visit and at end of treatment: full analysis set

Note: Only for subjects with baseline score ≥5.

Table 2-23 FDLQI total score by visit and end of treatment: full analysis set.

Table 2-24 Change in FDLQI total score from baseline to each visit and end of treatment: full analysis set.

Table 2-25 Subjects with FDLQI scores of 0 or 1 by visit and at end of treatment: full analysis set

Note: Only for subjects with baseline score >1.

Table 2-26 Subjects with ≥ 5 points improvement in FDLQI score from baseline by visit and at end of treatment: full analysis set

Note: Only for subjects with baseline score ≥5.
Tables and Figures, Safety Data (Module 4)

Tables

Table 3-1 Serum cortisol concentration at time 0 and at time 30 and 60 minutes after ACTH challenge at baseline and Week 4: per protocol analysis set

Table 3-2 Subjects with serum cortisol concentration <=18 mcg/dL at both 30 and 60 minutes after ACTH challenge at Week 4: per protocol analysis set

Table 3-3 Individual data for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge: per protocol analysis set.

Table 3-4 Albumin-corrected serum calcium by visit and end of treatment: safety analysis set

Table 3-5 Change in albumin-corrected serum calcium from baseline to Week 4 and end of treatment: safety analysis set

*Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.*

Table 3-6 Albumin-corrected serum calcium categorised as low, normal or high at Week 4 and end of treatment shown against baseline category: safety analysis set

Table 3-7 Albumin-corrected serum calcium by visit and end of treatment by 25-hydroxy vitamin D classifications: safety analysis set

Table 3-8 Change in albumin-corrected serum calcium from baseline to Week 4 and end of treatment by 25-hydroxy vitamin D classifications: safety analysis set

*Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.*

Table 3-9 Albumin-corrected serum calcium categorised as low, normal or high at Week 4 and end of treatment shown against baseline category by 25-hydroxy vitamin D classifications: safety analysis set

Table 3-10 24-hour urinary calcium excretion by visit and end of treatment: 24-hour urine HPA set.

Table 3-11 Change in 24-hour urinary calcium excretion from baseline to Week 4 and end of treatment: 24-hour urine HPA set.
Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.

Table 3-12 24-hour urinary calcium excretion categorised as low, normal or high at Week 4 and end of treatment shown against baseline category: 24-hour urine HPA set.

Table 3-13 24-hour urinary calcium excretion by visit and end of treatment by 25-hydroxy vitamin D classifications: 24-hour urine HPA set.

Table 3-14 Change in 24-hour urinary calcium excretion from baseline to Week 4 and end of treatment by 25-hydroxy vitamin D classifications: 24-hour urine HPA set.

Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.

Table 3-15 24-hour urinary calcium excretion categorised as low, normal or high at Week 4 and end of treatment shown against baseline category by 25-hydroxy vitamin D classifications: 24-hour urine HPA set.

Table 3-16 24-hour urinary calcium excretion by visit and end of treatment in subjects with complete urinary collection: 24-hour urine HPA set.

Table 3-17 Change in 24-hour urinary calcium excretion from baseline to Week 4 end of treatment in subjects with complete urinary collection: 24-hour urine HPA set.

Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.

Table 3-18 24-hour urinary calcium excretion categorised as low, normal or high at Week 4 and end of treatment shown against baseline category in subjects with complete urinary collection: 24-hour urine HPA set.

Table 3-19 24-hours urinary calcium:creatinine ratio by visit and end of treatment: 24-hour urine HPA set.

Table 3-20 Change in 24-hours urinary calcium:creatinine ratio from baseline to Week 4 and end of treatment: 24-hour urine HPA set.

Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.

Table 3-21 24-hours urinary calcium:creatinine ratio categorised as low, normal or high at Week 4 and end of treatment shown against baseline category: 24-hour urine HPA set.
Table 3-22 24-hours urinary calcium:creatinine ratio by visit and end of treatment by 25-hydroxy vitamin D classifications: 24-hour urine HPA set.

Table 3-23 Change in 24-hours urinary calcium:creatinine ratio from baseline to Week 4 and end of treatment by 25-hydroxy vitamin D classifications: 24-hour urine HPA set.

*Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.*

Table 3-24 24-hours urinary calcium:creatinine ratio categorised as low, normal or high at Week 4 and end of treatment shown against baseline category by 25-hydroxy vitamin D classifications: 24-hour urine HPA set.

Table 3-25 Calcium:creatinine ratio in spot urine by visit and end of treatment: spot urine non-HPA set.

Table 3-26 Change in calcium:creatinine ratio in spot urine from baseline to Week 4 and end of treatment: spot urine non-HPA set.

*Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.*

Table 3-27 Calcium:creatinine ratio in spot urine categorised as low, normal or high at Week 4 and end of treatment shown against baseline category: spot urine non-HPA set.

Table 3-28 Calcium:creatinine ratio in spot urine by visit and end of treatment by 25-hydroxy vitamin D classifications: spot urine non-HPA set.

Table 3-29 Change in calcium:creatinine ratio in spot urine from baseline to Week 4 and end of treatment by 25-hydroxy vitamin D classifications: spot urine non-HPA set.

*Note: Calculate 95% CI of mean change from baseline to week 4 and end of treatment.*

Table 3-30 Calcium:creatinine ratio in spot urine categorised as low, normal or high at Week 4 and end of treatment shown against baseline category by 25-hydroxy vitamin D classifications: spot urine non-HPA set.

Table 3-31 Haematology parameters by visit: safety analysis set

Table 3-32 Change in haematology parameters from baseline to Week 4: safety analysis set
Table 3-33 Haematology parameters categorised as low, normal or high at Week 4 shown against baseline category: safety analysis set

Table 3-34 Other biochemistry parameters by visit: safety analysis set

Table 3-35 Change in other biochemistry parameters from baseline to Week 4: safety analysis set

Table 3-36 Other biochemistry parameters categorised as low, normal or high at Week 4 shown against baseline category: safety analysis set

Table 3-37 Other 24-hour urinalysis parameters by visits: 24-hour urine HPA set.

Table 3-38 Change in other 24-hour urinalysis parameters from baseline to Week 4: 24-hour urine HPA set.

Table 3-39 Other 24-hour urinalysis parameters categorised as low, normal or high at Week 4 shown against baseline category: 24-hour urine HPA set.

Table 3-40 Other urinalysis parameters measured in spot urine by visits: spot urine non-HPA set.

Table 3-41 Change in other urinalysis parameters measured in spot urine from baseline to Week 4: spot urine non-HPA set.

Table 3-42 Other urinalysis parameters measured in spot urine categorised as low, normal or high at Week 4 shown against baseline category: spot urine non-HPA set.

Table 3-43 Presence of urinary glucose and ketones at week 4 against presence at baseline: safety analysis set.

Table 3-44 Duration and extent of exposure to IMP: safety analysis set

Table 3-45 Amount of IMP used (g): safety analysis set and per protocol analysis set.

Table 3-46 Average weekly amount of IMP used (g): safety analysis set and per protocol analysis set

Table 3-47 Average weekly amount of IMP used in defined usage categories: safety analysis set and per protocol analysis set
Note: Make the table from baseline to week 4 and end of treatment.

Table 3-48 Overall summary of adverse events: safety analysis set

Table 3-49 Adverse events by MedDRA primary system organ class: safety analysis set

Table 3-50 Adverse events by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-51 Severity of adverse events by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-52 Causal relationship of adverse events to IMP by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-53 Related adverse events by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-54 Severity of adverse drug reactions by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-55 Lesional/perilesional adverse events by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-56 Lesional/perilesional adverse events on the body by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-57 Lesional/perilesional adverse events on the scalp by MedDRA primary system organ class and preferred term: safety analysis set

Table 3-58 Adverse events by age group, MedDRA primary system organ class and preferred term: safety analysis set

Note: Only for subgroups.

Table 3-59 Adverse events by sex, MedDRA primary system organ class and preferred term: safety analysis set

Table 3-60 Adverse events by race, MedDRA primary system organ class and preferred term: safety analysis set
Table 3-61 Adverse events by baseline PGA on the body, MedDRA primary system organ class and preferred term: safety analysis set

Table 3-62 Adverse events by baseline PGA on the scalp, MedDRA primary system organ class and preferred term: safety analysis set

Table 3-63 Adverse events by baseline total extent of body and scalp psoriasis, MedDRA primary system organ class and preferred term: safety analysis set

Table 3-64 Adverse events by IMP usage, MedDRA primary system organ class and preferred term: safety analysis set

Table 3-65 Local safety and tolerability by visit: safety analysis set

Note: Both number and percentage of subjects in each of the four categories (‘Absent’ to ‘Severe’).

Table 3-66 Systolic blood pressure by visit: safety analysis set

Table 3-67 Change in systolic blood pressure from baseline to each visit: safety analysis set

Table 3-68 Diastolic blood pressure by visit: safety analysis set

Table 3-69 Change in diastolic blood pressure from baseline to each visit: safety analysis set

Table 3-70 Heart rate by visit: safety analysis set

Table 3-71 Change in heart rate from baseline to each visit: safety analysis set

Table 3-72 Temperature by visit: safety analysis set

Table 3-73 Change in temperature rate from baseline to each visit: safety analysis set

Figures

Figure 3-1 Average weekly amount of IMP used over the total treatment period against change from baseline to Week 4 in albumin corrected serum calcium: safety analysis set.

Figure 3-2 Average weekly amount of IMP used over the total treatment period against change from baseline to end of treatment in albumin corrected serum calcium: safety analysis set.
Figure 3-3 Average weekly amount of IMP used over the total treatment period against baseline extent of total BSA involvement: safety analysis set and per protocol analysis set.

**Patient Data Listings (Appendix 1)**

1-7: Subjects Receiving Investigational Product from Specific Batches

**Patient Data Listings (Appendix 2)**

Appendix 2.1: Discontinued Subjects

Listing 1-1: Screening failures

Listing 1-2: Reasons for withdrawal from trial

Appendix 2.2: Protocol Deviations

Listing 2-1: Protocol deviations

Listing 2-2: Comments from CRF

Appendix 2.3: Trial Analysis Sets

Listing 3-1: Trial Analysis Sets

Listing 3-2: Reasons for Exclusions from Analysis Sets

Appendix 2.4: Demographic Data

Listing 4-1: Demographics

Listing 4-2: Duration of Psoriasis Vulgaris

Listing 4-3: Actual Trial Period

Listing 4-4: Medical History
Listing 4-5: Concomitant Diagnoses at Baseline

Listing 4-6: Concomitant Medication

Appendix 2.5: Compliance and/or Investigational Product Concentration Data

Listing 5-1: Compliance

Listing 5-2: Drug Accountability

Listing 5-3: Exposure Dates

Appendix 2.6: Efficacy Data

Listing 6-1: Physician’s Global Assessment of Disease Severity

Listing 6-2: Physician’s Assessment of Extent of Psoriasis

Listing 6-3: Physician’s Assessment of Extent and Severity of Clinical Signs and PASI Score

Listing 6-4: Subject’s Global Assessment of Disease Severity

Listing 6-5: Subject’s Assessment of Itch

Listing 6-6: Subject’s Assessment of Itch-Related Sleep Loss

Listing 6-7: Children’s Dermatology Life Quality Index.

Listing 6-8: The Family Dermatology Life Quality Index

Appendix 2.7: Safety Data

Listing 7-1 Deaths

Listing 7-2 Serious Adverse Events
Listing 7-3 Subjects Withdrawn due to AE

Listing 7-4 Severe Adverse Events

Listing 7-5 Adverse Events

Listing 7-6 Dietary Calcium Intake

Listing 7-7 Albumin-Corrected Serum Calcium

Appendix 2.8: Listing of Laboratory Values by Subject

Listing 8-1 Physical Examination

Listing 8-2: Laboratory Measurements

Listing 8-3: Abnormal Laboratory Measurements

Listing 8-4: ACTH Challenge Test

Listing 8-5: Vital signs

Listing 8-6 PK Measurements

**Additional Tables for Results Reporting in Clinical Trial Data Registries**

Table 4-1 Age group: subjects assigned to treatment

Table 4-2 Non-serious AEs occurring in ≥[X]% subjects by MedDRA primary SOC and preferred term: safety analysis set
[Note: X% is 5% or smaller percentage]
<table>
<thead>
<tr>
<th>Reason for signing: Approved</th>
<th>Management / Lead Approver Verdict(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name: <strong>PPD</strong></td>
</tr>
<tr>
<td></td>
<td>Capacity: Biostatistics</td>
</tr>
<tr>
<td></td>
<td>Date of signature: 12-Jun-2018 12:14:53 GMT+0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for signing: Approved</th>
<th>Approver Verdict(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name: <strong>PPD</strong></td>
</tr>
<tr>
<td></td>
<td>Capacity: Biostatistics</td>
</tr>
<tr>
<td></td>
<td>Date of signature: 12-Jun-2018 12:18:59 GMT+0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for signing: Approved</th>
<th>Management / Lead Approver Verdict(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name: <strong>PPD</strong></td>
</tr>
<tr>
<td></td>
<td>Capacity: Medical</td>
</tr>
<tr>
<td></td>
<td>Date of signature: 12-Jun-2018 13:17:16 GMT+0000</td>
</tr>
</tbody>
</table>