Statistical Analysis Plan

Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	03AUG2023	
Amendment (v2.0)	**25SEP2023**	**Changes** **1. Revise the table for exploratory endpoints in section 2.1. And list all the added exploratory endpoints in section 10.** **Rationale: to keep all the added exploratory endpoints in Section 10.** **2.** [redacted] **Rationale: to be consistent with protocol defined subgroups.** **3. Reword the baseline definition for the apremilast exposure period in section 5.3.3.** **Rational: to improve clarity.** **4.** [redacted] **5. Reword the language about the listing for COVID-19 related PD in section 9.3.** **Rationale: to improve clarity.** **6. Reword the analysis description for the primary endpoint in section 9.5.1, including table 9-1.** **Rationale: to improve clarity and consistency.** **7. Remove the rounding in the first step of MI in section 9.5.1** **Rationale: rounding was included as an error.** **8. Update the analysis description for the exploratory endpoints in section 9.5.3, including table 9-3.** **Rationale: to improve clarity and consistency.**

		9. Reword the AE categories in section 9.6.2. **Rationale: to improve clarity.** **10. Reword the description in section 9.6.4 and 9.6.5.** **Rationale: to improve clarity.** **11. Add vital signs, physical measurement and laboratory test to the analysis window in Appendix B.** **Rationale: to improve clarity.** **12. Typo, redundancies and inconsistencies are addressed across the document.**

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List of Abbreviations

Abbreviation	Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BSA	body surface area
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CRF	case report forms
CSR	clinical study report
DARS	data acquisition requirements specifications
DLQI	dermatology life quality index
DMARD	disease modifying anti-rheumatic drug
DMP	data management plan
EOS	end of study
[redacted]	
ET	early termination
GSO-DM	global study operations-data management
IE	intercurrent event
IL	interleukin
IP	investigational product
IPD	Important protocol deviation
IRT	interactive response technology
ITT	intent-to-treat
MAR	missing at random
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
N/A	not applicable
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drugs
PAO	pustulotic arthro-osteitis
PDE4	phosphodiesterase-4
[redacted]	
PK	pharmacokinetic

Abbreviation	Explanation
PPP	palmoplantar pustulosis
PPPASI	palmoplantar pustulosis area and severity index
PPSI	Palmoplantar Pustulosis Severity Index
PRO	Patient-report Outcome
Q	Quantile
QoL	Quality of Life
SAP	statistical analysis plan
SAPHO	synovitis, acne, pustulosis, hyperostosis osteitis syndrome
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
TFLSD	table, figure, and listing shell document
ULN	upper limit of normal
VAS	visual analogue scale

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for the phase 3 study 20200195 of Apremilast in Japanese subjects with palmoplantar pustulosis (PPP) dated 30 March 2022. The scope of this plan includes the primary analysis (Week 16), supplemental analysis (Week 24), and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the efficacy of apremilast 30 mg twice daily (BID) compared with placebo in subjects with PPP	• Achieving at least 50% reduction from baseline in Palmoplantar Pustulosis Area and Severity Index (PPPASI) total score (PPPASI-50) at week 16
Secondary	
• To evaluate the efficacy of apremilast 30 mg BID compared with placebo in subjects with PPP	• Change from baseline in PPPASI total score at week 16 • Change from baseline in Palmoplantar Pustulosis Severity Index (PPSI) total score at week 16 • Change from baseline in subject's Visual Analogue Scale (VAS) assessment for PPP symptoms (pruritus and pain/discomfort) at week 16 • Change from Baseline in Dermatology Life Quality Index (DLQI) total score at week 16
• To evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo in subjects with PPP	• Treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs of interest • Clinically significant changes in body weight, vital signs, and laboratory abnormalities

Primary Estimand

The main estimand of primary interest for the primary efficacy endpoint (i.e., achievement of PPPASI-50 response defined as at least 50% reduction from baseline in PPPASI total score, at week 16) is defined in terms of the following attributes:

- The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria.
- The primary endpoint is the achievement of PPPASI-50 response at week 16.
- Intercurrent events (IEs) are investigational product (IP) discontinuation due to lack of efficacy, adverse event, or protocol-prohibited medication use. A subject will be considered a treatment failure after any of the IEs.
- The summary measure is the difference between apremilast 30 mg BID group and placebo group in proportion of responders based on the intent-to-treat (ITT) population including all randomized subjects.

A missing value after any of the IEs will be imputed as non-responders, otherwise, will be imputed with a multiple imputation (MI) method. A non-missing value after any of the IEs will also be imputed as non-responders.

Secondary Estimand(s)

The estimands for the secondary efficacy endpoints (i.e., change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms [pruritus and pain/discomfort], and DLQI total score) are defined in terms of the following attributes:

- The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria.
- The secondary endpoints are the change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain/discomfort), and DLQI total score.
- The IEs are IP discontinuation due to lack of efficacy, adverse event, or use of protocol prohibited medication. A subject will be considered a treatment failure after any of the IEs.
- The summary measure is the mean difference in change from baseline between apremilast 30 mg BID group and placebo group based on the ITT population.

A missing value after any of the IEs will be imputed using baseline value. Other missing values will not be imputed. A non-missing value after any of the IEs will also be imputed using baseline value.

Exploratory

[redacted]

2.2 Hypotheses and/or Estimations

Null Hypothesis

The treatment effect of apremilast 30 mg BID and placebo is equivalent.

Alternative Hypothesis

There is a difference in treatment effect between apremilast 30 mg BID and placebo.

3. Study Overview

3.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of apremilast 30 mg BID versus placebo in Japanese subjects with PPP.

Approximately 170 subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups: apremilast 30 mg BID or placebo. Subject randomization will be stratified by a subject's rounded PPPASI total score (≤20/ 21-30/ ≥31) and focal infection status (yes/no) at baseline.

Randomized subjects will receive either apremilast 30 mg BID or placebo for 16 weeks, the duration of the double-blind placebo-controlled treatment period. During the active treatment period (week 16 to week 52), all subjects will receive apremilast 30 mg BID. After the final dose treatment, subjects will enter a 30-day safety observational follow-up period. The total study duration including 4 weeks screening per subject is approximately 60 weeks.

The primary analysis will be performed after all subjects have either completed the week 16 visit (visit 8) or have discontinued the study. A supplemental analysis will be conducted after all subjects have either completed the week 24 visit (visit 10) or have discontinued the study. The final analysis will be conducted after all subjects have either completed the week 56 visit (visit 14) or discontinued the study.

3.2 Sample Size

The primary endpoint is the achievement of PPPASI-50 response at week 16. The sample size estimation is based on the results of the phase 2 study (CC-10004-PPP-001 [20200055]). Assuming a proportion of subjects achieving PPPASI-50 response at week 16 of 40% and 65% for the placebo group and the apremilast 30mg BID group, respectively, a sample size of approximately 170 subjects in total (85 subjects per group) provides 90% power using a chi-square test with a 2-sided alpha of 0.05. A dropout rate of 5% during double-blind placebo-controlled treatment period is anticipated.

4. Covariates and Subgroups

4.1 Planned Covariates

For the secondary endpoints to be analyzed with MMRM model (i.e., change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS for PPP

symptoms [pruritus and pain/discomfort], DLQI total score), the corresponding baseline value of the endpoint will be included as a covariate in the model.

4.2 Subgroups

The primary endpoint (PPPASI-50 response at week 16) and the selected key secondary endpoints such as change from baseline at week 16 in PPPASI total score and PPSI total score will be examined in the following subgroups to investigate the consistency of treatment effects. For each subgroup, a category with an insufficient number of subjects may be pooled.

- Age (< 40, ≥ 40 to < 65, ≥ 65 years)
- Sex (male, female)
- BMI category (< 25, ≥ 25 to < 30, ≥ 30 kg/m^2)
- Tobacco Use (current/former, never)
- Duration of PPP (< 2, ≥ 2 to < 6, ≥ 6 to < 10, ≥ 10 years)
- PPPASI total score range at baseline (clinical data) (≤ 20, ≥ 21 to ≤ 30, ≥ 31)
- Presence of focal infection at baseline (clinical data) (Yes, No)
- Presence of pustulotic arthro-osteitis (PAO) at baseline (Yes, No)
- Presence of nail lesion at baseline (Yes, No)
- Prior use of biologic disease modifying anti-rheumatic drugs (DMARDs) for PPP (Yes, No)
- History of focal infection including periodontitis, tonsilitis and sinusitis (Yes, No)
- [redacted]

5. Definitions

5.1 Safety Related Definitions

5.1.1 Treatment-emergent Adverse Events (TEAEs)

Any AEs that begin or worsen on or after the first dose of IP through 30 days after the last dose of IP or study treatment discontinuation date, whichever is later.

5.1.2 Treatment-related Adverse Events (TRAEs)

A treatment-related AE is any treatment-emergent AE with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been

caused by investigational medicinal product. In the unlikely event that the relationship is missing, the treatment-emergent event will be considered treatment-related and documented in a footnote of the treatment-related summary.

5.2 Study Dates/Timelines

5.2.1 Enrollment Date

Enrollment date is defined as the randomization date.

5.2.2 End of IP Admin Date

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP CRF page.

5.2.3 Last IP Dose Date

Last IP Dose Date for each subject is defined as the latest date IP is administered.

5.2.4 Randomization Date

Randomization date is defined as the date subject was allocated to a treatment group.

5.2.5 Study Day

The number of days from Study Day 1, inclusive, given by the following formula:

- Study Day = (Date of interest – Date of Study Day 1) + 1, if date of interest is on/after Study Day 1.
- Study Day = (Date of interest – Date of Study Day 1), if date of interest is before Study Day 1.

Study Day 1 is defined as the first day of IP administration after randomization. If a subject is randomized but never dosed, then set Study Day 1 to randomization date.

5.2.6 Study End Date

The Study End Date is defined as the last End of Study (EOS) date of all enrolled subjects.

5.2.7 Subject-level End of Study (EOS) Date

End of study for each subject is defined as the date the subject last completed a protocol-specified measurement.

5.2.8 Treatment duration

Last IP Dose Date minus Study Day 1 plus 1.

5.3 Baseline Related Definitions

5.3.1 Change from baseline

The arithmetic difference between a post-baseline value and baseline for a given time point: Change from baseline = (post-baseline value – baseline value).

5.3.2 Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as: 100 x [(value at given time point – baseline value) / baseline value]. Subjects with a zero value at baseline will be excluded from the summary of percent change from baseline.

5.3.3 Study Baseline

Study baseline is defined as the last non-missing value measured on or before Study Day 1.

For efficacy analyses and summary of baseline disease characteristics, baseline is defined as the last value measured on or before Study Day 1. For the summaries of laboratory parameters and vital signs parameters in the apremilast exposure period, baseline is defined as the last value measured on or before Study Day 1 **for subjects initially randomized to apremilast** for the placebo-controlled period, and defined as the last value measured on or before the day of the first apremilast dose for subjects initially randomized to placebo and switched to apremilast.

5.4 Study Endpoints

5.4.1 Palmoplantar Pustulosis Area and Severity Index (PPPASI)

PPPASI is a disease-specific efficacy assessment tool used by investigators established to detect a change of disease status on palms or soles. In the PPPASI system, the palms and soles are divided into 4 regions: the right palm, left palm, right sole, and left sole, which account for 20%, 20%, 30%, and 30% of the total body surface area (BSA) of the palms and soles, respectively. The scoring system for the signs of the disease (E = erythema, P = pustules/vesicle and D = desquamation/scale) is: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe. The scale for estimating the area of involvement for pustular lesions is: 0 = no involvement, 1 = 1% to 9% involvement, 2 = 10% to 29% involvement, 3 = 30% to 49% involvement, 4 = 50% to 69% involvement, 5 = 70% to 89% involvement, and 6 = 90% to 100% involvement.

The PPPASI total score formula is as below.

- PPPASI total score = (E + P + D)×Area×0.2 [right palm] + (E + P + D)×Area×0.2 [left palm] + (E + P + D)×Area×0.3 [right sole] + (E + P + D)×Area×0.3 [left sole]

PPPASI produces numeric total scores that can range from 0 to 72. A higher score indicates more severe disease.

The PPPASI sub-score is defined as the PPPASI total score including only one sub-domain of interest. For example, the PPPASI sub-score for erythema will be calculated as below.

PPPASI sub-score (Erythema) = (E)×Area×0.2 [right palm] + (E)×Area×0.2 [left palm] + (E)×Area×0.3 [right sole] + (E)×Area×0.3 [left sole]

PPPASI-50, PPPASI-75, and PPPASI-90 are defined as ≥ 50%, ≥ 75%, and ≥ 90% improvement (reduction) in PPPASI total score from baseline, respectively.

5.4.2 Palmoplantar Pustulosis Severity Index (PPSI)

PPSI is a disease-specific efficacy assessment tools by investigators. This is established to detect a change of disease status on a specified palm or sole. Evaluated skin lesion is identified by either right or left palm or sole, which has the most severe skin lesion at baseline and the identified skin lesion site will be assessed at all subsequent visits. Evaluation of skin lesion site are assessed separately for erythema (E), pustules/vesicle (P) and desquamation/scale (D), which are each rated on a scale of 0 to 4: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The severity of the disease is calculated with the PPSI total score formula as below.

- PPSI total score= (E + P + D)

PPSI sub-score (Erythema) = E.

The total score ranges from 0 to 12. A higher score indicates more severe disease.

PPSI-50 and PPSI-75 are defined as ≥ 50% and ≥ 75% improvement (reduction) in PPSI total score from baseline, respectively.

[redacted]

[redacted]

5.4.4 Pruritis and Pain Assessment with Subject Visual Analogue Scale (VAS) for PPP Symptoms

Subjects will use VAS (with scores ranging from 0 to 100, with 100 being most severe) to assess the degree of PPP pain/discomfort and pruritus on the hands and feet.

5.4.5 Dermatology Life Quality Index (DLQI)

DLQI is a skin disease-specific Quality of Life (QoL) questionnaire comprised of 10 items assessing the subject's status over the previous week. DLQI can be used to assess 6 different aspects that may affect QoL: symptoms and feelings, daily activities, leisure, work, or school performance, personal relationships, and treatment. Each item is scored on a 4-point Likert scale: 0 = not at all/not relevant; 1 = a little; 2 = a lot; and 3 = very much. The 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 [3], No, or Not relevant [0]), and if "No," then the subject is asked how much of a problem the status has been at work or study over the past week, with response alternatives being "a lot (2)," "a little (1)," or "not at all (0)". The DLQI total score is derived by summing all item scores, which has a possible range of 0 to 30 with higher scores indicating increased disease severity and correspond to poorer quality of life.

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.

DLQI response (score of 0 or 1) is defined as subject's DLQI total score achieving 0 or 1.

[redacted]

5.5 Analysis Phases

- Placebo-controlled Phase/Period – Weeks 0 to16

This period starts on the day of randomization (Week 0/Visit 2), and stops on below:

(1) the day of Week 16/Visit 8 if the subject continued study treatment to the active treatment phase

(2) the day of the discontinuation if the subject discontinued study treatment prior to or at Week 16/Visit 8

(3) the last known study day if the subject is lost to follow-up prior to or at Week 16/Visit 8

- Active Treatment Phase/Period – Weeks 16 to 52

This period starts on one day after the day of the dose of apremilast distributed at Week 16/Visit 8, and stops on either below.

(1) the day of Week 52/Visit 13

(2) the day of the discontinuation if the subject discontinued prior to or at Week 52/Visit 13

(3) the last known study day if the subject lost to follow-up prior to or at Week 52/Visit 13 during the phase

For safety analysis, the period starts on the day of the first dose of apremilast in the period.

- Safety Follow-up Phase/Period

Subjects who complete or discontinue the study treatment, will be followed up for 30 days after the end of treatment visit.

For adverse event analysis, data from the first 30 days after the last dose of IP will be included in the precedent treatment phase and data after the 30 days will be presented separately.

- Apremilast exposure period

This period starts on the date of either:

- the first dose of IP following randomization (Week 0/Visit 2) for subject who are treated with apremilast from Week 0

- the first dose of IP from the IP dispensed at Week 16/Visit 8 for subjects who were originally treated with placebo and are switched to apremilast at Week 16

This period stops on either: (1) data restriction date; or (2) the end of the study.

During the apremilast-exposure period, data are presented by treatment sequence, i.e., Placebo/30 mg BID, 30 mg BID as Initiated, and a total column of 30 mg BID as Treated.

6. Populations for Analysis

6.1 Intent-to-treat Population

The intent-to-treat (ITT) population will include all randomized subjects. Subjects will be included in the treatment group to which they are randomized. Efficacy analyses will be performed based on the ITT population, unless otherwise specified.

6.2 Safety Analysis Population

The safety analysis population will include all randomized subjects who received at least 1 dose of IP. The analysis of safety data will be based on the safety population. Subjects will be included in the treatment group corresponding to the IP they actually received (apremilast or placebo). Subjects who inadvertently received more than 1 type or dose of IP in the placebo-controlled period will be analyzed according to their actual treatment received, where subjects who received ≥ 1 dose of apremilast will be analyzed in the apremilast treatment group regardless of the randomized treatment. Safety analyses for the apremilast-exposure period will be based on the apremilast subjects as treated population, which includes all subjects who actually receive the apremilast 30 mg BID at the randomization or switched to the apremilast 30 mg BID at the week 16 visit.

6.3 Study-specific Analysis Sets

Not applicable.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis will be conducted prior to the primary analysis.

7.2 Primary Analysis

The primary analysis will be performed after all subjects have either completed week 16 or discontinued the study.

7.3 Supplemental Analysis

After all subjects have either completed week 24 (visit 10) or discontinued the study, a supplemental analysis will be conducted. Statistical comparisons of treatment

differences will not be performed for this supplemental analysis. All analyses for placebo-controlled period in PA will not be repeated.

7.4 Final Analysis

Final analysis will be conducted based on all study data collected after all subjects have either completed or discontinued the study. In FA, the descriptive analyses at SA will be updated using the data from the final database lock. All analyses for placebo-controlled period in PA will not be repeated.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses including data from RAVE database, Clinical Outcome Assessment (COA), Patient-reported Outcome (PRO), and laboratory data (outside of RAVE database). The database will be subjected to edit checks outlined in the Data Management Plan (DMP). Additional details will be provided in DMP and Data Acquisition Requirements Specifications (DARS).

8.3 Handling of Missing and Incomplete Data

Subjects may have missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing.

8.3.1 Missing Baseline

Missing at baseline evaluations will not be imputed.

8.3.2 Missing Post-Baseline Evaluation

In the primary endpoint analysis of PPPASI-50 response at week 16, the PPPASI-50 values will be imputed as non-responder for visits on and after a subject experiencing any of the IEs. The missing PPPASI-50 values due to other reasons will be imputed using MI method.

For the secondary endpoints (i.e., the change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms [pruritus and pain/discomfort], and DLQI total score), the corresponding endpoints' baseline value will

be assigned to the data on and after any of the IEs regardless of the observed data and no imputation will be applied to the missing data (PPPASI total score) due to other reasons. Similar approach will be applied to the other endpoints of responses and continuous variables, unless otherwise specified.

For safety data, missing post-baseline measurements/assessments will not be imputed.

8.3.3 Missing and Incomplete Dates

For any listings, missing or incomplete dates will be listed as is.

The handling of incomplete and partial dates for safety, medical history and concomitant/prior medication/procedures will be described in Appendix C.

8.4 Detection of Bias

This study has been designed to minimize potential bias using randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the study include:

- major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- subject level unblinding before the final database lock and formal unblinding
- IP dosing non-compliance
- reasons for early withdrawal from treatment or from study

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints, and would significantly affect subject's right, safety or wellbeing will be tabulated by treatment group in the Clinical Study Report (CSR). Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR.

8.5 Outliers

Descriptive summaries will be examined to identify unexpected values.

Outliers that are not due to data entry will be included in the analysis. If it is deemed necessary after the team reviews the output from the planned analyses after database snapshot, a post-hoc sensitivity analysis excluding subjects with outliers may be performed.

8.6 Distributional Characteristics

For categorical endpoints, descriptive summary will be provided. For continuous endpoints, normality will be assumed given the large sample size where central limit theorem applies.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or higher.

9. Statistical Methods of Analysis

9.1 General Considerations

The ITT principle will be used in statistical analyses for efficacy endpoints. For the placebo-controlled period (Weeks 0-16), efficacy evaluations will be conducted using the ITT population defined as all randomized subjects. Statistical comparisons for placebo-controlled period in Primary Analysis (PA) will be made between the two treatment groups (placebo and apremilast 30 mg BID). For the active treatment period (Weeks 16-52), analysis for differences between the two groups will not be performed although summaries of each group will be provided.

Descriptive statistics will be presented for appropriate endpoints at specified time points. Specifically, summary statistics for continuous variables will include the number of subjects (n), mean, SD, median, the 25^{th} (Q1) and 75^{th} (Q3) percentiles, minimum, and maximum. For efficacy variables, standard errors (SEs) for estimates will be included, unless otherwise specified. Frequency summary for categorical variables includes counts and percentages.

Statistical inferences will be provided for analyses of primary, secondary and the exploratory efficacy endpoints. Unless specified otherwise, all statistical tests are 2-sided with a significance level of 0.05; no statistical inference and imputation will be conducted for analyses of safety endpoints.

9.2 Subject Accountability

Frequency summary of subjects randomized, screened but not randomized among all screened subjects will be provided. The frequency of subjects who failed each inclusion/exclusion criteria will be included in the summary.

The number and percentage of subjects included in the ITT and safety analysis population will be summarized.

Subject disposition will be provided for placebo-controlled period and active treatment period based on ITT population respectively. Summary of safety follow-up period and study completion will be included in each disposition summary. The summaries include the number and percentage of subjects who entered the period, who completed the period, who completed IP, who ended IP and study with the reason. Subjects who ended IP are considered to enter the safety follow-up period unless the subjects ended the study on the same day.

Key study dates for the first subject screened and enrolled (randomized), last subject enrolled (randomized), data cut-off (last subject's week 16 and 24 visit), last subject end of IP, last subject end of study will be presented.

The number and percentage of subjects randomized will be tabulated by study site.

Listings of subject accountability will be provided.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study.

The number and percentage of subjects with at least one IPD will be summarized by each category in a table. The number of subjects reporting IPD and PD related to COVID-19 will be separately summarized. A by-subject listing of IPD will be provided. A COVID-19 related **PD** listing will also be provided.

9.4 Demographic and Baseline Characteristics

Summaries for the demographics, baseline characteristics, medical history, prior medication/procedure will be presented for the ITT population by treatment group and overall. Concomitant procedures/medications will be summarized based on the safety population.

Individual subject listings will be provided to support the summary tables.

9.4.1 Demographics

Summary statistics will be provided for the following continuous variables:

- Age
- Weight
- Height
- BMI (Weight [kg]/Height [m^2])

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

- Age (< 40, ≥ 40 to < 65, ≥ 65 years)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Other). If multiple races have been reported for a subject, the subject will be categorized as multiple-race, as well as by combination of races.
- BMI category (< 25, ≥ 25 to < 30, ≥ 30 kg/m^2)

9.4.2 Baseline Disease Characteristics

Summary statistics will be provided for the following continuous variables:

- Duration of PPP in years
- PPPASI total score
- PPSI total score
- VAS for PPP symptoms (pruritus and pain/discomfort)
- DLQI total score
- [redacted]
- [redacted]

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

- Tobacco Use (Current/Past User, Non-User)
- Duration of PPP (< 2, ≥ 2 to < 6, ≥ 6 to < 10, ≥ 10 years)
- PPPASI total score rounded range (clinical and IRT data) (≤ 20, ≥ 21 to ≤ 30, ≥ 31)
- [redacted]
- Presence of focal infection (clinical and IRT data) (Yes, No)
- Presence of pustulotic arthro-osteitis (PAO) (Yes, No)
- Presence of nail lesion (Yes, No)
- Prior use of biologic DMARDs for PPP (Yes, No)
- History of focal infection including periodontitis, tonsilitis and sinusitis (Yes, No)

9.4.3 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. A frequency summary (counts and percentage of subjects) of medical history will be presented by system organ class (SOC) and preferred term (PT). A similar table summarizing currently active medical histories that were not resolved/recovered by randomization will be provided. Medical history summaries of focal infection and PAO will be provided. Individual subject listings of medical history will be provided.

9.4.4 Prior and Concomitant Procedures

Prior procedures are defined as those started before Study Day 1 (whether or not ended before Study Day 1). Concomitant procedures are defined as procedures that were either initiated before Study Day 1 and continued during the study treatment, or initiated on/after the date of Study Day 1 and on/before the date of treatment discontinuation. Procedures initiated prior to the start of study treatment and were continued after the start of study treatment will be counted as both prior and concomitant procedures.

Frequency summaries of prior and concomitant procedures will be provided by verbatim term, and location.

A subject listing of prior and concomitant procedures will be provided.

9.4.5 Prior and Concomitant Medications

Prior and concomitant medications are defined similarly as prior and concomitant procedures, respectively.

Number and proportion of subjects receiving prior/concomitant medications will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary. The prior **and concomitant** medications for PPP, focal infection and PAO will be summarized separately.

A subject listing of prior and concomitant medications will be provided.

9.5 Efficacy Analyses

The efficacy analyses will be performed based on the ITT population.

To control the overall type I error at the level of 0.05 (2-sided), a fixed-sequence testing procedure will be applied. The secondary efficacy endpoints will be tested with the listed order in Section 9.5.2 if the primary endpoint achieves statistical significance.

Sensitivity analyses will be performed for the primary estimand.

Subject data listings of efficacy data will be provided.

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

The primary efficacy endpoint is the achievement of PPPASI-50 response at week 16. The proportion of subjects achieving PPPASI-50 response in apremilast 30 mg BID group and placebo group will be compared using Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factors for randomization [PPPASI total score range (≤20 / 21-30 / ≥31) at baseline and subject's focal infection status (yes/no) at baseline]. The testing will be conducted at the 2-sided 0.05 significance level. Subjects who discontinue IP prior to week 16 due to lack of efficacy, adverse event, or use of protocol prohibited medication will be considered as treatment failures as the result of the IE and the PPPASI-50 values for visits on and after the IE will be imputed as non-responders. The missing data (PPPASI total score) due to other reasons will be imputed using MI method.

The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided. Similarly, unadjusted treatment differences in proportions will also be provided.

Sensitivity analyses for the primary endpoint will be conducted using the non-responder imputation (NRI) method for any missing data **due to other reasons (not IE)**. Additionally, to assess sensitivity to departures from the missing data assumption (MAR), the tipping point analysis will be performed. Another sensitivity analysis for the primary endpoint will be performed based on data-derived stratification factors.

For MI method, the SAS procedure MI will be used to impute missing PPPASI scores at the scheduled analysis visits in the Placebo-controlled Phase (Week 0-16) to create M=50 complete datasets. The missing data patterns will be checked at the scheduled

analysis visits, i.e., Baseline (week 0), week, 2, 4, 6, 8, 12, and 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=50 imputed data sets with monotone missing patterns. The minimum and maximum values for imputation will correspond to the lowest and the highest scores. The seed will be set to 17813722, a single chain will be used to produce imputations. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary.
- In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 50 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with seed 55218164. The missing values at each visit will be imputed based on treatment**, stratification factor** and previous visits. The number of closest observations to be used in the selection will be K=2.

After the completion of imputation, the same analysis method/model will be used to analyze the 50 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
Achieving PPPASI-50 response at week 16	The treatment failures will be considered as non-responders on and after the IE and the missing value (PPPASI total score) due to other reasons will be imputed using MI method. **The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided. Similarly, unadjusted treatment differences in proportions will also be provided.**	– Tipping point analysis to assess sensitivity to departures from the missing data assumption (MAR) – NRI for any missing data – **Adjusting for the data-derived stratification factors instead of the factor from IRT**

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

For the secondary endpoints including change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain/discomfort), and DLQI total score, the MMRM with treatment group, visit time, treatment-by-time interaction, and stratification factors as fixed effect, and the baseline value as a covariate will be applied. An unstructured covariance matrix will be used to model the correlation among repeated measurements. For the treatment failures as the result of an IE (IP discontinuation prior to week 16 due to lack of efficacy, adverse event, or use of protocol prohibited medication), the corresponding endpoints' baseline value will be assigned to the data on and after the IE up to week 16, regardless of the observed data. The missing data due to other reasons will not be imputed considering MMRM application based on the assumption of MAR. The least square (LS) means and SEs along with 95%CI within-group and treatment differences (from placebo) in LS means and SEs along with 95%CI and two-sided p-values will be derived from the MMRM.

The secondary endpoints will be statistically tested in the following order if the primary analysis result achieve a statistically significant difference. The statistical testing will be performed in the sequence until one of the analyses has failed to show the statistically significant difference at a significance level of 0.05 (two-sided).

1. Change from baseline in PPPASI total score at week 16
2. Change from baseline in PPSI total score at week 16
3. Change from baseline in Subject's VAS assessment for PPP symptom (pruritus) at week 16
4. Change from baseline in Subject's VAS assessment for PPP symptom (pain/discomfort) at week 16
5. Change from baseline in DLQI total score at week 16

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint/Estimand	Summary and Analysis Method
– Change from baseline in PPPASI total score at week 16 – Change from baseline in PPSI total score at week 16 – Change from baseline in Subject's VAS assessment for PPP symptom (pruritus) at week 16 – Change from baseline in Subject's VAS assessment for PPP symptom (pain/discomfort) at week 16 – Change from baseline in DLQI total score at week 16	– LS mean (SE) along with 95%CI within-group derived from the MMRM – LS mean difference from placebo (SE) along with 95%CI and p-value (two-sided) based on the MMRM For the treatment failures, the corresponding endpoints' baseline value will be assigned to the data on and after the IE up to week 16, regardless of the observed data. The missing data due to other reasons will not be imputed considering the MMRM application based on the assumption of MAR.
Sensitivity analysis will not be performed for the secondary efficacy endpoints.	

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

[redacted]

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Summary and Analysis Method
[redacted]	

Endpoint	Summary and Analysis Method
[redacted]	

9.6 Safety Analyses

Safety analyses will be performed using the safety analysis population unless otherwise specified. Summaries of the safety analyses for the placebo-controlled period will be based on the safety population and presented by treatment group, and the safety analyses for the apremilast-exposure period will be based on the apremilast subjects as treated population and presented by treatment group (Placebo/30 mg BID, 30 mg BID as initiated and 30 mg BID as treated). The purpose of safety summary for the apremilast-exposure period is to provide safety data under apremilast 30 mg BID.

9.6.1 Analyses of Primary Safety Endpoint(s)

There is no primary safety endpoint. As a secondary endpoint, the safety and tolerability of apremilast 30 mg BID will be compared to placebo. No inferential testing for statistical significance will be performed for safety analyses.

Unless otherwise specified, the analyses of AEs and marked abnormalities (laboratory parameters and vital signs) for both the placebo-controlled period and apremilast-exposure period will be summarized by subject incidence rate. For safety summaries of apremilast-exposure period, the exposure-adjusted incidence rate will be presented to account for the difference exposure to the IP.

9.6.2 Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs) defined as any AEs that begin or worsen on or after the first dose of IP through 30 days after the last dose of IP or study treatment discontinuation date, whichever is later. The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher will be used to code all events categorized as adverse events to a system organ class and a preferred term.

An **overview** of the following AE categories will be provided.

AE Categories:

- TEAE
- Drug-related TEAE
- Severe TEAE
- Serious TEAE
- **Serious Drug-related TEAE**
- TEAE Leading to Drug Interruption
- TEAE Leading to Drug Withdrawal
- **TEAE Leading to Death**

Summary of the above AE categories for the subgroups in Section 4.2 will be provided.

Tables summarizing the incidence of TEAEs by SOC and/or PT will be generated for each of the followings:

- All TEAEs
- Drug-related TEAE
- TEAEs by maximum severity
- Serious TEAE
- **Serious** Drug-related TEAE
- TEAE Leading to Drug Interruption
- TEAE Leading to Drug Withdrawal
- **TEAE Leading to Death**
- First onset and new event of TEAE by exposure interval
  - Placebo controlled period (weeks): ≤ 1, > 1 to ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12 to ≤ 16, > 16
  - Apremilast-exposure period (weeks): ≤ 1, > 1 to ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12 to ≤ 16, > 16 to ≤ 28, > 28 to ≤ 40, > 40 to ≤ 52, > 52
- TEAE for the subgroups in Section 4.2

Tables summarizing the incidence of TEAEs by PT will be generated for each of the followings:

- TEAEs by NSAIDs status
- Most frequent TEAEs (subject incidence ≥ 5% in any group or another cut-off if justified)
- Most frequent TEAEs by maximum severity (subject incidence ≥ 5% in any group or another cut-off if justified)
- Most frequent TEAE for the subgroups in Section 4.2 (subject incidence ≥ 5% in any group or another cut-off if justified)
- First onset of most frequent TEAE by exposure interval (subject incidence ≥ 5% in any group or another cut-off if justified)
  - Placebo controlled period (weeks): ≤ 1, > 1 to ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12 to ≤ 16, > 16
  - Apremilast-exposure period (weeks): ≤ 1, > 1 to ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12 to ≤ 16, > 16 to ≤ 28, > 28 to ≤ 40, > 40 to ≤ 52, > 52

For the summary of the new events of TEAE by exposure interval, each subject is counted once for either subject incidence or EAIR for each applicable specific TEAE in each exposure interval where an event started. The denominator of a subject incidence is the number of subjects with exposure time exceeding the lower bound of the particular exposure interval, while the denominator of an EAIR is the sum of the exposure time during the exposure interval (up to the first event start date for subjects with at least one event starting in the interval) among the same number of subjects as in the denominator of the corresponding subject incidence. The exposure time for a subject without the specific event is the treatment duration, 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. For the summary of the first onset of TEAE by exposure interval, only the first onset of specific TEAE is considered for each subject.

Following TEAEs of interest will be summarized according to their categories and PT by severity (mild, moderate, severe), relationship, action taken with IP, fatality, and seriousness.

- Depression: MedDRA narrow scope SMQ of Depression (excluding suicide and self-injury)
- Serious infection: MedDRA primary SOC of Infections and infestations and the events assessed as serious
- Risk of Triggering Suicide: MedDRA narrow scope sub-SMQ of Suicide/self-injury
- Serious Diarrhea, Nausea, and Vomiting: definition can be found in TFLSD.
- Malignancies: definition can be found in TFLSD.
- Vasculitis and Vasculopathy: MedDRA narrow scope SMQ of Vasculitis.
- Serious Hypersensitivity: MedDRA narrow scope SMQ of Hypersensitivity.
- Weight Change (Weight decrease): definition can be found in TFLSD.

Subject listings of AEs including non-treatment-emergent AEs will be provided.

9.6.3 Laboratory Test Results

Summary statistics of observed values and changes from baseline in the selected laboratory parameters will be provided over time. Frequency summary of shifts from baseline to the worst post-baseline value in terms of normal/abnormal will be provided. The selected laboratory parameters with abnormalities criteria are available in the Appendix A. For the purposes of the summary, 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.

Individual subject data of all laboratory data will be listed and values outside of the normal reference range will be flagged.

9.6.4 Vital Signs

The analyses of vital signs including summary statistics **of observed values and changes from baseline** over time will be provided. Frequency summaries of shifts from baseline to the worst post-baseline value in terms of normal/abnormal(low/high) will be provided for **heart rate** and blood pressure. Normal ranges are defined as: 60-90 mmHg for diastolic blood pressure, 90-140 mmHg for systolic blood pressure, and 60-100 beats/minute for **heart rate**.

A subject data listing of all vital signs will be provided.

9.6.5 Physical Measurements

The **observed values and** change from baseline for weight and BMI will be summarized.

A subject data listing of physical measurements will be provided.

9.6.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment group. Treatment duration (in weeks) is calculated as (the date of the last dose of IP – the date of the first dose of IP + 1)/7. Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories (placebo-controlled period: < 4, ≥ 4 to < 8, ≥ 8 to < 12, ≥ 12 to < 16, ≥ 16, active treatment period: ≥ 16 to < 20, ≥ 20 to < 24, ≥ 24 to < 32, ≥ 32 to < 44, ≥ 44 to < 52, ≥ 52 weeks) will be provided.

Treatment duration for apremilast-exposure period is calculated from the date of the first apremilast administered, which is the date of the first administration of apremilast on/after the randomization at week 0 (visit 2) or switched to apremilast at week 16 (visit 8), to the last apremilast administered date of subjects who discontinue before the study completion or who complete the study at week 52 (visit 13).

For treatment compliance, descriptive statistics will be provided. The treatment compliance (%) for each subject will be computed as 100 times the total number of tablets actually taken (sum of dose per administration) over the period divided by the intended total number of tablets that should have been taken over the same period. It is assumed that a subject takes 2 tablets per day from the first through the last IP administered date.

A subject data listing of IP administration will be provided.

9.6.7 Exposure to Prior/Concomitant Medication and Procedures

Prior medications and procedures are defined as medications that were started before the start of the study treatment and either ended before the start of the study treatment or continued after study treatment. Concomitant medications and procedures are defined as medications that were either initiated before the first dose of IP and continued during the study treatment or initiated on/after the date of the first dose of IP and on/before the date of treatment discontinuation. Medications and procedures initiated prior to the start of study treatment and were continued after the start of study treatment will be counted as both prior and concomitant medications and procedures.

Number and proportion of subjects receiving prior/concomitant medications and procedures will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary. The prior **and concomitant** medications for PPP, focal infection and PAO will be summarized.

A subject listing of prior and concomitant medications and procedures will be provided.

9.7 Other Analyses

PK and Biomarker analyses are planned separately.

9.7.1 Analyses of Pharmacokinetic Endpoints

Detailed descriptions of PK analysis will be documented separately.

9.7.2 Analyses of Biomarker Endpoints

Detailed descriptions of biomarker analysis will be documented separately, and the result will be separately reported.

10. Changes From Protocol-specified Analyses

Added additional exploratory endpoints:

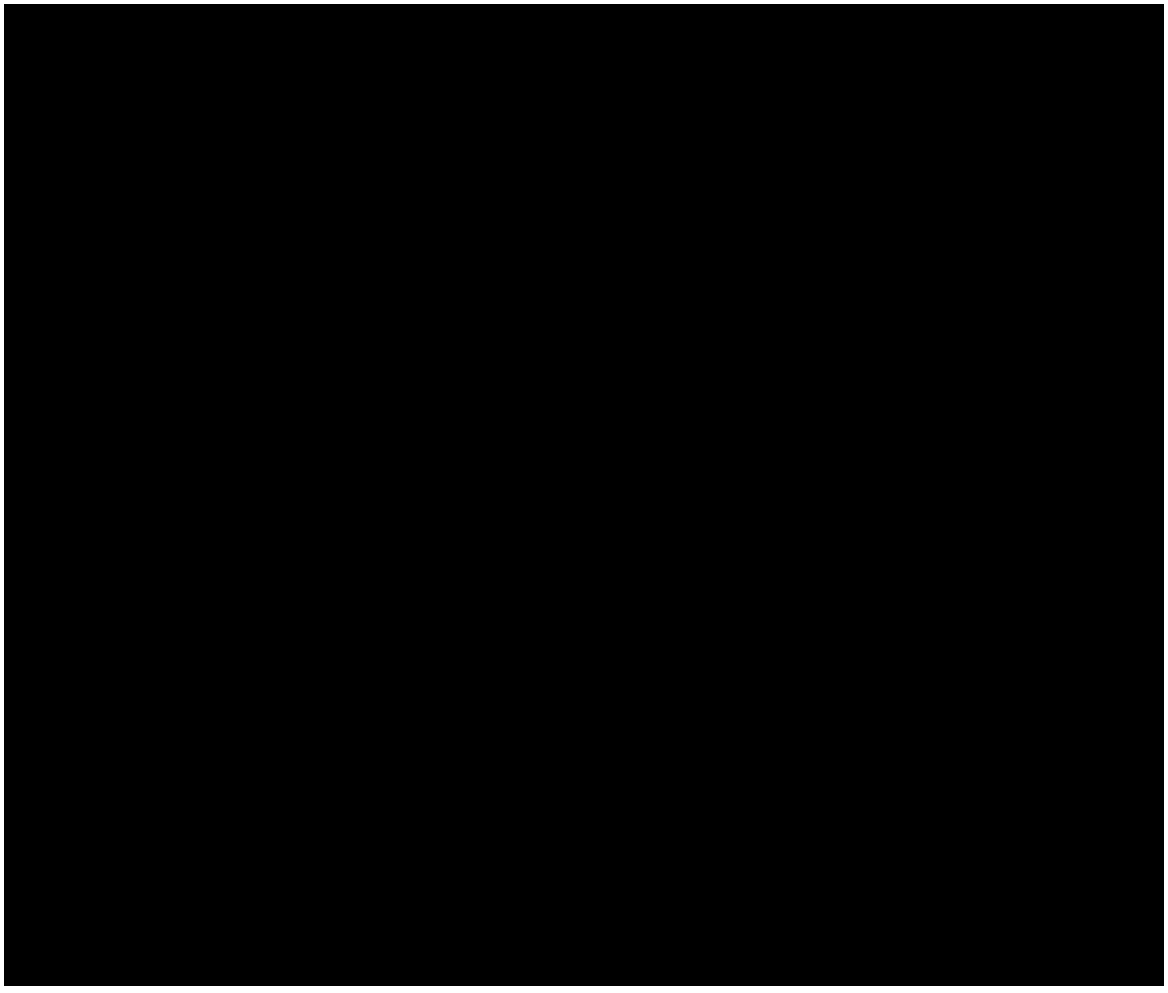

Table 10-1. Additional Exploratory Efficacy Endpoint Summary Table

Endpoint	Summary and Analysis Method
[redacted]	

[redacted]

11. Literature Citations / References

van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012 Jul-Aug;15(5):708-15

12. Prioritization of Analyses

Not applicable

13. Data Not Covered by This Plan

A detailed description of PK and biomarker analysis will be documented separately.

14. Appendices

Appendix A. Criteria for Marked Changes in Laboratory Values

Category	Analyte	Abnormality Criteria
Chemistry	Sodium	>150, <130 mmol/L
	Potassium	>5.5, <3.0 mmol/L
	Albumin	<25 g/L
	Calcium	>3.0, <1.8 mmol/L
	Magnesium	> 1.2 mmol/L
	Phosphorus	>1.60, <0.64 mmol/L
	Glucose	>13.9, <2.8 mmol/L
	BUN or Urea *Blood Urea Nitrogen	> 24 mmol/L
	Creatinine	>1.5×ULN umol/L
	Uric acid	> 480 umol/L
	Total bilirubin	>1.8×ULN umol/L
	ALP *Alkaline Phosphatase	>400 U/L
	LDH *Lactate Dehydrogenase	> 2xULN U/L
	AST (SGOT) *Aspartate Aminotransferase	>3.0×ULN U/L
	ALT (SGPT) *Alanine Aminotransferase	>3.0×ULN U/L
	Cholesterol	> 7.8 mmol/L
	Triglycerides	> 3.4 mmol/L
Hematology	Hemoglobin	>150, <110 g/L
	Platelets	>600, <75 10^9/L
	WBC *Leukocytes	< 2.0 10^9/L
	Lymphocytes	<0.8 10^9/L
	Neutrophils, Segmented	< 1.5 10^9/L

Appendix B. Analytical Windows

Per protocol, visits are to be performed within 2 days of the protocol-specified study day for placebo-controlled period, and within 4 days for the active treatment period. To allow for variations in scheduling, the following visit windows will be applied to selected efficacy evaluations to assign a most appropriate nominal visit for analysis. If more than one assigned visit falls within the same defined window, the closest visit to the target day (ie, scheduled visit week × 7 + 1) will be considered for analysis. If two assessment dates are the same distance from the target day, then the latest visit will be considered for analysis.

Analysis window for PPPASI, PPSI, [redacted] Vital Signs and Physical Measurement

Visit Week	Target Day	Window Definition
Week 0 (Visit 2: Baseline)	1	Last Evaluation prior to or on Study Day 1
Placebo-controlled Period		
Week 2 (Visit 3)	15	Study Day 2 – 22
Week 4 (Visit 4)	29	Study Day 23 – 36
Week 6 (Visit 5)	43	Study Day 37 – 50
Week 8 (Visit 6)	57	Study Day 51 – 71
Week 12 (Visit 7)	85	Study Day 72 – 99
Week 16 (Visit 8)	113	Study Day 100 – End of the Period
Active Treatment Period		
Week 20 (Visit 9)	141	One day after the first apremilast dosing day on Visit 8* – 155
Week 24 (Visit 10)	169	Study Day 156 – 197
Week 32 (Visit 11)	225	Study Day 198 – 267
Week 44 (Visit 12)	309	Study Day 268 – 337
Week 52 (Visit 13)	365	Study Day 338 – End of the Period

Analysis window for Subject's VAS assessment for PPP symptom for palms and soles

Visit Week	Target Day	Window Definition
Week 0 (Visit 2: Baseline)	1	Last Evaluation prior to or on Study Day 1
Placebo-controlled Period		
Week 2 (Visit 3)	15	Study Day 2 – 22
Week 4 (Visit 4)	29	Study Day 23 – 36
Week 6 (Visit 5)	43	Study Day 37 – 50
Week 8 (Visit 6)	57	Study Day 51 – 71
Week 12 (Visit 7)	85	Study Day 72 – 99
Week 16 (Visit 8)	113	Study Day 100 – End of the Period
Active Treatment Period		

Visit Week	Target Day	Window Definition
Week 24 (Visit 10)	169	One day after the first apremilast dosing day on Visit 8 – 197
Week 32 (Visit 11)	225	Study Day 198 – 295
Week 52 (Visit 13)	365	Study Day 296 – End of the Period

Analysis window for DLQI, [redacted] and Laboratory Test

Visit Week	Target Day	Window Definition
Week 0 (Visit 2: Baseline)	1	Last Evaluation prior to or on Study Day 1
Placebo-controlled Period		
Week 8 (Visit 6)	57	Study Day 2 – 85
Week 16 (Visit 8)	113	Study Day 86 – End of the Period
Active Treatment Period		
Week 24 (Visit 10)	169	One day after the first apremilast dosing day on Visit 8 – 197
Week 32 (Visit 11)	225	Study Day 198 – 225
Week 52 (Visit 13)	365	Study Day 226 – End of the Period

Active treatment period start point for adverse event data shall be the first apremilast dosing day on Visit 8.

Appendix C. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Start Dates

The reference date for the following rules is the date of first dose of apremilast.

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**Missing**
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	**= 1st dose *yyyymm***	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.
- If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.
- If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume date last known to be alive is in error, set death date to the first day of the death month.

If month and day are missing and year of death is known:

- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, assume date last known to be alive is in error, set death date to the first day of the death year.

If a death date is totally missing:

- Set death date to the day after the date last known to be alive. If the date last known to be alive is a partial date, set it to the first day of the month last known to be alive or first day of the year last known to be alive if month is also missing.