STATISTICAL ANALYSIS PLAN

A PHASE 4, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE IMPACT OF APREMILAST (CC-10004) ON QUALITY OF LIFE, EFFICACY, AND SAFETY IN SUBJECTS WITH MANIFESTATIONS OF PLAQUE PSORIASIS AND IMPAIRED QUALITY OF LIFE

STUDY DRUG: Apremilast (CC-10004)

PROTOCOL NUMBER: CC-10004-PSOR-020

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1. LIST OF ABBREVIATIONS

Table 1 Abbreviations and Specialist Terms

ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
BSA	Body Surface Area
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract Research Organization
[redacted]	
CTCAE	Common Terminology Criteria for Adverse Events
DAO	Data as Observed
DMC	Data Monitoring Committee
DLQI	Dermatology Life Quality Index
EAIR	Exposure-Adjusted Incidence Rate
EQ-5D	European Quality of Life 5-Dimension Questionnaire
GCP	Good Clinical Practice
Hgb	Hemoglobin
ICH	International Council for Harmonization
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
LDH	Lactic dehydrogenase
LOCF	Last Observation Carried Forward

MedDRA	Medical Dictionary for Regulatory Affairs
MCMC	Markov Chain Monte Carlo
MI	Multiple Imputation
NA	Not applicable
NAPSI	Nail Psoriasis Severity Index
NRI	Non-responder Imputation
NRS	Numeric Rating Scale
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PP	Per-Protocol
PPPGA	Palmoplantar Psoriasis Physician Global Assessment
PBI	Patient Benefit Index
PNQ	Patient Needs Questionnaire
PBQ	Patient Benefit Questionnaire
PT	Preferred Term
SAP	Statistical Analysis Plan
STDEV	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
ScPGA	Scalp Physician Global Assessment
SOC	system organ class
sPGA	Static Physician Global Assessment
sPGA-G	Static Physician Global Assessment-Genitalia
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale

WHO DD	World Health Organization Drug Dictionary
WPAI: PSO	Work Productivity and Activity Impairment Questionnaire: Psoriasis

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Amgen's protocol CC-10004-PSOR 020 "A Phase 4, Multi-Center, Randomized, Double-blind, Placebo-Controlled Study of the Impact of Apremilast (CC-10004) on Quality of Life, Efficacy, and Safety in Subjects with Manifestations of Plaque Psoriasis and Impaired Quality of Life" version 1.0, which was issued on 12Oct2020. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of Quality of Life, efficacy and safety.

No interim analysis is planned. There will be a Week 16 data transfer on all the data collected after all subjects have completed the Week 16 Visit (or discontinued from the study) for publication purpose; unblinded data will only be made available to selected Sponsor and Contract Research Organization (CRO) team members involved with publication preparations. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the final study completion. After all subjects have completed the Observational Follow-up Phase following the Week 52/discontinuation visit, the final data base will be locked and transferred for all analyses planned in the SAP to generate the Clinical Study Report (CSR) of the study. Only one CSR will be generated including the analyses for both the primary Week 16 timepoint and the other timepoints from the open label extension phase.

Throughout this SAP, the treatment groups will be referred to as Apremilast 30 mg BID arm and placebo arm according to the original treatment assignment or treatment received during the Placebo-controlled Phase. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to the access to unblinded data. This SAP will be finalized and signed prior to Week 16 data transfer. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to assess the impact of Apremilast, compared to placebo, on Health-related Quality of Life (QOL) in subjects with manifestations of plaque psoriasis and impaired quality of life at Week 16

3.2. Secondary Objectives

The secondary objectives are:

- To assess the efficacy and safety of Apremilast compared to placebo in patients with manifestations of plaque psoriasis and impaired quality of life at Week 16
- To assess the long-term effects of Apremilast with respect to quality of life, efficacy, and safety at Weeks 32 and 52

3.3. Exploratory Objectives

The exploratory objectives are:

- To assess the efficacy of Apremilast compared to placebo in subgroups of patients with specific manifestations

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 4, multicenter, randomized, double-blind, placebo-controlled study of the impact of Apremilast on quality of life, efficacy, and safety in subjects with manifestations of plaque psoriasis and impaired quality of life. Approximately 276 subjects in 6-10 countries in Western Europe meeting inclusion criteria will be randomized in 2:1 ratio to receive Apremilast 30 mg BID or placebo, and to each of the stratification factors of manifestations of psoriasis (scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, and psoriasis in visible locations). For patients with multiple manifestations, they will be allocated to the manifestation which is most severe, as determined by the patients.

- Subjects randomized to the Apremilast treatment group will receive a 5-day titration with Apremilast followed by Apremilast 30 mg BID orally for 16 weeks. The subjects will continue with Apremilast 30 mg BID until Week 52 (i.e., a total of 52-week treatment with Apremilast). There is a dummy 5-day titration at Week 16 to maintain the blind to the original treatment assignment at randomization.
- Subjects randomized to the placebo treatment group will start with a dummy 5-day titration and receive placebo tablets (identical in appearance to the Apremilast 30 mg tablets) orally twice daily for 16 weeks. Beginning at Week 16 and after a 5-day titration with Apremilast, subjects will receive Apremilast 30 mg BID until Week 52 (i.e., a total of 36-week treatment with Apremilast).

The study consists 4 phases:

- Screening Phase – up to 5 weeks (35 days)
- Double-blind Placebo-controlled Phase – Weeks 0 through 16

  Subjects will receive treatment with either

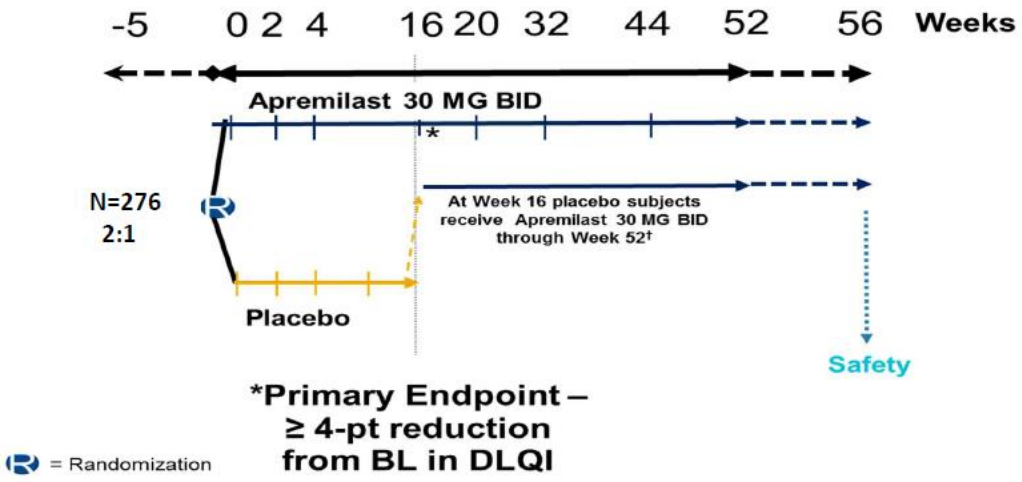
  – Apremilast 30 mg tablets orally BID, or

  – matched placebo tablets orally BID
- Apremilast Extension Phase – Weeks 16 through 52

  – All subjects will be switched to (or continue with) Apremilast 30 mg BID at Week 16 (after a 5-day titration for subjects initially randomized to placebo). All subjects will maintain this dosing through Week 52.
- Post-treatment Observational Follow-up Phase

  – 4-week post-treatment observational follow-up phase for all subjects who complete the study on treatment or discontinue from the study treatment early.

Figure 1: Overall Study Design



The study will be conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint(s)

The primary endpoint is achieving a ≥ 4-point reduction from baseline in the Dermatology Life Quality Index (DLQI) at Week 16.

4.2.2. Secondary Efficacy Endpoint(s)

The secondary endpoints are

- Achieving a ≥ 4-point reduction from baseline at weeks 32 and 52
- Change from baseline in DLQI at weeks 16, 32, and 52
- Change from baseline in Itch Numeric Rating Scale (NRS) at weeks 16, 32, and 52
- Change from baseline in Skin Discomfort/Pain Visual Analog Scale (VAS) at weeks 16, 32, and 52
- Percent change from baseline in Body Surface Area (BSA) at weeks 16, 32, and 52
- Achieving Psoriasis Area and Severity Index (PASI) score <3 at weeks 16, 32, and 52
- Achieving Patient Benefit Index (PBI) score ≥1 at weeks 16, 32, and 52
- Percent change from baseline in European Quality of Life 5-Dimension Questionnaire (EQ-5D) at weeks 16 and 52

- Change from baseline in Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO) at weeks 16 and 52

4.2.3. Exploratory Efficacy Endpoint(s)

The Exploratory efficacy endpoints are:

- [redacted]
- Achieving Static physician global assessment (sPGA) score of 0 or 1 at Weeks 16, 32, and 52 among the subjects randomized to the strata with moderate to severe psoriasis in visible areas, defined as sPGA≥3 at baseline, which include the dorsal hand, face, neck, or hairline.
- Achieving ScPGA score of 0 or 1 at weeks 16, 32, and 52 among the subjects randomized to the strata with moderate to severe scalp psoriasis (ScPGA ≥3 at baseline).
- Achieving Nail Psoriasis Severity Index (NAPSI) score of 0 in the target fingernail at weeks 16, 32, and 52 among the subjects randomized to the strata with presence of nail psoriasis, defined as onycholysis and onychodystrophy in at least 2 fingernails at baseline.
- Achieving Static Physician Global Assessment-Genitalia (sPGA-G) score of 0 or 1 at weeks 16, 32, and 52 among the subjects randomized to the strata with moderate to severe genital psoriasis (sPGA-G ≥3 at baseline).
- Achieving Palmoplantar Psoriasis Physician Global Assessment (PPPGA) score of 0 or 1 at weeks 16, 32, and 52 among the subjects randomized to the strata with moderate to severe palmoplantar psoriasis (PPPGA ≥3 at baseline).

4.2.4. Safety Endpoints

Safety endpoints will include:

- Adverse events (AE)
- Pregnancy tests for females of child bearing potential (FCBP)
- Vital signs
- Clinical laboratory tests
- Body weight and waist circumference

4.2.5. Derivations of Efficacy Endpoints

The derivation of each efficacy endpoint is described below in separate sections. Baseline definition for all efficacy endpoints is given in Section 5.4. Change from baseline is calculated as on-treatment value minus the baseline value. Percent change from baseline is defined as 100* Change from baseline/Baseline value (%). Handling of time points is described in Section 5.5.

4.2.5.1. Dermatology Life Quality Index (DLQI)

The DLQI (Finlay, 1994) was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease. The instrument contains 10 items dealing with the subject's skin. With the exception of Item Number

7, the subject responds on a four-point scale, ranging from "Very Much" (score 3) to "Not at All" or "Not relevant" (score 0). Item Number 7 is a multi-part item, the first part of which ascertains whether the subject's skin prevented them from working or studying (Yes or No, scores 3 or 0 respectively), and if "No," then the subject is asked how much of a problem the skin has been at work or study over the past week, with response alternatives being "A lot," "A little," or "Not at all" (scores 2, 1, or 0 respectively). The DLQI total score is derived by summing all item scores, which has a possible range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best.

If one of the 10 items are left unanswered, it is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more of the ten items are left unanswered, DLQI total score will be left missing. When using sub-scales, if the answer to one item in a sub-scale is missing, the score is set to missing for that sub-scale.

4.2.5.2. Itch Numeric Rating Scale (NRS) Assessment

The Itch NRS is a single-item patient-reported outcome that asks subjects to assess the worst severity of itch over the past 24 hours and select a number on a scale of 0 to 10, where "0" represents no itching, and "10" represents the worst itch imaginable (Naegeli, 2015). The number selected by the subject will be recorded in the database.

4.2.5.3. Skin Discomfort/Pain Visual Analog Scale (VAS)

The subject will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents no skin discomfort/pain, and the right-hand boundary represents skin discomfort/pain as severe as can be imagined. The number corresponding to the stroke will be recorded in the database.

4.2.5.4. Body Surface Area (BSA)

Body surface area is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint"), which equates to approximately 1% of total BSA.

4.2.5.5. Patient Benefit Index (PBI)

The PBI is a validated patient-reported instrument to assess patient-relevant benefits of psoriasis treatment and represents the subject benefits realized as a function of most important subject needs (Feuerhahn, 2012). PBI consist of 2 questionnaires:

- Patient Needs Questionnaire (PNQ): Prior to starting therapy, subjects are asked to assess their treatment expectations by completing the PNQ. Individual importance of treatment objectives is collected by marking the importance of a total of 25 treatment goal statements. The score ranges from 0 (no important at all) to 4 (very important) for each treatment objective will be recorded in the database.
- Patient Benefit Questionnaire (PBQ): After a period of treatment, subjects are then asked to assess the benefits of treatment by completing the PBQ with the same 25 treatment goal statements. The score ranges from 0 (not at all) to 4 (very) will be recorded in the database.

A global score is calculated for each subject at a given visit by weighing the achievement values of the treatment objectives by their importance to the individual patient using the following Algorithm. Using this algorithm, the importance of each treatment goal is divided by the sum of all importance values of the respective patient and is multiplied with the goal attainment values. The resulting products are added up:

$$PBI = \sum_{i=1}^{k} \frac{PNQ_i}{\sum_{i=1}^{k} PNQ_i} PBQ_i$$

$$i = the\ ith\ treatment\ goal\ statement$$

$$k = total\ number\ of\ the\ \ applicable\ preference\ items\ (PNQ)\ and\ benefit\ items\ (PBQ)$$

For score calculation, both "does/did not apply" and "question unanswered" will be treated as missing values. The global score will be calculated using only the items pairs (i.e., importance item and benefit items) for which the patient has given a response other than "does/did not apply" in both PNQ and PBQ. For example, importance items for which the corresponding benefit item has been rated as "did not apply" (or vice versa) will not be included in the denominator within the algorithm.

4.2.5.6. Psoriasis Area and Severity Index (PASI)

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI is a validated instrument that has become standard in clinical trials for psoriasis.

Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. The PASI score will be set to missing if any severity score or degree of involvement is missing. PASI scores will be presented with one digit after the decimal point.

4.2.5.7. The European Quality of Life 5-Dimension Questionnaire (EQ-5D)

EQ-5D-3L (The EuroQol Group, 1990) measures the subject's general health state as a vertical VAS and 5 quality of life domains as multiple-choice questions: mobility, self-care, main activity (work, study, housework, family/leisure activities), pain/discomfort, and anxiety/depression. The EQ-5D VAS scores range from 0 to 100, where score 0 indicates the worst imaginable health states and score 100 indicates the best imaginable health state. Using the 5-domain scores, EQ-5D index values using the UK scoring algorithm will be derived, where a higher score indicates a better health state.

4.2.5.8. The Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)

The WPAI: PSO questionnaire is a validated, 6-item self-administered instrument used to assess the impact of disease on work productivity in psoriasis due to specified health problem during the last 7 days. The 6 questions are: Q1 = currently employed; Q2 = hours missed due to problems associated with psoriasis; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while working (using a 0 to 10 Visual Analogue Scale (VAS)); Q6 = degree health affected productivity in regular unpaid activities (VAS) [Reilly, 2012] The sum of work time missed and work impairment while working yielded the overall work impairment measure. Four types of scores were calculated as following. All scores were expressed as percentages, with higher scores indicating greater impairment.

1) percent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed;

2) percent impairment while working due to health = Q5/10 for those who were currently employed and actually worked in the past seven days;

3) percent overall work impairment due to health Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) × (Q5/10)) for those who were currently employed. For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to health will be equal to the percent work time missed due to health;

4) percent activity impairment due to health Q6/10 for all respondents.

4.2.5.9. Static Physician Global Assessment (sPGA) of visible locations

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. In this study, sPGA is used to evaluate psoriasis only in visible locations, defined as dorsal hand, face, neck and hairlines.

The sPGA is a 5-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. When making the assessment of overall severity, the Investigator should factor in areas that have already been cleared (i.e., have scores of 0) and not just evaluate remaining lesions for severity, i.e., the severity of each sign is averaged across all areas of visible locations, including cleared lesions.

4.2.5.10. Scalp Physician Global Assessment (ScPGA)

The ScPGA is a measurement of overall scalp involvement. The ScPGA is a 5-point scale that assesses three dimensions (Plaque Elevation, Scaling, and Erythema) on a scale of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe).

4.2.5.11. Nail Psoriasis Severity Index (NAPSI) Assessment

The number of fingers with psoriasis nail involvement, defined as onycholysis and onychodystrophy, will be counted.

The NAPSI (Rich, 2003) will assess one target thumb nail or fingernail representing the worst nail psoriasis involvement at Baseline. The total NAPSI score ranging from 0 to 8 (most severe) will be recorded in the database.

4.2.5.12. Modified Static Physician Global Assessment-Genitalia (sPGA-G)

The modified sPGA-G is the assessment by the Investigator of the overall disease severity at the time of evaluation of the genital regions. As with the sPGA, it is a 5-point scale, ranging from 0 (clear) to 4 (severe).

4.2.5.13. Palmoplantar Psoriasis Physician Global Assessment (PPPGA)

The PPPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation of palms and soles (Leonardi, 2007). The scale ranges from 0 (clear) to 4 (severe).

4.3. Stratification, Randomization, and Blinding

Randomization is carried out using an Interactive Voice Response System (IVRS). Treatment assignment is following a 2:1 ratio between Apremilast 30 mg BID arm and placebo arm. Randomization method is based on permutated-block randomization. Subjects were targeted to be randomized within each of the 5 manifestations of plaque psoriasis (i.e., scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, and psoriasis in visible locations). If subjects present with multiple manifestations, they will be allocated to the manifestation which is most severe, as determined by the subject.

Data analysis and reporting will be performed for publication after all subjects have completed the double-blind placebo-controlled phase at Week 16/Visit 5 or have discontinued early. A copy of the 16-week data extraction will be transferred for analysis after medical/scientific review has been completed, protocol violations/deviations have been identified, and the data have been declared cleaned. Selected members of the study team and external partner who do not have direct interaction with subjects are unblinded for the analysis of the Week 16 data. These persons may include but are not limited to the following: Therapeutic Area Head, Study lead, Medical Director and the Statistician. The results from these analyses may be published prior to the end of the study.

Subjects, Investigators and persons responsible for the ongoing conduct of the study will continue to be blinded to the original treatment assignment until the 52-week database lock at end of the study. These persons are those individuals who have direct interaction with subjects and/or subject assessments and may include but are not limited to the following: Clinical Trial Manager, Data Manager, Clinical Research Associates and Site Monitors.

For the purpose of the data analyses supporting the CSR after all subjects have completed the post-treatment observational follow-up or have discontinued early, the 52-week database will be locked after medical/scientific review has been performed, protocol violations/deviations have been identified, and the data have been declared final and complete.

4.4. Sample Size Determination

For the primary endpoint, i.e., the response rate (π) defined as the proportion of subjects achieving a $\geq$ 4-point reduction from baseline in DLQI at Week 16, the superiority of Apremilast 30 mg BID versus placebo will be tested. The hypotheses on superiority are defined as:

H_0: $\pi_{APR} - \pi_{PBO} = 0$

versus

H_1: $\pi_{APR} - \pi_{PBO} > 0$

Using an exploratory analysis on a subset of subjects meeting the following criteria: a) ScPGA $\geq$ 3 or b) NAPSI $\geq$ 1 or c) PPPGA $\geq$ 3 at baseline and DLQI $\geq$ 10 at baseline in the PSOR-008 and PSOR-009 Phase 3 studies, it was estimated that the proportion of subjects who achieved a $\geq$ 4-point reduction from baseline in DLQI was 0.50 (97 responders out of 193 subjects) and 0.83 (337 responders out of 406 subjects) for placebo and Apremilast 30 mg BID, respectively.

Assuming a placebo DLQI responder proportion of 0.50 at Week 16, a minimum total sample size of 210 subjects (140 allocated to Apremilast 30 mg and 70 allocated to placebo) is needed to detect a 0.20 difference in the DLQI responder rate between Apremilast and placebo with at least 0.807 power using a two-sided test at the 0.05 level of significance. This sample size calculation is based on an unpooled variance, and determined using the commercial software EaST, Version 6.3. Allowing for an 24% discontinuation rate prior to Week 16, the sample size of 276 subjects should be sufficient.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- The statistical test on the primary endpoint is at a 2-sided 0.05 significance level, any p-values reported for other endpoints are considered as summary statistics;
- P-values are rounded to 4 decimal places. P-values that round to 0.0000 are presented as '<0.0001' and p-values that round to 1.000 are presented as '>0.9999';
- Confidence intervals (CIs) are presented as 2-sided 95% CIs;
- Summary statistics consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, Standard Deviation (STDEV), minimum, and maximum for continuous variables;
- All mean and median values are formatted to one more decimal place than the measured value, standard deviation values are formatted to two more decimal places than the measured value, minimum and maximum values are presented to the same number of decimal places as the measured value, and the 95% CI are formatted to two more decimal places than the measured value;
- All percentages are rounded to one decimal place. The number and percentage of responses are presented in the form XX (XX.X), where the percentage is in the parentheses, and the 95% CI are presented to two decimal places. Exact 100% that is not rounded from a percent >99.50% is presented in the format xx (100);
- All listings are sorted for presentation in order of treatment arm, study center, subject, and date of procedure or event;
- All analysis and summary tables have the analysis population sample size (i.e., number of subjects);
- All laboratory data will be reported using standard international (SI) units.

5.2. Analysis Phases or Periods

Data summary and analysis will be provided for the following analysis phases/periods.

5.2.1. Placebo-controlled Phase – Weeks 0 to16

The Placebo-controlled phase is per protocol specification. All the efficacy and safety analyses for the primary time point at Week 16 are based on placebo-controlled phase, including data collected from Day 1 for the core baseline (defined in Section 5.4). The end date is defined as following:

(1) One day prior to the first dose date of Apremilast dispensed at Week 16/Visit 5 for patients who are entering the Apremilast Extension Phase;
(2) the day of the discontinuation visit if the subject discontinued prior to or at Week 16/Visit 5;

(3) the last known study day if the subject is lost to follow-up prior to Week 16/Visit 5.

All by-treatment tabulations based on the data from Placebo-controlled Phase are grouped by Apremilast 30 mg BID vs. placebo.

5.2.2. Apremilast Extension Phase – Weeks 16 to 52

The Apremilast Extension Phase is per protocol specification. Quality of life and efficacy endpoints, patient disposition, protocol deviation/violation, and study treatment compliance are summarized based on data from this study phase.

The Apremilast Extension Phase starts on the day that the first dose of treatment is dispensed for the phase at Week 16/visit 5 and the end date is defined as the following:

(1) the day of Week 52/Visit 9 for patients who complete the study on treatment;

(2) the day of the discontinuation visit if the subject discontinued prior to or at Week 52/Visit 9;

(3) the last known study day if the subject is lost to follow-up prior to Week 52/Visit 9.

All by-treatment tabulations are grouped by Apremilast 30 mg BID arm vs. placebo arm, i.e., the original treatment during the placebo-controlled phase.

5.2.3. Apremilast Exposure Period

In addition to the above defined phases, Apremilast Exposure Period will be used for safety analyses. This period starts on the date of either:

(1) the first dose of IP following randomization (Week 0/Visit 2) for subjects who are treated with Apremilast 30 mg BID first;

(2) the first dose of IP from the IP dispensed at Week16/Visit 5 for subjects who were originally treated with placebo and are treated with Apremilast 30 mg BID at Week 16.

This period stops on either:

(1) data cut-off date;

(2) the day of the treatment discontinuation if the subject discontinued prior to or at Week 52/Visit 9;

(3) the last known study day if the subject is lost to follow-up prior to Week 52/Visit 9;

(4) Week 52/Visit 9 visit date.

Study treatment duration will also be summarized for the Apremilast Exposure Period. The outputs based on the Apremilast exposure period only have one Apremilast 30 mg BID arm.

5.2.4. Follow-up Phase

For all subjects who complete the study or discontinue the study early, the Four-week Observational Follow-up Phase starts at the completion or discontinuation visit and stops at the follow-up visit or the last assessment date.

Concomitant medications are summarized based on the follow-up phase including data collected after the last dose of the study treatment up to the 28 days post-treatment for subjects who entered the observational follow-up phase.

5.3. Analysis Populations

5.3.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all subjects who are randomized. Subjects will be included in the treatment arm to which they are randomized.

This is the primary population for the primary endpoint and all other quality of life and efficacy analyses. Baseline summaries and treatment compliance summaries are also based on the ITT population.

5.3.2. Per-Protocol Population

The per-protocol (PP) population includes all subjects who are in the ITT population, who receive at least one dose of IP, have both baseline and at least one post-treatment DLQI evaluation, and have no major protocol deviations which may affect analyses in the Placebo-controlled Phase. The PP population is only used to supplement the primary endpoint ITT analysis.

5.3.3. Safety Population

The safety population includes all subjects who are randomized and receive at least one dose of study drug. If a subject receives study drug other than the subject's randomized treatment assignment, then the subject is assigned to the treatment arm reflecting the treatment that the subject actually received during the study. All safety endpoints, study treatment duration, and concomitant medication summaries for the placebo-controlled phases are based on the safety population.

5.3.4. Apremilast Exposure Population

The Apremilast exposure population consists of only those subjects who receive at least one dose of Apremilast treatment, i.e., all subjects in the Apremilast 30 mg BID arm from the safety population and the subset of subjects in the placebo arm from the safety set who also enter the Apremilast Extension Phase with at least one treatment of Apremilast. The Apremilast Exposure population are only used for the safety endpoints.

5.4. Definition of baseline

Core baseline (Week 0) is used for all efficacy analyses, safety analyses for the placebo-controlled period, and summary of baseline disease characteristics.

For efficacy analysis and summary of baseline disease characteristics data, baseline is defined as the last value measured prior to or at the randomization visit.

For safety summaries, baseline is defined as the last value measured on or before the day of the first dose of double-blind treatment.

Apremilast treatment baseline is used for the summaries of safety analyses for the Apremilast Exposure Period. It is defined as the last value measured on or before the day of the first Apremilast dose.

5.5. Time Points

Time points in all analyses are based on the visits/study weeks using the following visit mapping algorithm, which may or may not be the same as the visits/study weeks as recorded in the database.

Post baseline time points in all analyses will be captured based on analysis visit window (range of study days) around the target day for each analysis visit, based on the actual day of evaluation relative to a reference date. Appropriate dates will be used to calculate the study day, e.g., date of measurement or date of specimen collection will first be used, and then the date of visits/study weeks as recorded in the database will be used. If there are multiple measurements within a time point based on the study day, then the non-missing value from the closest measurement to the planned study day will be used for that visit. If the value at a scheduled visit is missing and there is no value available within the time window based on the study day, the value at the study week will be missing.

Table 2: Table for Visit Mapping for by Time Point Analysis

Analysis Visit	Target Day	Visit Window
Baseline	1	≤ 1
Placebo-controlled Phase (for all endpoints)		
Week 2	15	2 – 21
Week 4	29	22 – 70
Week 16	113	71 – End of Placebo-controlled Phase
Apremilast Extension Phase (for efficacy endpoints)		
Week 20	141	Start of Apremilast Extension Phase – 182
Week 32	225	183 – 294
Week 52	365	295 – End of Apremilast Extension Phase
Apremilast Extension Phase (for safety endpoints)		

Week 20	141	Start of Apremilast Extension Phase – 182
Week 32	225	183 – 266
Week 44	309	267 –337
Week 52	365	338 – End of Apremilast Extension Phase

Note: Target day and visit window are relative to the date of Visit 2/Week 0 (Day 1) for randomization. Definitions for baseline and start or end of the phases are specified in Section 5.25.2 and 5.4 for both efficacy and safety analysis.

Time points in the analyses or summaries of efficacy data over time include the scheduled study weeks per protocol, the end of a study phase, and the observational follow-up visit. Appropriate dates (e.g., date of measurement or date of specimen collection) will first be used to ensure only data (including data from scheduled, unscheduled, container visits, discontinuation, and observational follow-up visits) measured or collected within the specific analysis phase (as defined in Section 5.2) being analyzed or summarized are included, and then the visits/study weeks as recorded in the database will be used to assign one value (possibly missing) to each time point at the subject level. It is possible that multiple assessment values will fall into the same visit window. The following rule may be used to select the unique value for that analysis visit:

1. Among all assessments in the same visit window for the analysis visit, select the value with the assessment date closest to the target day of the analysis visit;
2. If the relative days from 2 assessments are equally close to, but on different sides of the target day, then the latter assessment will be used for that analysis visit;
3. If multiple assessments are available on the same relative day, then the highest value of these assessments will be used for that relative day.

The time points for summaries of safety data (laboratory parameters, vital signs and weight) are based on study week/visit for the placebo-controlled phase. For the Apremilast Exposure Period, the scheduled study weeks for placebo subjects who are treated with Apremilast 30 mg BID at Week 16 will be mapped to reflect the study weeks relative to the first dose of Apremilast (see table below).

Table 3: Adjustment and Mapping of Study Weeks for Placebo Subjects who are Treated with Apremilast 30 mg BID after Week 16 in Summary of Safety Data over Time

Original Visit	**Re-Mapped Visit for subjects initially randomized to placebo**
Week 16	Baseline
Week 20	Week 4
Week 32	Week 16
Week 44	Week 28
Week 52	Week 36

6. SUBJECT DISPOSITION

The number and percentage of screened subjects randomized (as recorded in the IVRS database) and not randomized will be summarized. The failed inclusion/exclusion criteria of subjects who were screened and not randomized will be included in the summary. The percentages will be based on the number of subjects screened. For patients who were rescreened, the last screening status will be considered for the summary.

Randomized subjects included in the ITT population, PP population, safety population, and Apremilast Exposure population will be summarized by treatment arm.

The numbers and percentages of randomized subjects who entered, completed, and discontinued from the following protocol phases will also be summarized by treatment arm. All the percentages will be based on the number of subjects randomized.

- Placebo-controlled Phase – Weeks 0 to16: The summary on the numbers and percentages of the following subjects will be provided.
    - Subjects who completed the phase and entered the Apremilast Extension Phase (Weeks 16 to 52)
    - Subjects who completed the phase and did not enter the Apremilast Extension Phase (Weeks 16 to 52) as well as the reason
    - Subjects who discontinued early from the phase as well as the reason
- Apremilast Extension Phase – Weeks 16 to 52: The number and percentage of subjects who entered the phase, had at least one dose of Apremilast in the phase, completed the phase, and discontinued early will be provided. The primary reason for discontinuation from the treatment in this phase will also be summarized.
- Observational Follow-up Phase (4 weeks): Summary will be provided on the number and percentage of subjects who entered the phase, if not, the primary reason for not entering the phase, subjects who completed the phase, and if discontinued, the primary reason for not fulfilling follow-up visit 4 weeks after the completion or discontinuation of the study treatment.

The number and percentage of subjects randomized by study site and treatment arm will be tabulated. The percentages will be calculated based on the number of randomized subjects.

Listings will be provided for randomized subjects in analysis populations, for the reason of treatment or phase discontinuation, and for subjects excluded from the PP population along with the reason.

7. PROTOCOL DEVIATIONS

The protocol deviations and important protocol deviations were identified and assessed by clinical research physician or designee following company standard operational procedure. The protocol deviations and important protocol deviations will be summarized by treatment arm for the ITT population for the Placebo-controlled Phase and for the Apremilast Extension Phase.

A by-subject listing of subjects with protocol deviations and important protocol deviations in the ITT population will be provided. The important protocol deviations that lead to the exclusion of the subjects from the PP population will be flagged.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics, baseline characteristics, medical history, and Prior Psoriasis Medications will be summarized for the ITT population by treatment and overall. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

Summary statistics will be provided for the following continuous variables:

- Age (years)
- Weight (kg)
- Height (cm)
- Baseline Body Mass Index (BMI; kg/m^2), BMI will be calculated as: BMI (kg/m^2) = Weight (kg)/ Height (m^2)
- Waist circumference (cm)

Number and percentage will be provided for the following categorical variables:

- Age category (< 65, ≥ 65 years)
- Sex (Male, Female)
- Race
- Country
- Alcohol intake (Current use, Former use, or Never use)
- Tobacco use (Never Smoked, Past Smoker, Current Smoker)
- Baseline BMI category (<18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2)

8.2. Baseline Disease Characteristics

Baseline clinical characteristics will be summarized descriptively by treatment arm, which will include the following:

- Duration of plaque psoriasis (from date of diagnosis to the date of informed consent; year, presented one digit after the decimal point)
- Duration of plaque psoriasis categories (< 10, 10 to < 20, ≥ 20 years)
- The primary manifestations for stratifications: scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, and psoriasis in visible locations
- Baseline DLQI total score
- Baseline DLQI score categories (>10 to 20, >20)

- Baseline sPGA score of visible locations: 0 (clear), 1 (almost clear), 2 (mild), 3 (Moderate), 4 (Severe)
- Baseline ScPGA score: 0 (clear), 1 (almost clear), 2 (mild), 3 (Moderate), 4 (Severe)
- Number of affected nails: 0, 1, ≥2
- Baseline NAPSI score for the target nail
- Baseline sPGA-G score: 0 (clear), 1 (almost clear), 2 (mild), 3 (Moderate), 4 (Severe)
- Baseline PPPGA score: 0 (clear), 1 (almost clear), 2 (mild), 3 (Moderate), 4 (Severe)
- Baseline pruritus NRS score
- Baseline skin discomfort/Pain VAS score
- Baseline PASI score
- Baseline PASI score categories (3 to 5, >5 to 10)
- Baseline BSA (%)
- Baseline BSA (%) category (≤3, >3 to 5, >5 to 10, >10)
- Baseline EQ-5D vas and EQ-5D index value
- Baseline WPAI: PSO: percentage of work missed due to Psoriasis and overall work impairment for those who were currently employed; percentage of work impairment and percentage of daily activity impairment due to Psoriasis among all subjects
- Baseline PNQ: the importance of each of the 25 treatment goals will be summarized with count (%) by missing, does not apply to me, not at all, somewhat, moderately, quite and very.

8.3. Medical History

A summary of relevant medical history and concomitant diseases will be presented by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Affairs (MedDRA) version 23.1 or higher, using frequency distributions (counts and percentages).

8.4. Prior Psoriasis Therapy

Prior Psoriasis therapy are summarized descriptively by treatment arm for the following:

- Number of prior conventional systemic therapies
- Number of failed prior conventional systemic therapies for subjects who had prior conventional systemic therapies
- Number of prior systemic therapies
- Number of failed prior systemic therapies for subjects who had prior systemic therapies

- Number of prior biologic therapies
- Number of failed prior biologic therapies for subjects who had prior biologic therapies
- Number of prior topical therapies
- Number of failed prior topical therapies for subjects who had prior topical therapies
- Number of prior photo therapies
- Number of failed prior photo therapies for subjects who had prior photo therapies

8.5. Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using the MedDRA Version 22.1 or higher.

8.5.1. Prior Procedures

Prior procedures are defined as those started before the start of the study treatment (whether or not ended before the start of the study treatment) at the time of randomization.

A frequency tabulation of the number of subjects with each previous procedure will be given for the ITT population by treatment arm, system organ class (SOC), and preferred term (PT).

8.5.2. Concomitant Procedures

Concomitant procedures that started during each of the following three study phase/period are summarized by SOC and PT: (1) Placebo-controlled Phase (Weeks 0 to16) using safety population by treatment, (2) Apremilast Exposure Period using Apremilast Exposure Population and (3) Observational Follow-up Phase for subjects who entered this phase.

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version DDE B3 March 2019 or higher) is used to group the prior and concomitant medications into the WHO therapeutic drug class (ATC2 level) and generic drug name.

8.5.3. Prior Medications

Only prior medications that are not discontinued at or before the time of consent are collected. Prior medications are defined as medications that were started before the start of the study treatment at the time of randomization and ended before the start of the study treatment. Medications initiated prior to the start of study treatment and continued after the start of study treatment are counted as both prior and concomitant medications.

The number (%) of subjects receiving at least one prior medication are summarized for the ITT population by treatment arm, ATC2 level, and standardized medication name.

Note that the prior psoriasis medications are summarized along with other baseline characteristics and not included in the prior medication summary.

8.5.4. Concomitant Medications

Concomitant mediations are defined as non-study medications started during a study phase/period of interest or started before the study phase/period of interest but ended or remain ongoing during this study phase/period.

The number (%) of subjects receiving at least one concomitant medication, the number (%) of subjects receiving at least one medication within a relevant category, and each concomitant medication are summarized for (1) Placebo-controlled Phase (Weeks 0 to 16) using safety population by treatment, (2) Apremilast Exposure Period using Apremilast Exposure Population, and (3) Observational Follow-up Phase for subjects who entered this phase.

8.6. Study Treatment Duration

Study treatment duration in weeks is calculated as (the date of the last dose of study treatment – the date of the first dose of study treatment + 1) / 7 and rounded to one decimal place for each subject for a given analysis phase/period.

Study treatment duration will be summarized based on the safety population for the Placebo-Controlled Phase (Weeks 0 to 16) by treatment and based on the Apremilast Exposure Population for the Apremilast Exposure period.

Summary statistics for treatment duration as well as a frequency summary of treatment duration categories specified in Table 4 will be provided.

Table 4 Definitions of time intervals used to summarize exposure to study Medication

Duration category	Duration in terms of days
Placebo-Controlled Phase	
<4 weeks	<28 days
>= 4 to < 8 weeks	>= 28 to < 56 days
>= 8 to < 12 weeks	>= 56 to < 84 days
>= 12 to < 16 weeks	>= 84 to < 112 days
>= 16 weeks	>= 112 days
Apremilast Exposure period	
>= 4 weeks	>=28 days
>= 8 weeks	>=56 days
>= 12 weeks	>=84 days
>= 16 weeks	>=112 days
>= 20 weeks	>=140 days
>= 24 weeks	>=168 days
>= 28 weeks	>=196 days
>= 32 weeks	>=224 days
>= 36 weeks	>=252 days
>= 40 weeks	>=280 days
>= 44 weeks	>=308 days
>= 48 weeks	>=336 days
>= 52 weeks	>=364 days

The treatment duration is from the first non-zero dose and the last non-zero dose of the study treatment recorded on the study drug exposure form for the corresponding study phase/period.

A subject data listing of study drug records including the reasons for missed dose will be provided.

8.7. Treatment Compliance

Summaries on the compliance rate are provided based on the ITT population for the Placebo-Controlled Phase (Weeks 0 to 16) and the Apremilast Extension Phase (Weeks 16-52) for subjects who entered the Apremilast Extension Phase by treatment.

The treatment compliance (in %) for each subject will be computed as 100 times the total number of tablets taken (the total number of tablets dispensed minus the total number of tablets returned) over the analysis phase of interest divided by the intended total number of tablets that should have been taken over the same phase. The algorithm on how the intended total number of tablets is calculated is provided in Appendix 15.3.

Of note, compliance rate will not be calculated for subjects (if exist) who have only the dispense record at Week 0/Visit 2 and no other drug accountability records.

Both the summary statistics for compliance rate (%) and a frequency summary with the following categories: <75%, 75% to 120%, and >120% are provided. A subject data listing of drug accountability records is also provided.

9. EFFICACY ANALYSIS

9.1. General Approaches to Efficacy Analysis

All efficacy evaluations will be conducted using the ITT population. Supplemental analysis of the primary efficacy endpoint using the PP population will be conducted.

The summary and analyses of the primary and secondary endpoints evaluated at or prior to Week 16 will be performed by treatment (placebo vs. apremilast 30 mg BID). Statistical comparisons will be made between apremilast 30 mg BID and placebo; the null hypothesis is that the effects of the two treatments (i.e., placebo vs. apremilast 30 mg BID) have no difference.

Descriptive statistics (n, mean, stdev, median, Q1, Q3, min, max) will be presented for appropriate endpoints at specified time points. Specifically, for continuous variables, descriptive statistics for baseline and change (or percentage change) from baseline will be provided. Categorical variables will be summarized with frequency tabulations at baseline or by time point; shift tables will be provided when appropriate.

For the primary and the secondary efficacy endpoints during the Double-blind Placebo-controlled Phase, the following analysis will be performed:

- For binary endpoints, missing data from the original continuous-like score will be handled by multiple imputation (MI) as the primary approach. The response variable will then be derived based on the continuous score. Statistical outputs from each of the imputed complete data sets will be combined in making statistical inferences. For the combined inference, the response rates for each treatment arm and differences for treatment comparison were the averages from the 25 imputed data sets. The response rate and its 95% confidence interval (CI) will be calculated by treatment. The difference of the response rate (Apremilast 30 mg BID - placebo) and its 95% CI as well as the p-value will be produced using the Cochran-Mantel-Haenszel (CMH) test and adjusting for the stratification factor at randomization (i.e., the manifestations of scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, or psoriasis in visible locations). SAS PROC FREQ with the COMMONRISKDIFF (TEST=MH) option will be used for the analysis.
- For continuous endpoints, the primary approach for handling missing data will be the multiple imputation (MI) method. Data will be analyzed using the analysis of covariance (ANCOVA) model with baseline values, treatment group and stratification factors (i.e., the manifestations of scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, or psoriasis in visible locations) as independent variables. SAS Proc Mixed will be used for the analysis. The least square mean (LS mean) with 95% CI for each treatment and difference of LS mean (Apremilast 30 mg BID - placebo) with 95% CI as well as the p-value will be provided.

Efficacy results will be considered statistically significant after consideration of the strategy for controlling the Type I error rate that is described in Section **Error! Reference source not found.**. A ll statistical tests will be two-sided and be conducted at the 0.05 significance level, and p-values will be reported. For the efficacy endpoints evaluated after Week 16, only the treatment effect

estimates and the corresponding 95% confidence intervals (CIs) within each treatment arm will be provided to show the long-term treatment profile. No between group comparison will be conducted. Time plots on response rate or mean change (percent change) from baseline by treatment over the Placebo-controlled Phase and the Apremilast Extension Phase will be provided to show the maintenance of the treatment effect over time.

Data listings for quality of life assessments and efficacy assessments over the Placebo-controlled Phase and the Apremilast Extension Phase will be provided. An analysis phase flag will be included in each listing to indicate the phase that a record belongs to.

9.2. Multiplicity

The primary and some secondary efficacy endpoints will be hierarchically ranked for testing in order to control the overall type I error rate in claiming statistical significance at the 2-sided 0.05 significance level. Specifically, for the primary efficacy endpoint (DLQI response at Week 16), if the 2-sided p-value from the comparison between Apremilast 30 mg BID and placebo is below 0.05, the outcome will be considered statistically significant and Apremilast 30 mg BID will be declared effective. For any secondary endpoint, statistical significance will be claimed only if its 2-sided p-value is below 0.05 and tests for the primary endpoint and all previous secondary endpoints are significant at the 2-sided 0.05 level. The proposed test sequence for the primary and some secondary efficacy endpoints is listed as the following:

- Achieving DLQI response at Week 16 (defined as $\geq$ 4-point reduction in DLQI from baseline at Week 16) from baseline in DLQI at Week 16
- Change from baseline in DLQI at Week 16
- Percent change in Body Surface Area (BSA) affected by psoriasis at Week 16
- Change from baseline in Pruritus Numeric Rating Scale (NRS) score at Week 16
- Change from baseline in skin discomfort/pain Visual Analog Scale (VAS) at Week 16
- Achieving Psoriasis Area Severity Index (PASI) < 3 at Week 16
- Achieving Patient Benefit Index (PBI) global score of $\geq$ 1 at Week 16
- Percent change from baseline in European Quality of Life 5-Dimension (EQ-5D) score at Week 16
- Change in Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO) domain scores at Week 16

9.3. Analysis of Primary Efficacy Endpoint

The primary endpoint is subjects achieving DLQI response at Week 16 (defined as $\geq$ 4-point reduction in DLQI from baseline at Week 16). The primary endpoint will be analyzed using the ITT population. A supplemental analysis will be performed using the PP population.

The treatment difference in proportions of DLQI response between Apremilast 30 mg BID and placebo will be compared using CMH test adjusted for the stratification factor at randomization

(i.e., the 5 difficult to treat manifestation types). This form of the CMH test will use the sample sizes in each of the strata as weights when estimating the adjusted difference in the treatment proportions, constructing 95% Wald confidence intervals for the difference, and conducting a statistical test of no difference between the treatment proportions (i.e., H_0: $\pi_{APR} - \pi_{PBO} = 0$ as the null hypothesis). The difference of the response rate (Apremilast 30 mg BID - placebo) and its 95% CI as well as the p-value will be produced using the Cochran-Mantel-Haenszel (CMH) test and adjusting for the stratification factor at randomization (i.e., the manifestations of scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, or psoriasis in visible locations). SAS PROC FREQ with the COMMONRISKDIFF (TEST=MH) option will be used for the analysis.

All reasonable attempts will be made to prevent missing data from occurring in the study. However, in the case of missing data at Week 16, a multiple imputation (MI) method (SAS Institute Inc. 2008) will be incorporated as the primary analysis. such that unbiased estimation and valid statistical inferences (i.e., confidence intervals and hypothesis testing) can be made.

The SAS procedure MI will be used to impute missing DLQI scores at the scheduled assessments in the Placebo-controlled Phase (Weeks 0 to16) to create M=25 complete data sets. The missing data patterns will be checked by treatment and stratification factor at the core baseline (Week 0), Week 2, Week 4, and Week 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. The minimum and the maximum values for imputation will be 0 and 30, which correspond to the lowest and the highest DLQI scores. The seed will be set to 804529, the imputed values will be rounded to integers and a single chain will be used to produce imputations. In case there are convergence issues, the imputation will be done by treatment only. If the convergence issue remains, then the imputation will be done on data pooled from both treatment arms.

In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 25 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with seed 447159. The missing values at each visit will be imputed based on treatment, stratification factor, and DLQI scores at the core baseline and previous visits. In presence of convergence issue, a simplified regression model without stratification factor will be used. The number of closest observations to be used in the selection will be K=5.

After the completion of imputation made on the continuous-like scale of the total DLQI score, the primary endpoint will then be derived by dichotomizing the DLQI score prior to performing the CMH analysis described above. The same CMH method will be used to analyse the 25 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

In addition to the primary analysis using MI method and the supplemental analysis in PP population, the following supportive analyses using CMH method for the primary endpoint will be performed for: (1) ITT population treating missing values using the last observation carried

forward (LOCF) method, (2) ITT population treating missing values using the non-responder imputation (NRI) method.

In order to assess the impact of Covid-19 on the DLQI data collection, a sensitivity analysis will be conducted by excluding the data collected via paper version of the DLQI questionnaire.

Similar analysis planned for Week 16 will be repeated for DLQI response at Week 2 and Week 4.

9.4. Analyses of Secondary Efficacy Endpoints

The analyses on secondary efficacy endpoints are discussed according to the analysis phase in the following two sections.

9.4.1. Secondary Efficacy Endpoints in the Placebo-controlled Phase

All analyses will be conducted using ITT population including data from the Placebo-controlled Phase (Week 0 to Week 16). Table 5 is the summary on how the secondary efficacy endpoints at Week 16 will be analyzed.

Table 5 Analysis on the Secondary Efficacy Endpoints at Week 16

Summary Measure of Endpoint	Primary Analysis	Supportive Analysis
Mean change from baseline in DLQI at Week 16	ANCOVA model adjusted by baseline DLQI score, treatment, stratification factor on data with MI	ANCOVA model adjusted by baseline DLQI score, treatment, stratification factor on data with LOCF
Mean percent change in Body Surface Area (BSA) affected by psoriasis at Week 16	ANCOVA model adjusted by BSA score, treatment, stratification factor on data with MI	ANCOVA model adjusted by BSA score, treatment, stratification factor on data with LOCF
Mean change from baseline in Pruritus Numeric Rating Scale (NRS) score at Week 16	ANCOVA model adjusted by baseline NRS score, treatment, stratification factor on data with MI	ANCOVA model adjusted by baseline NRS score, treatment, stratification factor on data with LOCF
Mean change from baseline in skin discomfort/pain Visual Analog Scale (VAS) at Week 16	ANCOVA model adjusted by baseline VAS score, treatment, stratification factor on data with MI	ANCOVA model adjusted by baseline VAS score, treatment, stratification factor on data with LOCF
Proportion of subjects who achieve Psoriasis Area Severity Index (PASI) < 3 at Week 16	CMH test adjusting for the stratification factor on data with MI	CMH test adjusting for the stratification factor on data with LOCF and data with NRI
Proportion of subjects who achieve Patient Benefit Index (PBI) global score of ≥ 1 at Week 16	CMH test adjusting for the stratification factor on data with MI	CMH test adjusting for the stratification factor on data with LOCF and data with NRI
Mean percent change from baseline in European Quality of	ANCOVA model adjusted by baseline EQ-5D score*, treatment,	ANCOVA model adjusted by baseline EQ-5D score*, treatment,

Life 5-Dimension (EQ-5D) score* at Week 16	stratification factor on data collected on scheduled Week 16 visit	stratification factor on end of phase assessment
Mean change in Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO) domain scores** at Week 16	ANCOVA model adjusted by baseline Psoriasis WPAI score**, treatment, stratification factor on data collected on scheduled Week 16 visit	ANCOVA model adjusted by baseline Psoriasis WPAI score**, treatment, stratification factor on end of phase assessment
*two variables will be evaluated individually: EQ-5D VAS and EQ-5D index value **four variables will be evaluated individually: percentage work missed, work impairment, overall work impairment, and activity impairment		

For each continuous-like efficacy assessments, the SAS procedure MI will be used to impute missing values for each scheduled visit in the Placebo-controlled Phase (Weeks 0 to16). There are exceptions for the EQ-5D assessment and WPAI: PSO assessment, which are only assessed at Week 16/discontinuation visit in the Placebo-controlled Phase. For these two endpoints, no missing data imputation will be conducted and the analyses will be conducted on assessments collected at the scheduled Week 16 visit as well as on assessments collected at end of phase (section 5.5).

For MI, the missing data patterns will be checked by treatment and stratification factor at Baseline (Week 0), and Weeks 2 (if applicable), 4, and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process. In case of convergence issue, same strategy as for the primary endpoint will be followed.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing data by baseline value, treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. The minimum and the maximum values for imputation will set depending on the rage of the corresponding score of interest. The seed will be set to 804529, the imputed values will be rounded to integers and a single chain will be used to produce imputations. This step will be skipped if the data missing pattern is monotone.

In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 25 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with seed 447159. The missing values at each visit will be imputed based on treatment, stratification factor, and the score of interest at baseline and previous visits. The number of closest observations to be used in the selection will be K=5 for DLQI, skin discomfort/pain VAS, BSA, as well as PASI and K=2 for PBI.

The binary endpoints at Week 16 will be analysed similarly as the primary endpoint. Missing data from the original continuous-like score will be handled by multiple imputation (MI) as the primary approach. The response variable will then be derived based on the continuous score. Statistical outputs from each of the imputed complete data sets will be combined in making statistical inferences. For the combined inference, the response rates for each treatment arm and differences

for treatment comparison were the averages from the 25 imputed data sets. The difference of the response rate (Apremilast 30 mg BID - placebo) and its 95% CI as well as the p-value will be produced using the Cochran-Mantel-Haenszel (CMH) test and adjusting for the stratification factor at randomization. SAS PROC FREQ with the COMMONRISKDIFF (TEST=MH) option will be used for the analysis. Same analyses will also be conducted for other scheduled assessment visits (e.g., at Week 2 and Week 4) during the Placebo-controlled Phase. In addition to the MI method, supportive analyses using CMH method for the binary endpoints will be performed on data with LOCF and data with NRI. Same analyses will be repeated for assessments scheduled at time points before Week16.

For continuous endpoints, missing data will be imputed by MI as the primary approach. Change (or percent change) from baseline in each score at Week 16 will be analyzed using the same analysis of covariance (ANCOVA) model to analyze the 25 complete datasets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences. The ANCOVA model will use the change (or percent change) from baseline as the dependent variable and will include treatment group and stratification factor as independent variables as well as the baseline value as a covariate variable. Within-group least-squares (LS) mean changes from baseline at Week 16, the associated standard errors (SEs) and 2-sided 95% CIs, treatment differences in LS mean changes from baseline, and the associated 2-sided 95% CIs and p-values, will be derived from the ANCOVA model based on each of the 25 complete datasets. Same analyses will also be conducted for other scheduled assessment visits (i.e., at Week 2 and Week 4) during the Placebo-controlled Phase. In addition to the MI method, supportive analyses using ANCOVA model for the continuous endpoints will be performed on data with LOCF. The same analyses will be repeated for assessments scheduled at time points before Week16. Summary statistics will also be provided by treatment and time point based on Data as Observed (DAO) for each continuous variable.

9.4.2. Secondary Efficacy Endpoints in the Apremilast Extension Phase

The analyses will be conducted using the ITT population for subjects who entered the Apremilast Extension Phase. For binary endpoints, frequency tables will be provided by time point based on data with NRI. For continuous endpoints, summary statistics will be provided by time point (including end of phase assessment) on DAO.

9.5. Subgroup Analysis

The consistency of the treatment effect on DLQI response at Week 16 will be assessed across the following subgroups:

- The randomization stratum based on the primary manifestation of plaque psoriasis: scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, and psoriasis in visible locations
- Sex (Male, Female)
- Race (White, Others)

- Age category (< 65, ≥ 65 years)
- Baseline BMI category (< 25, 25 to < 30, ≥ 30 kg/m^2)
- Prior conventional systemic therapies (Yes/No)
- Prior biologic therapies (Yes/No)

Analysis will be based on ITT population and missing values will be imputed using MI method. The number (%) of subjects with improvement (≥ 4-point reduction) in DLQI and the between group difference will be summarized for each subgroup category. The adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata (i.e., the 5 difficult to treat manifestation types) with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided within each subgroup. For subgroups based on primary manifestation, the adjusted estimates mentioned above are not applicable; unadjusted treatment differences in proportions and the associated 2-sided 95% CI using a normal approximation will be provided. Similarly, for other classification variables, if no subject falls into a stratum of the primary manifestation strata in a treatment group, unadjusted treatment differences in proportions and the associated 2-sided 95% CI using a normal approximation will be provided. Forest plot on rate difference and 95% CI by subgroups will be provided.

9.6. Analyses of Exploratory Efficacy Endpoints

For exploratory efficacy endpoints, descriptive summary statistics or proportion of subjects achieving pre-specified criteria will be summarized by treatment arm by time points.

[redacted]

9.6.2. Manifestation specific clinical endpoints at Week 16, Week 32, and Week 52

The following is the list of manifestation specific endpoints according to the pre-specified treatment improvement criteria.

- Achieving Static Physician Global Assessment (sPGA) score of 0 or 1 (among subjects randomized to the strata with moderate to severe psoriasis in visible areas, defined as sPGA ≥ 3 at baseline, which include the dorsal hand, face, neck, or hairline) at Weeks 16, 32, 52
- Achieving Scalp Physician Global Assessment (ScPGA) score of 0 or 1 (among subjects randomized to the strata with moderate to severe scalp psoriasis, ScPGA ≥ 3 at baseline) at Weeks 16, 32, 52

- Achieving Nail Psoriasis Severity Index (NAPSI) score of 0 in the target fingernail (among subjects randomized to the strata with presence of nail psoriasis, defined as onycholysis and onychodystrophy in at least 2 fingernails at baseline) at Weeks 16, 32, 52
- Achieving Static Physician Global Assessment-Genitalia (sPGA-G) score of 0 or 1 (among subjects randomized to the strata with moderate to severe genital psoriasis, sPGA-G $\geq$ 3 at baseline) at Weeks 16, 32, 52
- Achieving Palmoplantar Psoriasis Physician Global Assessment (PPPGA) score of 0 or 1 (among subjects randomized to the strata with moderate to severe palmoplantar psoriasis, PPPGA $\geq$ 3 at baseline) at Weeks 16, 32, 52

The number and percentage of subjects with improvement among the subgroup of subjects demonstrating the corresponding manifestation at baseline by time point (including all visits with scheduled assessments and end of phase assessment) will be summarized based on data with NRI (including end of phase assessment). Shift tables for each of the manifestation assessment shift from baseline to post-baseline visits and end of phase assessment in all subjects will be provided based on DAO. The new onset on subject without such manifestations at baseline will also be assessed using shift tables.

Similar to the analysis mentioned above, all the manifestation specific endpoints will also be summarized based on subjects who met each specific condition regardless of whether they were stratified to the specific manifestation group.

9.7. Assessing Study Center Effect and Treatment-by-Center Interaction

This study is a multicenter study and has approximately 75 study sites from 6 Europe countries. Given the small sample size, no sufficient number of subjects will be available to allow a meaningful within-site analysis of treatment difference in proportions of DLQI response stratified by the manifestations at baseline. Thus the assessment on study center effect won't be conducted for this study.

10. SAFETY ANALYSIS

Safety will be assessed via descriptive statistics and point estimates on observed data.

All safety analyses described in this section will be performed for both the Placebo-controlled Phase and the Apremilast Exposure Period. The safety analyses for the Placebo-controlled Phase will be based on the safety population and presented by treatment arm (placebo, and Apremilast 30 mg BID). The safety analyses for the Apremilast Exposure Period will be based on the Apremilast Exposure Population and presented by Apremilast dose group (i.e., Apremilast 30 mg BID) irrespective of the start time of Apremilast exposure (at Week 0 or 16). In addition, selected summaries on AEs for the Observational Follow-up Phase will be listed.

For the analyses of AEs and laboratory marked abnormalities, both subject incidence and exposure-adjusted incidence rate (EAIR) per 100 subject-years for the Placebo-controlled Phase (Weeks 0 to16) and for the Apremilast Exposure Period will be provided. The point estimates of subject incidence and EAIR are distinguished as following:

- Subject incidence: is defined as the number of subjects with the specific event divided by the number of subjects included in the analysis (i.e., percentage [%] used in a frequency summary). Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator.
- Exposure-adjusted incidence rate (EAIR) per 100 subject-years: The EAIR per 100 subject-years is defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator. The exposure time for a subject without the specific event is the treatment duration (i.e., last dose date-first dose date+1), whereas the exposure time for a subject with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event. The total exposure time in years is calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365.25. The EAIR per 100 subject-years is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 subject-years of exposure to the IP.

Descriptive statistics will be provided for vital signs, weight, waist circumference, laboratory values (continuous measurements) by treatment and visit, including the end of phase/period visits. The baseline value, value at the time point, and change from baseline (also percent change from baseline if applicable) will be summarized for subjects who have values at baseline and at the time point.

Shift tables, that is, tables summarizing the baseline categories (normal, abnormal) versus the category at the end of the respective periods or versus the worst post-baseline category, include subjects who have values at baseline and at least one post-baseline value. Similarly, in frequency summaries of shifts from baseline at scheduled study weeks per protocol, only subjects who have values at baseline and at the corresponding time point will be included.

10.1. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study drug or the end of study phase/period date, whichever is earlier All AEs will be coded using the Medical Dictionary for Regulatory Affairs® (MedDRA) dictionary Version 22.1 or higher.

Unless otherwise specified, all TEAEs will be summarized by SOC and PT, with SOCs presented in the standard international order and PTs within SOCs will be presented in descending order of subject incidence of the 30mg BID and, if applicable, the placebo arms.

All TEAEs will be summarized by age category (< 65, ≥ 65 years), sex, and race.

10.1.1. Overall Summary of TEAEs

An overall summary of the following TEAE categories will be provided for the Placebo-controlled Phase (Weeks 0 to16) and for the Apremilast Exposure Period:

- Any TEAE
- Any drug-related TEAE
- Any severe TEAE
- Any serious TEAE
- Any serious drug-related TEAE
- Any TEAE leading to drug interruption
- Any TEAE leading to drug withdrawal
- Any TEAE leading to death

10.1.2. All TEAEs

The incidence and EAIR will be summarized for all TEAEs by SOC and PT as well as by PT only (in descending order of subject incidence) for the Placebo-controlled Phase (Weeks 0 to16) and the Apremilast Exposure Period.

The incidence and EAIR of TEAEs by SOC and PT will also be provided for each of the following:

- Common TEAE with subject incidence ≥ 5% (or another cut-off if justified) in any treatment group
- Drug-related TEAEs
- Serious TEAEs
- Serious drug-related TEAEs
- TEAEs leading to drug interruption
- TEAEs leading to drug withdrawal

Serious TEAEs and TEAEs leading to drug withdrawal will also be summarized by age category (< 65, ≥ 65 years), sex, and race.

Listings for all AEs, drug-related AEs, serious AEs, AEs leading to drug interruption and AEs leading to drug withdrawal during the Placebo-controlled Phase and the Apremilast Extension Phase will be presented with a flag indicating the Phase when the AE started.

A listing for non-treatment-emergent AEs will also be provided for safety population.

10.1.3. TEAEs by Maximum Severity

All TEAEs will be summarized with incidence and EAIR by SOC/PT as well as by maximum severity (mild, moderate, severe, and, if needed, missing). If subject reports multiple occurrences of a specific event within a specific analysis phase or period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all the occurrences, the subject will be counted only once in the "missing" category of severity.

10.1.4. Deaths

A subject data listing of all AEs leading to death will be provided.

10.2. Clinical Laboratory Evaluations

The endpoints for clinical laboratory evaluations include:

- Laboratory marked abnormalities (see section 15.4)
- Observed value and change from baseline over time in the following laboratory parameters
  - Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC Morphology, mean corpuscular volume (MCV), white blood cell (WBC) count (with differential), and platelet count.
  - Chemistry panel including sodium, potassium, calcium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH). A lipid panel will be included in the standard chemistry panel.
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal (low or high) in the above hematology and serum chemistry parameters. Normal range will be used to determine the categories of High, Low, and Normal for lab tests.

Summary statistics (N, Mean, STDEV, Median, Minimum, and Maximum) of observed values and changes from baseline in laboratory parameters will be provided over time by scheduled visit and

for the end of Phase/Period assessment. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points and to the worst post-baseline value during the given study phase/period in terms of normal/abnormal will be provided.

Laboratory marked abnormalities will be summarized; subject incidence and EAIR for each abnormality will be calculated based on subjects with a baseline value and at least one post-baseline value for criteria requiring baseline or subjects with at least one post-baseline value for criteria not requiring baseline. A subject data listing of laboratory marked abnormalities during the Placebo-controlled Phase and the Apremilast Exposure Phase will be presented.

Laboratory marked abnormalities will also be summarized for subjects with normal values at baseline and for subjects with abnormal values at baseline separately. For the purposes of these summaries, subjects with abnormal (normal) values at baseline are defined as those whose baseline value is low (not low) for criteria concerning low values and those whose baseline value is high (not high) for criteria concerning high values; both low and high are relative to the laboratory normal range.

A subject data listing of all laboratory data, including Pregnancy test, with abnormal flags and study phase/period flags will be provided.

10.3. Vital Sign, Weight, and Waist Circumference Measurements

The endpoints for vital sign parameters, weight, and waist circumference include:

- Observed value and change from baseline over time in vital sign parameters including temperature, pulse, and blood pressure
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal in pulse and blood pressure (normal ranges are defined as: 60-100 beats/minute for pulse, 90-140 mmHg for systolic blood pressure, and 60-90 mmHg for diastolic blood pressure)
- Observed value, change and percent change from baseline over time in weight and waist circumference

Summary statistics (N, Mean, STDEV, Median, Minimum, and Maximum) of observed values, changes from baseline, and percent change from baseline (applicable for weight and waist circumference) will be provided over time. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal will be provided for pulse and blood pressure.

Frequency summaries of percent change in weight from baseline to the end of the study phase/period will be provided by baseline BMI category (<18.5, 18.5 to < 25, 25 to < 30, ≥30 kg/m2) and by baseline weight category (< 70, ≥ 70 to < 85, ≥85 to < 100, and ≥100 kg). The categories of weight change (kg) and percent change (%) are < -20, ≥-20 to < -10, ≥-10 to < -5, ≥-5 to < 0, 0, > 0 to ≤ 5, > 5 to ≤ 10, > 10 to ≤ 20, and > 20.

A subject data listing of all vital sign parameters, weight, and waist circumference data with abnormal flags where applicable and study phase/period flags will be provided.

11. QUALITY OF LIFE ANALYSIS

The Quality of life endpoints, including DLQI (the primary endpoint), EQ-5D (secondary endpoint and WPSI:PSO (secondary endpoint) have been addressed in section 9.

12. INTERIM ANALYSIS

No interim analysis will be conducted. No DMC is planned for this study either.

For publication purpose, analyses on the data up to the primary timepoint of Week 16 are planned based on a Week 16 data transfer after all subjects have completed the Week 16 Visit (or discontinued from the study). However, unblinded data will only be made available to selected Sponsor and Contract Research Organization (CRO) team members involved with Week 16 data analysis and publication preparations. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the final study completion. After all subjects have completed the Observational Follow-up Phase following the Week 52/discontinuation visit in the Apremilast Extension Phase (Weeks 16 to 52), the final database will be locked and transferred for all analyses planned in this SAP, based on which, a Clinical Study Report will be generated.

13. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

In order to control the overall type I error rate, the multiplicity adjustment is made to the primary endpoint and some secondary endpoints by following the hierarchical rank for testing in Section 9.2. This is deviated from Section of 9.6.5 in the protocol, where no multiplicity adjustment is planned.

Per-protocol (PP) population includes all subjects who are in the ITT population, who receive at least one dose of IP, have both baseline and at least one post-treatment DLQI evaluation, and have no major protocol deviations which may affect analyses in the Placebo-controlled Phase. This definition is deviated from Section 5.3.2 in the protocol.

14. REFERENCES

SAS Institute Inc. 2008. SAS/STAT® 9.2 User's Guide. Cary, NC: SAS Institute Inc.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210-6.

Feuerhahn J, Blome C, Radtke M, Augustin M. Validation of the patient benefit index for the assessment of patient-relevant benefit in the treatment of psoriasis. Arch Dermatol Res. 2012;304(6):433–41.

EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199–208.

Reilly Associates. Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO). 2012. [cited 2018 May 01]. Available from: http://www.reillyassociates.net/WPAI_References3.html. Accessed May 01.

Leonardi C, Sobell J, Sofen H, Krell J. Phase IV study to evaluate the safety and efficacy of efalizumab for treatment of hand and foot plaque psoriasis. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; 2007 Feb 2-6; Washington, DC.

Naegeli, AN, Flood, E, Tucker J, Devlen J, Edson-Heredia E. The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis. Int J Dermatol 2015; 54:715-22.

Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003;49(2):206–12.

Carey W, Glazer S, Gottlieb AB, Lebwohl M, Leonardi C, Menter A, et al. Relapse, rebound and psoriasis adverse events: An advisory group report. J Am Acad Dermatol. 2006;54: S171-81.

Mehrotra, DV, and Railkar, R. Minimum risk weights for comparing treatments in stratified binomial trials. Statist. Med., 2000; 19: 811–825.

15. APPENDICES

15.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS).

15.1.1. Calculation Using Dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. The generalized calculation algorithm for relative day is the following:
    - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
    - Else use STUDY DAY = TARGET DATE – DSTART.

  Depending on the study day definition, DSTART can be Day 1 for core baseline or the Day 1 for Apremilast treatment baseline. Negative study days are reflective of observations obtained before the corresponding baseline. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.
- Age (in years) at the time of informed consent is collected.
    - When age in years is not available, age in days is calculated as (informed consent date – July 15 on the year of birth) + 1. Then age in years will be transformed to years by dividing age in days by 365.25 days, then truncating
    - If year of birth is also missing, set age missing
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4167

15.2. Date Imputation Guideline

15.2.1. Adverse Events

Partially missing AE start dates will be imputed in the ADaM dataset for AEs, but partially missing AE end dates will not be imputed. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

Subjects who were treated with Apremilast at Week 0/Visit 2

The principle of the imputation rules for subjects who were treated with Apremilast initially is to treat the AE as treatment-emergent, i.e., occurring on or after the date of the first dose of Apremilast, if possible.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", and the date of the first dose of Apremilast as "$D_{APR}/M_{APR}/Y_{APR}$". The following table gives the imputation rules for partially missing AE start dates for subjects who were treated with Apremilast initially at Week 0/Visit 2.

Table 6 Imputation Rules for Partially Missing AE Start Dates for Subjects Who Were Treated with Apremilast Initially

Scenario	Condition	Imputation Rule
Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{APR}$	$12/31/Y_{Event}$
2	Otherwise, i.e., $Y_{APR} \leq Y_{Event}$	Max (date of first dose of Apremilast, $1/1/Y_{Event}$)
Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{APR}$, or ($Y_{Event} = Y_{APR}$ and $M_{Event} < M_{APR}$)	Last date of M_{Event}/Y_{Event}
2	Otherwise, i.e., $Y_{APR} < Y_{Event}$, or ($Y_{APR} = Y_{Event}$ and $M_{APR} \leq M_{Event}$)	Max (date of first dose of Apremilast, $1/M_{Event}/Y_{Event}$)

Subjects who were treated with placebo at Week 0/Visit 2

The principle of the imputation rules for subjects who were treated with placebo initially and started Apremilast treatment at Week 16 is to consider the AE starting on or after the date of the first dose of Apremilast, if possible; if the partially missing start date suggests that it is prior to the date of the first dose of Apremilast, the AE will be considered starting on or after the date of the first dose of placebo, if possible.

The following are 4 scenarios considered in the imputation rules:

1. The partially missing AE start date suggests the date is prior to the date of the first dose of placebo: impute it by the latest possible date (determined by the non-missing field of the date);

2. The partially missing AE start date suggests the date is after the date of the first dose of Apremilast following Week 16: impute it by the earliest possible date (determined by the non-missing field of the date);
3. The partially missing AE start date is in the same year (if both month and day are missing), or the same year/month (if only day is missing) of the first dose of Apremilast following Week 16: impute it by the date of the first dose of Apremilast;
4. The partially missing AE start date suggests the date is no earlier than the date of the first dose of placebo but prior to the date of the first dose of Apremilast following Week 16: impute it by the date of the first dose of placebo, or the earliest possible date (determined by the non-missing field of the date), whichever occurs later.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", the date of the first dose of placebo as "$D_{PBO}/M_{PBO}/Y_{PBO}$", and the date of the first dose of Apremilast following Week 16 as "$D_{APR}/M_{APR}/Y_{APR}$". The following table gives the imputation rules for partially missing AE start dates.

Table 7 Imputation Rules for Partially Missing AE Start Dates for Subjects Who Were Treated with Placebo Initially

Scenario	Condition	Imputation Rule
Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{PBO}$	$12/31/Y_{Event}$
2	$Y_{Event} > Y_{APR}$	$1/1/Y_{Event}$
3	$Y_{Event} = Y_{APR}$	Date of first dose of Apremilast following Week 16
4	Otherwise, i.e., $Y_{PBO} \leq Y_{Event} < Y_{APR}$	Max (date of first dose of PBO, $1/1/Y_{Event}$)
Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{PBO}$, or ($Y_{Event} = Y_{PBO}$ and $M_{Event} < M_{PBO}$)	Last date of M_{Event}/Y_{Event}
2	$Y_{Event} > Y_{APR}$, or ($Y_{Event} = Y_{APR}$ and $M_{Event} > M_{APR}$)	$1/M_{Event}/Y_{Event}$
3	$Y_{Event} = Y_{APR}$ and $M_{Event} = M_{APR}$	Date of first dose of Apremilast following Week 16
4	Otherwise, i.e., $Y_{PBO} < Y_{Event} < Y_{APR}$, or ($Y_{PBO} = Y_{Event} < Y_{APR}$ and $M_{PBO} \leq M_{Event}$), or ($Y_{PBO} = Y_{Event} = Y_{APR}$ and $M_{PBO} \leq M_{Event} < M_{APR}$), or ($Y_{PBO} < Y_{Event} = Y_{APR}$ and $M_{Event} < M_{APR}$)	Max (date of first dose of placebo, $1/M_{Event}/Y_{Event}$)

15.2.2. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

15.2.3. Medical History

Partially missing medical history start dates will be imputed in the ADaM dataset for medical history (for the purposes of calculating durations of PsA and psoriasis). The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

15.2.4. Treatment Duration

Partially or completely missing last dose dates will be imputed in the ADaM dataset for treatment duration.

When partially missing last dose date is available, set last dose date to the maximum of [the earliest possible date given the non-missing field(s) of last dose date, the minimum of (the latest possible date given the non-missing field(s) of last dose date, last known date in database, first non-missing Early Termination (ET) visit date)]

When last dose date is completely missing, set last dose date to the minimum of (last known date in database, first non-missing Early Termination (ET) visit date)

Last known date in database is defined as maximum of the observed dates (i.e., last visit date, lab, vital signs, AE start or end dates, concomitant medications start or end dates, concomitant procedure date, last dose date from 'Disposition- Treatment' page, treatment exposure start or end dates where doses were completely or partially taken, death date).

15.3. Tablets Intended to be Taken for Treatment Compliance Calculation

During the Placebo-controlled Phase (Weeks 0 to 16), blister cards with 33 rows of tablets (i.e., a maximum 33-day supply) will be supplied. A subject takes the first 5 rows of tablets (6 tablets per row/day) on each complete blister card before taking the remaining rows (2 tablets per row/day), and completes the first 28 rows, skips rows 29-33 (5-day extra supply) and starts a new blister card. It is also assumed that a subject takes the full day's tablets from a new blister card on a study drug dispense date.

The intended total number of tablets is calculated as follows. First order the first dose date, the second dispense date, the third dispense date, etc., and the last dose date. The first and last dose dates are defined in the same way as those defined for treatment duration calculations. The intended number of tablets between any 2 consecutive dates is calculated as

$2 \times n + 4\times \text{int}[(n + 27) / 28] + 4 \times \text{int}[(n + 26) / 28] + 4 \times \text{int}[(n + 25) / 28] + 4\times \text{int}[(n + 24) / 28] + 4 \times \text{int}[(n + 23) / 28]$

where n denotes the number of days between the 2 consecutive dates (ie, the second date minus the first date for all pairs of consecutive dates, and the second date minus the first date plus 1 for the last pair), and "int" denotes the integer part of the result. Then the intended total number of tablets is the sum of all intended numbers of tablets as calculated above from the first dose date through the last dose date.

During the Apremilast Extension Phase (Weeks 16 to 52), blister card with 33 rows of tablets will be supplied at Week 16 visit and open label bottles will be supplied at Week 20 through Week 52.

The intended number of tablets is calculated as follows. First order the first dose date, the second dispense date, the third dispense date, etc., and the last dose date. The first and last dose dates are for the treatments during the Apremilast Extension Phase. The intended number of tablets between any 2 consecutive dates is calculated as:

- $2 \times n + 4\times \text{int}[(n + 27) / 28] + 4 \times \text{int}[(n + 26) / 28] + 4 \times \text{int}[(n + 25) / 28] + 4\times \text{int}[(n + 24) / 28] + 4 \times \text{int}[(n + 23) / 28]$ for records on drugs in blister cards
- $2 \times n$ for records on drugs in open label bottles.

Then the intended total number of tablets is the sum of all intended numbers of tablets as calculated above from the first dose date through the last dose date.

15.4. Laboratory Marked Abnormalities Criteria

Table 8 Laboratory Marked Abnormalities Criteria

Category / Analyte	SI Units	Criteria
Chemistry		
Alanine Aminotransferase (SGPT)	U/L	> 3*ULN
Albumin	Kg/m3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 3*ULN
Total Bilirubin	µmol/L	> 1.8*ULN
Blood Urea Nitrogen	mmol/L	> 15
Calcium	mmol/L	< 1.8 > 3.0
Creatinine	µmol/L	> 1.7*ULN
Glucose	mmol/L	< 2.8

Category / Analyte	SI Units	Criteria
		> 13.9
Hemoglobin A1C	%	> 9
Lactate Dehydrogenase	U/L	> 3*ULN
Magnesium	mmol/L	>1.2
Phosphate	mmol/L	< 0.64 >1.60
Potassium	mmol/L	3.0 5.5
Sodium	mmol/L	< 130 > 150
Triglycerides	mmol/L	> 3.4
Urate	umol/L	Male: > 590; Female: > 480
Hematology		
Hemoglobin	g/L	Female < 8.5, Male < 10.5 Female > 17, Male > 18.5
Leukocytes	10^9/L	< 1.5
Lymphocytes	10^9/L	< 0.8
Neutrophils	10^9/L	< 1.0
Platelets	10^9/L	< 75 > 600
Total cholesterol	mmol/L	> 7.8