STATISTICAL ANALYSIS PLAN

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN JAPANESE SUBJECTS WITH PALMOPLANTAR PUSTULOSIS

STUDY DRUG: **Apremilast (CC-10004)**

PROTOCOL NUMBER: **CC-10004-PPP-001**

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SAP TITLE	Statistical Analysis Plan for a Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in Japanese Subjects with Palmoplantar Pustulosis
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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CSR	Clinical Study Report
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying Antirheumatic Drug
EAIR	Exposure-adjusted Incidence Rate
eCRF	electronic Case Report Form
EQ-5D	EuroQol 5 Dimension
GI	Gastrointestinal
IL	Interleukin
IL	Interleukin
IP	Investigational Product
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LS	Least-squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities

MI	Multiple Imputation
MMRM	Mixed-effect Model for Repeated Measures
NRI	Non-responder Imputation
NSAIDs	Non-steroidal Anti-inflammatory Drugs
PAO	Pustulotic Arthro-osteitis
PD	Protocol Deviation
PGA	Physician's Global Assessment
PP	Per Protocol
PPP	Palmoplantar pustulosis
PPPASI	Palmoplantar Pustular Area and Severity Index
PPSI	Palmoplantar Severity Index
PT	Preferred Term
Q	Quantile
QoL	Quality of Life
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SMQ	Standardised MedDRA Querie
SOC	System Organ Class
SRO	Subject's Reported Outcome
TEAE	Treatment-emergent Adverse Event
TNF	Tumor Necrosis Factor
VAS	Visual Analogue Scale
WHO DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Amgen's protocol CC-10004-PPP-001 "A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in Japanese Subjects with Palmoplantar Pustulosis". It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed for the primary data analysis. No interim analysis is planned prior to this primary data analysis. At the end of the study, after all subjects have completed, or have been discontinued from the active treatment phase (Weeks 16 to 32) and the post-treatment observational follow-up phase, the final analysis will be performed, and a final clinical study report (CSR) will be generated.

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 database restriction and any data analysis for unblinding. This SAP will be finalized and signed prior to unblinding of the Week 16 database. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to evaluate the efficacy of apremilast 30 mg twice daily (BID) compared with placebo in Japanese subjects with palmoplantar pustulosis (PPP).

3.2. Secondary Objective

The secondary objective is to evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo in Japanese subjects with PPP.

3.3. Exploratory Objectives

The exploratory objectives are:

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

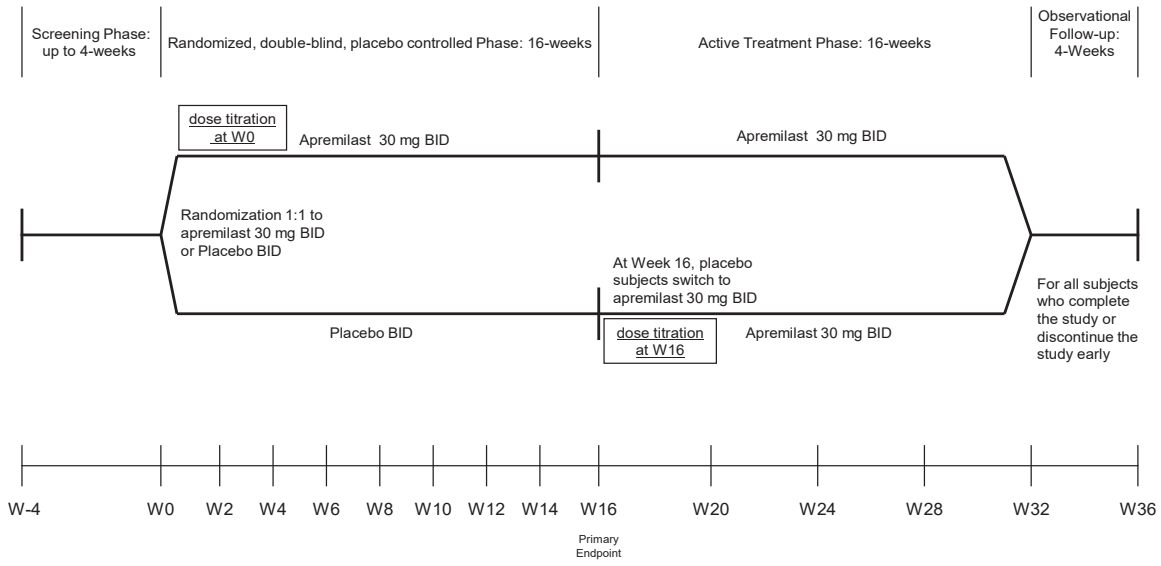
This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study of apremilast in Japanese subjects with PPP and inadequate response to treatment with topical steroid and/or topical vitamin D3 derivative preparations.

This study consists of a screening phase for up to 4 weeks, a 16-week placebo-controlled phase, a 16-week active treatment phase, and a 4-week post-treatment observational follow-up phase at any time the subject completes or discontinues the treatment. To mitigate potential gastrointestinal (GI) side effects (primarily mild to moderate nausea and diarrhea), dose titration (using blister cards) will be implemented over a 5-day period starting at the baseline visit (Week 0) for subjects randomized to apremilast 30 mg BID or Placebo. Subjects randomized to placebo will receive blister cards with dummy dose titration. All subjects will be switched to (or continue with) apremilast 30 mg BID at Week 16 and will maintain this dosing through Week 32. Subjects who discontinue treatment with investigational product (IP: apremilast 30 mg BID or Placebo) or withdraw during the treatment phase will be also asked to enter the 4-week observational follow-up phase after early termination assessment.

Approximately 86 subjects who meet eligibility criteria for the study will be randomized in a 1:1 ratio to one of the two treatment groups. Subject randomization for treatment assignments will be stratified according to a rounded subject's palmoplantar pustular area and severity index (PPPASI) score (≤20 / 21-30 / ≥31) at randomization, and whether a subject has any focal infection (yes/no) at randomization.

The study schematic is presented below.

Figure 1: Overall Study Design



4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is PPPASI-50 at Week 16: achieving a PPPASI-50 response defined as ≥ 50% improvement in PPPASI total score from baseline at Week 16

4.2.2. Secondary Efficacy Endpoint(s)

The secondary endpoints include below.

Table 2: Secondary Efficacy Endpoints

Assessment	Description	Timeframe
PPPASI: PPPASI-50	Achieving a PPPASI-50 response	By visit in double blind, placebo-controlled phase
PPPASI: PPPASI-75	Achieving a PPPASI-75 response	By visit in double blind, placebo-controlled phase
PPPASI total score	AUC	Week 0-16
	Percent change from baseline.	By visit in double blind, placebo-controlled phase
PPSI total score	AUC	Week 0-16
	Percent change from baseline	By visit in double blind, placebo-controlled phase
PGA score for palms and soles	Change from baseline	By visit in double blind, placebo-controlled phase
	Achieving a PGA score of cleared (0) or minimal (1)	By visit in double blind, placebo-controlled phase
	Achieving a PGA score of cleared (0) or minimal (1) with at least a 2-grade improvement	By visit in double blind, placebo-controlled phase
SRO: Subject's VAS assessment for PPP symptoms	Change from baseline	By visit in double blind, placebo-controlled phase (except for baseline)

AUC = Area under the curve; PGA = Physician's Global Assessment; PPP = Palmoplantar Pustulosis; PPPASI = Palmoplantar Pustular Psoriasis Area Severity Index; PPPASI-50 = defined as ≥ 50% improvement in PPPASI total score from baseline; PPPASI-75 = defined as ≥ 75% improvement in PPPASI total score from baseline; PPSI = Palmoplantar Severity Index; SRO: Subject's Reported Outcome; VAS = Visual Analogue Scale.

4.2.3. Exploratory Efficacy Endpoint(s)

The exploratory endpoints include below.

Table 3: Exploratory Efficacy Endpoints

Assessment	Description	Timeframe
PPPASI: Three sub scores (Erythema, Pustules/Vesicle, Desquamation/Scale)	Change from baseline of individual sub scores	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up
Modified PPPASI: modified PPPASI-50	Achieving a modified PPPASI-50 response	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up
Modified PPPASI: modified PPPASI-75	Achieving a modified PPPASI-75 response	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up
Modified PPPASI total score Modified PPPASI: Two sub scores (Pustules, Vesicle)	AUC	Week 0-16
	Percent change from baseline	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up
	Change from baseline of individual sub scores	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up
SRO: Subject's assessment for each sign/finding of PPP (Erythema, Pustules/Vesicle and Desquamation/Scale) (PPSI scale is used for assessment)	Change from baseline	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up
SRO: DLQI	Change from baseline	Week 8, 16, 24 and 32
SRO: EQ-5D	Change from baseline of the utility index and VAS score	Week 8, 16, 24 and 32
PPPASI: PPPASI-50	Achieving a PPPASI-50 response	By visit in active treatment phase
PPPASI: PPPASI-75	Achieving a PPPASI-75 response	By visit in active treatment phase
PPPASI total score	Percent change from baseline	By visit in active treatment phase
PPSI total score	Percent change from baseline	By visit in active treatment phase
PGA score for palms and soles	Change from baseline	By visit in active treatment phase
	Achieving a PGA score of cleared (0) or minimal (1)	By visit in active treatment phase
	Achieving a PGA score of cleared (0) or minimal (1) with at least a 2-grade improvement	By visit in active treatment phase

Assessment	Description	Timeframe
SRO: Subject's VAS assessment for PPP symptoms	Change from baseline	By visit in active treatment phase
AUC = Area under the curve; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5 Dimension; modified PPPASI-50 = defined as ≥50% improvement of modified PPPASI total score from baseline; modified PPPASI-75 = defined as ≥75% improvement of modified PPPASI total score from baseline; PGA = Physician's Global Assessment; PPP = Palmoplantar Pustulosis; PPPASI = Palmoplantar Pustular Psoriasis Area Severity Index; PPPASI-50 = defined as ≥ 50% improvement in PPPASI total score from baseline; PPPASI-75 = defined as ≥ 75% improvement in PPPASI total score from baseline; PPSI = Palmoplantar Severity Index; SRO: Subject's Reported Outcome; VAS = Visual Analogue Scale.		

Additional exploratory endpoints include below.

- Time to response for PPPASI-50 and PPPASI-75

4.2.4. Derivation of Efficacy Endpoints

The definition and derivation of efficacy endpoints are described below and in the appendices of the protocol. Change from baseline is calculated as post-baseline visit value - the baseline value. Percent change from baseline is defined as 100*change from baseline/baseline value (%). Baseline definition for all efficacy endpoints is given in Section 5.3. Handling of time points is described in Section 5.4.

4.2.4.1. PPPASI

The PPPASI is a disease-specific efficacy assessment tool used by investigators for assessing and grading the severity and area of palmoplantar pustulosis lesions and their response to therapy. PPPASI is established to detect a change of disease status on palms or soles. The right/left palm and right/left sole are evaluated for 3 signs of the disease (erythema, pustules/vesicle and desquamation/scale) as sub-scores. PPPASI produces numeric scores that can range from 0 to 72 and a higher score indicates more severe disease.

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. Each of these areas is assessed separately for erythema, pustules and desquamation, which are each rated on a scale of 0 to 4.

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 outlined below.

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:

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)

4.2.4.1.1. PPPASI-50, 75

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

4.2.4.1.2. AUC for PPPASI total score

The AUC for PPPASI total score from baseline through a timepoint is the sum of the AUCs in each time interval specified by the dates of the visits. The individual AUC for any given time interval is calculated based on the linear trapezoidal method, which uses linear interpolation between data points to calculate the AUC. The AUC_{wk16} which is AUC from baseline (Visit 2/Day 1) through Week 16 (Visit 10/Day 113) is given by

$$\mathrm{AUC}_{\mathrm{wk16}} = \frac{113}{(t_{10} - t_2)} \times \sum_{i=2}^{10-1} \frac{1}{2}(S_i + S_{i+1})(t_{i+1} - t_i)$$

where S_i = PPPASI total score for i_{th} visit and t_i = PPPASI assessment dates of i_{th} visit. When Week 16 does not exactly coincide with the target Day 113, the AUC through Week 16 will be adjusted for the actual study duration by diving the total AUC by total study duration (in days) and multiplying this quantity by 113 days.

4.2.4.1.3. PPPASI sub-scores (Erythema, Pustules/Vesicle, Desquamation/Scale)

The PPPASI sub-score is defined the PPPASI total score including only one sub-domain (E = erythema, P = pustules/vesicle or D = desquamation /scale). For example, score of erythema as PPPASI sub-score 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)

4.2.4.2. Modified PPPASI

Modified PPPASI is an exploratory disease-specific efficacy assessment by investigators, which emphasizes on pustules and vesicles. The right/left palm and right/left sole are evaluated for 4 signs of the disease (E = erythema, P = pustules, V = vesicle and D = desquamation/scale) as sub-scores. The development of vesicles followed by pustule in palm and sole is distinctive pathophysiology in PPP. Modified PPPASI is modified from PPPASI by distinguishing between pustules and vesicle. The range of modified PPPASI score is from 0 to 96. A higher score indicates more severe disease.

The modified PPPASI formula is:

Modified PPPASI total score = (E + P + V+ D)×Area×0.2 (right palm) + (E + P + V + D)×Area×0.2 (left palm) + (E + P + V + D)×Area×0.3 (right sole) + (E + P + V + D)×Area×0.3 (left sole)

4.2.4.2.1. Modified PPPASI-50, 75

Modified PPPASI-50 and Modified PPPASI-75 are defined as ≥ 50% and ≥ 75% improvement in Modified PPPASI total score from baseline, respectively.

4.2.4.2.2. AUC for modified PPPASI total score

The AUC for modified PPPASI total score is similarly defined as the AUC for PPPASI (Section 4.2.4.1.2).

4.2.4.2.3. Modified PPPASI sub-scores (Pustules, Vesicle)

The modified PPPASI sub-score is similarly defined as the PPPASI sub-scores (Section 4.2.4.1.3). The modified PPPASI sub-score for erythema and desquamation/scale are same as the PPPASI sub-score for erythema and desquamation/scale, respectively.

4.2.4.3. PPSI

PPSI is a disease-specific efficacy assessment tool used by investigators for assessing and grading the severity of palmoplantar pustulosis lesions and their response to therapy. In the PPSI system, evaluation skin lesion sites are identified by either palms or soles, which has the most severe skin lesion at screening. Any identified skin lesion site will be assessed at all subsequent visits. Evaluation of skin lesion sites are assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4. The PPSI produces a numeric score that can range from 0 to 12. A higher score indicates more severe disease.

The severity of the disease is calculated as follows.

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 total score will be calculated by: PPSI total score= (E + P + D)

4.2.4.3.1. AUC for PPSI total score

The AUC for PPSI total score is similarly defined as the AUC for PPPASI (Section 4.2.4.1.2).

4.2.4.4. Subject's assessment for each sign/finding of PPP (Erythema, Pustules/Vesicle and Desquamation/Scale of PPSI scale)

A subject's assessment for each sign/finding on hands or feet (erythema, pustules/vesicles and desquamation/scale) are an exploratory disease-specific efficacy assessment. Worst status by a subject's own assessment between visits will be recorded. A part of PPSI assessment is used as a questionnaire. A subject will evaluate skin lesion sites which has the most severe skin lesion assessed by an investigator for evaluation of PPSI at screening. Any identified skin lesion site will be assessed at all subsequent visits.

A numeric score is produced for each sign/finding of PPP and the range is from 0 to 4 (0 = none, 1 = minimal, 2 =moderate, 3 = severe, and 4 = very severe) and the total score will be 0 to 12.

4.2.4.5. PGA for palms and soles

PGA for palms and soles is a physician's global assessment localized to palms and soles, which is skin lesions of PPP. Physician's global assessment is commonly used for assessment of the intervention. PGA for palms and soles also produces numeric score that can range from 0 to 5. A higher score indicates more severe disease.

Lesions on palms and soles will be graded based on the scales: 0 = Clear, 1 = Almost clear, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Very severe

4.2.4.6. Subject's VAS Assessment for PPP Symptom

VAS is a tool used to help a person to rate the intensity of certain sensations and feelings, such as pain. Each score ranges from 0 to 100. The left-hand boundary (0) represents no itch/pain and the right-hand boundary (100) represents itch/pain as severe as can be imagined. Subject assesses a degree of pruritus and pain as symptoms on hands and feet caused by PPP. Worst status by a subject's impression between visits will be recorded. PPP-related symptoms should be included in these assessments.

4.2.4.7. DLQI

The DLQI is a Quality of Life (QoL) questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease. The instrument contains 10 items pertaining to the subject's skin status over the last one week.

With the exception of the 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). 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 or No, score 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" (score 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.

The DLQI can be grouped into six subscales: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores indicate more severe disease and correspond to poorer quality of life.

4.2.4.8. EQ-5D

EQ-5D is a general and comprehensive QoL questionnaires which assesses the subject status on the visit day. The EQ-5D is a generic health status measure composed of a descriptive system which comprises the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each of which has 5 levels: no problems, slight problems, moderate problems, severe problems and unable, and a VAS asking individuals to rate their own health on a vertical, visual analog scale where the endpoints are labeled 'Best imaginable health state' (score of 100) and 'Worst imaginable health state' (score of 0). EQ-5D health states will be converted into a single index value by applying country specific value set (Ikeda, 2015).

4.2.5. Safety Endpoints

Safety endpoints will include:

- Treatment-emergent adverse event (TEAE): type, frequency and incidence rate, severity, and relationship of TEAEs to IP
- Clinically significant changes in body weight, vital signs, and/or laboratory findings

4.3. Stratification, Randomization, and Blinding

At Visit 2 (Week 0 [Day 1]), subjects who meet eligibility criteria will be randomized using a permuted block randomization in parallel with 1:1 ratio to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). Eligible subjects will be stratified according to a subject's rounded PPPASI score (≤20 / 21-30 / ≥31) at randomization and whether a subject has or not any focal infection (yes/no) at randomization.

This study will be conducted as a double-blind study for the placebo-controlled treatment phase. During the active treatment phase, the IP will remain blinded, to prevent study personnel and subjects from knowing the IP assignment in the placebo-controlled phase. After 16 weeks of treatment, all subjects originally randomized to the placebo arm at the baseline visit will be switched to receive apremilast 30 mg BID.

The primary data analysis will be conducted 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 analysis of the data. Prior to the primary data analysis, the selected sponsor and CRO team members will be required to give their consent to declare not to disclose any subject-level data to maintain the data integrity of this study. 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 end of the study.

4.4. Sample Size Determination

A total of approximately 86 subjects will be randomized 1:1 ratio to receive apremilast 30 mg BID or placebo. The study has 80% power (based on a chi-square test at a 2-sided significance level of 0.10) to demonstrate the superiority of apremilast 30 mg BID over placebo with respect to the primary endpoint of PPPASI-50 at Week 16, assuming the PPPASI-50 rates of 45% (apremilast 30 mg BID) and 20% (placebo), respectively. The PPPASI-50 rate of 20% at Week 16 in placebo is based on the PPPASI-50 placebo rate of 21% at Week 16 in guselkumab Phase 2 study (Terui, 2018). Considering at least 20% difference as a clinically meaningful difference, apremilast 30 mg BID PPPASI rate of 45% is expected in this study. The sample-size was estimated using SAS 9.4 power procedure.

For the skin biopsy RNA expression analysis, N=13 subjects per arm will provide 80% probability to observe the lower limit of the 90% confidence interval (CI) of a decrease of IL8 mRNA expression from baseline to Week 16 in the apremilast treated arm is over -44%, based on the mean and standard deviation (SD) change observed in a 12 weeks apremilast psoriasis study CC-10004-PSOR-004 (Gottlieb, 2013). For the serum protein biomarker analysis, N=17 subjects per arm will provide 80% probability to observe the lower limit of the 90% CI of an

absolute difference of decrease from baseline to Week 16 of IL17A levels in the apremilast arm is over 60%, based on the mean and SD change observed in the psoriasis study in Japan, CC-10004-PSOR-011 (Garcet, 2018).

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary statistics for continuous variables include sample size (n), mean, standard deviation (SD), median, minimum, and maximum, also the 25th (Q1) and 75th (Q3) percentiles may be included in summary statistics. All mean, median and percentile values will be formatted to one more decimal place than the measured value and SD values will be formatted to two more decimal places than the measured value, if applicable. Minimum and maximum values will be presented to the same number of decimal places as the measured value. Frequency summary for categorical variables includes number and percentage. All percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x%). All analysis and summary tables will have the population sample size for each treatment group in the column heading, if applicable. All p-values (2 sided) will be presented with 4 decimal places. All laboratory data will be reported using standard international (SI) units.

5.2. Study Phases and Analysis Periods

The study includes 4 phases:

1. Screening phase for up to 4 weeks (28 days)
2. Sixteen weeks, double-blind, placebo-controlled phase (apremilast 30 mg BID and placebo)
3. Sixteen weeks, active treatment phase (apremilast 30 mg BID)
   - Subjects randomized to apremilast continue apremilast treatment
   - Subjects randomized to placebo treatment switch to apremilast treatment in a blind manner
4. Four weeks post-treatment observational follow-up phase at any time the subject completes or discontinues the treatment

5.2.1. Analysis Periods

Per protocol specification, data summary and analysis will be provided for the following periods, if appropriate.

- Placebo-controlled Phase/Period

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

(1) the day of Week 16/Visit 10 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 10

(3) the last known study day if the subject is lost to follow-up prior to Week 16/Visit 10

The two treatment arms are apremilast 30 mg BID or Placebo.

- Active Treatment Phase/Period

This period starts on one day after the day of the first dose of apremilast at Week 16/Visit 10, and stops on either below.

(1) the day of Week 32/Visit 14

(2) the day of the discontinuation if the subject discontinued prior to or at Week 32/Visit 14

(3) the last known study day if the subject lost to follow-up prior to Week 32/Visit 14 during the phase

The two treatment arms are 30 mg BID/30 mg BID, and Placebo/30 mg BID.

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

- Observational Follow-up Phase/Period

Subjects who complete or discontinue the study treatment, will be followed up for 28 days after last dose of IP.

For adverse event analysis, data from the first 28 days after the last dose of IP will be included in the precedent treatment phase and data after the 28 days will be presented separately.

- Apremilast-exposure Period

This period starts on the date of either:

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

(2) the first dose of IP from the IP dispensed at Week16/Visit 10 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.

5.3. Baseline Definitions

Baseline is defined as the last value measured on or before the day of the first IP.

For efficacy analyses and summary of baseline disease characteristics, baseline is defined as the last value measured on or before the day of the first dose of IP. For the summaries of laboratory parameters, and vital signs parameters, baseline is defined as the last value measured on or before the day of the first dose of IP in the summaries for the placebo-controlled phase, 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 in the summaries for the apremilast exposure period.

5.4. Time points

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

All visit-based data, except for those with the recorded visit being a follow-up visit, will be assigned to analysis visits based on study day (the date of assessment/collection relative to the reference date) and the defined analysis visit windows as below, rather than the recorded visit. The only exception is that the data with a recorded visit being a follow-up visit will be assigned to the analysis visit corresponding to the follow-up visit.

Table 4 Table for Visit Mapping for by Time Point Analysis

Analysis Visit	Target Day	Analysis Window
Week 0 (Visit 2: Baseline)	1	≤ 1
Placebo-controlled Period		
Week 2 (Visit 3)	15	2 – 21
Week 4 (Visit 4)	29	22 – 35
Week 6 (Visit 5)	43	36 – 49
Week 8 (Visit 6)	57	50 – 63
Week 10 (Visit 7)	71	64 – 77
Week 12 (Visit 8)	85	78 – 91
Week 14 (Visit 9)	99	92 – 105
Week 16 (Visit 10)	113	106 – End of the Period
Active Treatment Period		
Week 20 (Visit 11)	141	One day after the first apremilast dosing day on Visit 10* – 154
Week 24 (Visit 12)	169	155 – 182
Week 28 (Visit 13)	197	183 – 210
Week 32 (Visit 14)	225	211 – End of the Period
* The first apremilast dosing day on Visit 10 shall be used for adverse event data		

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 post-treatment observational follow-up phase when applicable. 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:

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;

1. 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;
2. If multiple assessments are available on the same relative day, then the highest (worst) value of these assessments will be used for that relative day.

5.5. Analysis Populations

Analysis populations except for biomarker are defined as follows:

- Intent-to-Treat Population

  The intent-to-treat (ITT) population will be defined as all randomized subjects who received at least one dose of IP. Subjects will be included in the treatment group to which they are randomized.

- Safety Population

  The safety population will include all randomized subjects who received at least one dose of IP. The analysis of safety data in this study will be based on the safety population and subjects will be included in the treatment to which they actually received. Safety analyses for the apremilast-exposure period will be based on the apremilast subjects as treated population, which will include all subjects who actually receive the apremilast 30 mg BID at the randomization visit or switched (at the Week 16 visit) to the apremilast 30 BID. Subjects will be included in the treatment sequence they actually received.

- Per-Protocol Population

  The per protocol (PP) population will include all subjects in the ITT population who have no important protocol deviations that may substantially affect the efficacy results during the 16 weeks placebo-controlled treatment phase. The final determination of protocol deviation criteria to define the PP population will be made prior to the unblinding of the database and will be documented separately.

6. SUBJECT DISPOSITION

Subject disposition will be provided. The number of subjects screened, the number and percentage of subjects randomized and not randomized among all subjects screened will be summarized. The failed inclusion/exclusion criteria of subjects who were screened and not randomized will be included in the summary.

The number and percentage of subjects included in the ITT, PP, and safety analysis population and apremilast subjects as treated among all subjects randomized will be summarized.

The number of subjects who entered, and the number and percentage of subjects who completed, and discontinued of each phase will be summarized according to reasons of discontinuation.

Reasons for discontinuation will be summarized with the following categories in the eCRF:

- Adverse Event
- Lack of Efficacy
- Lost to Follow-up
- Pregnancy
- Death
- Protocol Deviation
- Study Terminated by Sponsor
- Withdrawal by Subject

A listing of subject eligibility/analysis population and a listing of subjects who discontinue the study early and reasons for discontinuation will be provided.

The number and percentage of subjects by site for ITT population will be tabulated.

7. PROTOCOL DEVIATION AND IMPORTANT PROTOCOL DEVIATION

The protocol deviations (PD) and important protocol deviations (IPD) will be identified and assessed by clinical research physician or designee. A list of PD and IPD for all subjects for Week 16 analysis will be defined prior to the Week 16 database restriction and unblinding (i.e., prior to the unblinding of double-blind placebo-controlled phase data). The list of PD and IPD for all subjects for final analysis will be finalized prior to the final DBL. This list of PD and IPD for Week 16 analysis will also identify which subjects are to be excluded from the PP population.

Summary tables showing the number and percentage of subjects with at least one PD and IPD and by each category of PD and IPD will be provided for the ITT population and subjects who entered active treatment phase. A by-subject listing of subjects with PD/IPD will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the ITT population. 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 programmatically calculated as BMI (kg/m^2) = Weight (kg)/ Height (m^2) based on the last weight measurement taken prior to the first dose of IP and the height measurement taken at screening.

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

- Age category (< 40, ≥ 40 to < 65, ≥ 65 to < 75, ≥ 75)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Collected or Unknown)
- Weight category (< 50, ≥ 50 to < 60, ≥ 60 to < 70, ≥ 70 to < 85, ≥ 85)
- BMI category (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30)
- Tobacco Use (Current User, Past User, Non-User)
- Alcohol Use (Current User, Past User, Non-User)

8.2. Baseline Characteristics

Baseline clinical characteristics indicated below will be summarized descriptively:

- Duration of Palmoplantar Pustulosis (PPP) (time [in years] from first diagnosis to the informed consent date)
- Duration of PPP category (< 2, ≥ 2 to < 6, ≥ 6 to < 10, ≥ 10 years)
- PPPASI score range based on IRT and clinical data (≤ 20, ≥ 21 to ≤ 30, ≥ 31)
- Presence of focal infection based on IRT and clinical data (Yes/Presence, No/Absence)
- History of focal infection including periapical pathosis, periodontitis, tonsillitis, and sinusitis (Yes, No)
- Presence of pustulotic arthro-osteitis (PAO) (Presence, Absence, Unknown)

- Regular dental examination status (Presence, Absence)

8.3. Medical History

A summary of medical history will be presented by MedDRA version 21.1 or higher system organ class (SOC) and preferred term (PT). A similar summary will be generated for the currently active abnormalities only, by SOC and PT.

8.4. Prior and Concomitant Medications/Procedures

Prior medications/procedures will be summarized for the ITT population. Concomitant medications/procedures will be summarized for the safety population, apremilast subjects as treated, and subjects who entered the observational follow-up phase.

8.4.1. Prior and Concomitant Medications

Prior medications 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 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 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.

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version MAR 2019 or higher) will be used to group prior and concomitant medications into relevant categories.

A frequency tabulation of the number of subjects with the different types of prior and concomitant medications will be presented. Similar summaries will be provided for the prior and concomitant medications for palmoplantar pustulosis. A subject data listing of prior and concomitant medications will be provided.

8.4.2. Prior and Concomitant Procedures

Prior procedures are defined as those started before the first dose of IP (whether or not ended before the first dose of IP). Concomitant procedures are defined similarly as concomitant medications. The MedDRA will be used for coding. Frequency summaries of prior and concomitant procedures will be provided. A subject data listing of prior and concomitant procedures will be provided.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided on the safety population and apremilast subjects as treated. Descriptive statistics will be provided for treatment duration and compliance. A subject data listing of drug administration and accountability records will be provided.

9.1. Treatment Duration

Treatment duration will be descriptively summarized. 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. Imputation rule for partially or completely missing last dose date is specified in Section 17.2.4. Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories (placebo-controlled phase: < 4, ≥ 4 to < 8, ≥ 8 to < 12, ≥ 12 to < 16, ≥ 16, active treatment phase: ≥ 16 to < 20, ≥ 20 to < 24, ≥ 24 to < 28, ≥ 28 to < 32, ≥ 32 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 10, to the last apremilast administered date for subjects who discontinue in the first 32 weeks or who complete the study at Week 32/Visit 14. Imputation rule for partially or completely missing last dose date is specified in Section 17.2.4.

9.2. Treatment Compliance

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 taken (the total number of tablets dispensed minus the total number of tablets returned minus the number of tablets lost) over the period divided by the intended total number of tablets that should have been taken over the same period.

It is assumed that from the first through the last IP administered date, 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, in case the subject visit at the planned date. 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

$$The\ intended\ total\ number\ of\ tablets = \begin{cases} 6 \times n & (when\ n < 6) \\ 30 + 2 \times (n - 5) & (when\ n \geq 6) \end{cases}$$

where n denotes the number of days between the returned date and dispensed date (ie, the date of return minus the date of dispense).

Summary statistics for compliance rate (%) will be provided. A frequency summary of compliance rate will also be presented with the following categories: < 75%, ≥ 75% to ≤ 100%, > 100% to ≤ 120% and > 120%.

10. EFFICACY ANALYSIS

The efficacy analyses will be based on the ITT population, and analyses of the primary efficacy endpoint will also be provided using the PP population. Statistical comparisons between apremilast 30 mg BID and placebo will be made for the primary endpoint. No inferential testing for statistical significance will be performed for the other endpoints. The statistical test will be two-sided at the significance level of $\alpha = 0.10$, and the corresponding p-values and two-sided confidence intervals (CIs) for point estimates will be presented. A subject data listing of efficacy data will be provided.

10.1. Multiplicity

Planned statistical test will be conducted for the primary efficacy endpoint. Secondary efficacy endpoints will be tested without multiplicity adjustment, therefore, other than the primary efficacy endpoint, nominal 2-sided p-value will be computed as a measure of the strength of the association between the endpoint and the treatment effect rather than formal tests of hypotheses.

10.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint which is achieving a PPPASI-50 response at Week 16 will be analyzed using a chi-square test at the two-sided 0.10 significant level. The two-sided 90% CI for the treatment difference of the PPPASI-50 response rate will be provided. The two-sided 95% CI will also be provided for reference. Missing values at Week 16 will be imputed using non-responder imputation (NRI) as the primary method, by which a subject without sufficient data for the response determination will be considered a non-responder. Last observation carried forward (LOCF) method imputing the last post-baseline observation to missing data at the time point under consideration will be applied as sensitivity analysis. In addition to the primary analysis using the ITT population, an analysis using the PP population will be provided.

To support the primary analysis, sensitivity analysis using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors [PPPASI total score range (≤ 20, 21-30, ≥ 31) and focal infection status (Yes, No)] will be conducted. The two-sided p-values (nominal) 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.

10.3. Analyses of Secondary and Exploratory Efficacy Endpoints

The secondary efficacy endpoints will be tested without multiplicity adjustment, therefore, both secondary and exploratory endpoints analyses are described in this section.

10.3.1. Binary Variables

The binary variables for secondary and exploratory endpoints include:

Subjects achieving a

- PPPASI-50 response
- PPPASI-75 response

- PGA score of cleared (0) or minimal (1)
- PGA score of cleared (0) or minimal (1) with at least a 2-grade improvement
- Modified PPPASI-50 response
- Modified PPPASI-75 response

For these binary endpoints, proportion at each visit will be displayed along with 95% CIs. The treatment difference between apremilast 30 mg BID and placebo will be compared using difference in proportions and CMH test adjusting for the stratification factor. The two-sided p-values (nominal) 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. The two-sided 95% CI based on the Clopper-Pearson method will be provided for un-adjusted difference. Missing values will be imputed using NRI. For the exploratory purpose, LOCF will be applied to the data of the placebo-controlled phase.

10.3.2. Continuous Variables

The continuous variables for secondary and exploratory endpoints in placebo-controlled phase include the following:

- AUC for PPPASI total score from baseline through Week 16
- PPPASI total score change from baseline at Week 16
- AUC for PPSI total score from baseline through Week 16
- PPSI total score change from baseline at Week 16
- AUC for modified PPPASI total score from baseline through Week 16
- Modified PPPASI total score change from baseline at Week 16
- Subject's assessment for PPP sign/finding (PPSI total score) at Week 16

The analysis of covariance (ANCOVA) model with treatment and stratification factor as the fixed effects, the associated baseline value as the covariate and multiple imputation (MI) method to impute the missing data will be applied. Within-group least-squares (LS) means, the associated standard error (SE), and treatment differences in LS means, the associated SE, and associated 2-sided 95% CIs and 2-sided p-values (nominal) will be derived from the model.

Missing value of at Week 16 will be imputed using the MI method (SAS Institute Inc. 2015) except for AUC. The SAS procedure MI will be used to impute missing scores to create M=100 complete data sets. The missing data patterns will be checked by treatment at baseline, and Week 2, 4, 6, 8, 10, 12, 14, and 16. If there are non-monotone missing patterns, following two separate imputation procedures will be used to complete the imputation process.

1. In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing scores by treatment to create M=100 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 at random, 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.

2. In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 100 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with a random seed. The missing values at each visit will be imputed based on treatment 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 100 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

Following continuous variables for secondary and exploratory endpoints will be summarized by time point. Change and percent change from baseline will be provided. The mixed-effect model for repeated measures (MMRM) will be applied for the endpoints; PPPASI and modified PPPASI, PPSI, and subject's VAS assessment for PPP symptoms. The MMRM model will use the change from baseline as the response variable and include treatment group, visit time, treatment-by-time interaction, and stratification factor as fixed effects, and the baseline value as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements. Within-group LS means and the associated SEs and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values (nominal) will be derived from the MMRM model.

- PPPASI total score
- Individual PPPASI sub-score (Erythema, Pustules/Vesicle, Desquamation/Scale) change and percent change from baseline at each visit
- PPSI total score
- Subject’s VAS assessment for PPP symptoms
- Modified PPPASI total score
- Modified PPPASI sub-score (Pustules, Vesicle)
- Subject’s assessment for PPP sign/finding (PPSI total score)
- DLQI
- EQ-5D index value
- EQ-5D VAS

Analyses of time to PPPASI response during the placebo-controlled phase will use Kaplan-Meier method to estimate the median response time and its 2-sided 95% CIs. The stratified log-rank test will be used for calculating 2-sided p-values (nominal) for treatment comparison. The hazard ratio and 2-sided 95% CIs will be estimated using a stratified Cox model. For the time to PPPASI response, the baseline score will be included as covariate in the Cox model. The treatment comparison will only be conducted if appropriate. Kaplan-Meier curves for time to event endpoints will be provided.

10.3.3. Categorical Variables

A shift table from baseline to applicable analysis visits will be provided for the categorical variables including PPSI score, PGA score for palms and soles, and subject's assessment for PPP Sign/Finding using PPSI score.

10.4. Subgroup Analysis

Subgroup analyses for comparisons of subjects achieving PPPASI-50 at Week 16 between apremilast 30 mg BID and placebo, based upon following classification variables will be provided to determine whether the treatment effect is consistent across various subgroups. The categorical groups of each subgroup may be pooled based on the number of observations available.

- Age category (< 40, ≥ 40 to < 65, ≥ 65 to < 75, ≥ 75)
- Sex (Male, Female)
- BMI category (< 25, ≥ 25 to < 30, ≥ 30)
- Tobacco Use (Current/Past User, Non-User)
- Duration of PPP category (< 2, ≥ 2 to < 6, ≥ 6 to < 10, ≥ 10 years)
- PPPASI score range at randomization from clinical data (≤ 20, ≥ 21 to ≤ 30, ≥ 31)
- Presence of focal infection at randomization from clinical data (Yes, No)
- History of focal infection (Yes, No)
- Presence of pustulotic arthro-osteitis (PAO) (Yes, No)
- Prior Disease-modifying antirheumatic drugs (DMARDs) (Yes, No)

The consistency of the treatment effect will be assessed in the context of the primary efficacy analysis model with terms for treatment, stratum, and the covariate. Treatment effects and nominal 95% confidence intervals by category for the classification variables listed above will be provided. Formal statistical testing of these interactions will not be performed.

11. SAFETY ANALYSIS

Safety analyses will be performed using the safety population. The safety analyses for the placebo-controlled phase 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).

For safety analyses in the placebo-controlled phase, baseline will be relative to the first dose date following randomization at Week 0. For safety analyses in apremilast-exposure period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the active treatment phase (Weeks 16 to 32).

Unless otherwise specified, the analyses of AEs and marked abnormalities (laboratory parameters and vital signs) for both the placebo-controlled phase and apremilast-exposure period will include the subject incidence rate. To account for the different exposure to the IP, the exposure-adjusted incidence rate will also be presented.

- Subject incidence: Subject incidence (i.e., percentage [%] used in a frequency summary) is defined as the number of subjects with the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific phase or analysis period will be counted only once in the numerator. If a subject experiences multiple AEs under the same preferred term (system organ class), then the subject will be counted only once for that preferred term (system organ class).
- 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 phase or analysis period will be counted only once in the numerator. 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. 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 IP.

For safety analysis, no inferential testing for statistical significance will be performed.

Individual subject listings will be provided for all safety data obtained.

As necessity requires, additional safety information may be provided.

11.1. 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 first dose of IP through 28 days after the last dose of IP or study treatment discontinuation date, whichever is later. All AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification

system version 21.1 or higher. Unless otherwise specified, AEs will be summarized by system organ class (SOC) and preferred term (PT), with SOCs presented in the standard international order and PTs within SOCs will be presented in descending order of subject incidence.

A treatment-related TEAE is defined as TEAE which was suspected to be related to the study drugs.

AEs and marked abnormalities will be summarized by subject incidence and EAIR for the placebo-controlled phase (Weeks 0 to16) and for the Apremilast-exposure period. In addition, selected summaries for the active treatment phase (Weeks 16 to 32) and the observational follow-up phase (4 weeks) will be presented.

An overall summary of the following AE categories will be provided.

- TEAE
- TEAE related to study drug
- Severe TEAE
- Serious TEAE
- Serious TEAE Related to Study Drug
- TEAE leading to dose reduction
- TEAE leading to drug interruption
- TEAE leading to drug withdrawal
- TEAE leading to death

In addition, for apremilast-exposure period overall summary of TEAEs will also be provided.

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

- All TEAEs
- Most frequent TEAEs (subject incidence ≥ 5% or another cut-off if justified)
- Treatment-related TEAEs
- TEAEs by maximum severity
- Serious TEAEs and treatment-related serious TEAEs
- TEAE leading to dose reduction
- TEAE leading to drug interruption
- TEAE leading to drug withdrawal
- TEAE leading to death
- First onset and new events of TEAE by exposure interval
  - placebo controlled phase (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 ≤ 24, > 24 to ≤ 32, > 32

- TEAE for the subgroups in Section 10.4

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 treatment duration 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. For the summary of the first onset of TEAE by exposure interval, only the first onset of specific TEAE is considered for each subject.

Listings for the corresponding summary tables will be presented separately. A listing including non-treatment-emergent AEs will be provided.

11.2. Adverse Events of Special Interest

The following TEAEs of special interest will be summarized:

- Depression: MedDRA narrow scope sub-SMQ of Depression (excluding suicide and self-injury)
- Serious infection: MedDRA primary PTs from the SOC of Infections and infestations. Only the events that were assessed as serious
- Risk of Triggering Suicide: MedDRA narrow scope SMQ of Suicide/self-injury

The following summaries will be provided for TEAEs included in the above-mentioned AEs of interest:

- All TEAEs;
- Severe TEAEs;
- Serious TEAEs;
- TEAEs leading to treatment discontinuation;
- TEAEs leading to dose reduction/interruption;
- TEAEs leading to death.

11.3. Clinical Laboratory Evaluations

The endpoints for clinical laboratory evaluations include:

- Laboratory marked abnormalities
- Observed value and change from baseline over time in the following selected laboratory parameters
  - Hematology: platelets, hemoglobin, leukocytes, neutrophils, segmented, lymphocytes

- Serum chemistry: hemoglobin A1C, magnesium, sodium, potassium, total bilirubin, glucose, lactate dehydrogenase, calcium, albumin, creatinine, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, urate, phosphate, triglycerides, cholesterol

- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal (low and/or high) in the above hematology and serum chemistry parameters

Summary statistics of observed values and changes from baseline in laboratory parameters 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.

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. 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.

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

11.4. Vital Sign Measurements

Vital sign measurements, including weight, will be summarized descriptively by visit. In addition, shift tables summarizing the baseline categories (normal, abnormal) versus the category at the end of the respective periods or versus the worst post-baseline category and including subjects who have values at baseline and at least one post-baseline value will be provided. Similarly, in frequency summaries of shifts from baseline at scheduled study weeks per protocol, only subjects who have values at baseline and at the time point will be included. The change from baseline for each of the vital signs including weight will be summarized. A subject data listing of all vital signs and weight data will be provided.

11.5. Physical Examination

A subject data listing of general physical examination will be provided.

12. ANALYSIS FOR COVID-19 IMPACT

The following summary and listing to assess impact of Coronavirus Disease 2019 (COVID-19) will be provided.

- Summary tables showing the number and percentage of subjects with at least one PD and IPD related to COVID-19 and by each category of PD and IPD
- A listing of PD and IPD related to COVID-19
- A listing of treatment-emergent AE related to COVID-19

[redacted]

13.2. Definition of Baseline

Baseline is defined as the value from a sample collected from that subject at the Week 0 randomization visit, prior to dosing of apremilast or placebo.

13.3. Baseline Demographic and Disease Background Characteristics

Subject disposition will be provided. Demographic and baseline characteristics will be summarized descriptively by treatment group (placebo and apremilast 30 mg BID) for the [redacted], based on the subjects' randomization assignments. No formal statistical tests will be performed to assess the comparability of the treatment groups at baseline. Descriptive statistics will be provided for the following demographic variables at baseline: age, age category, sex, race, ethnicity, weight and weight category, height, body mass index (BMI), BMI category, and alcohol and tobacco use.

Descriptive statistics will be provided for the following disease background variables at baseline: duration and duration category of PPP; PPPASI total score, PPSI total score, PGA score for palms and soles; prior use of immunosuppressants, colchicines, oral corticosteroids, topical corticosteroids, biologics, non-steroidal anti-inflammatory drugs (NSAIDs), and other analgesics/anesthetics.

[redacted]

14. INTERIM ANALYSIS

No interim analysis is planned prior to the analysis of the primary efficacy endpoint at Week 16.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

No changes to the statistical analyses section of the protocol are made in this SAP.

16. REFERENCES

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17. APPENDICES

17.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Section 17.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, response etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression) or an assessment date. They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

17.1.1. Calculation Using Dates

Calculations using dates (*eg*, subject's age or relative day after the first dose of IP) 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.

Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period. 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 (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
  - Preference is for using calculated age from clinical database. When not available, calculated age from CRF or IVRS may be used
  - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- 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

17.2. Date Imputation Guideline

17.2.1. 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 in the same dataset. 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, ie, occurring on or after the date of the first dose of IP, if possible.

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

Table 5: 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)		

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

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 IP, 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 IP: 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 filed 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 IP but prior to the date of the first dose of apremilast following Week 16: impute it by the date of the first dose of IP, 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 IP as "$D_{IP}/M_{IP}/Y_{IP}$", 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 6: 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	$Y_{Event} < Y_{IP}$	$12/31/Y_{Event}$
2	$Y_{Event} > Y_{APR}$	$1/1/Y_{Event}$

Scenario	Condition	Imputation Rule
3	$Y_{Event} = Y_{APR}$	Date of first dose of apremilast following the early escape
4	Otherwise, ie, $Y_{IP} \leq Y_{Event} < Y_{APR}$	Max (date of first dose of IP, $1/1/Y_{Event}$)
Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{IP}$, or ($Y_{Event} = Y_{IP}$ and $M_{Event} < M_{IP}$)	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 the early escape
4	Otherwise, ie, $Y_{IP} < Y_{Event} < Y_{APR}$, or ($Y_{IP} = Y_{Event} < Y_{APR}$ and $M_{IP} \leq M_{Event}$), or ($Y_{IP} = Y_{Event} = Y_{APR}$ and $M_{IP} \leq M_{Event} < M_{APR}$), or ($Y_{IP} < Y_{Event} = Y_{APR}$ and $M_{Event} < M_{APR}$)	Max (date of first dose of IP, $1/M_{Event}/Y_{Event}$)

17.2.2. 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.

- **Incomplete Start Date:**

  Missing day and month

  If the year is

  - the same as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
  - prior to the year of first dosing date, then December 31 will be assigned to the missing fields.
  - after the year of first dosing, then January 1 will be assigned to the missing fields.

  Missing day only

  - If the month and year are the same as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
  - If either the year of the partial date is before the year of the first dosing date, or the year of the partial date and the first dosing date are the same but the month of partial date is before the month of the first dosing date, then the last day of the month will be assigned to the missing day.
  - If either the year of the partial date is after the year of the first dosing date, or the years of the partial date and the first dosing date are the same but the month of partial date is after the month of the first dosing date, then the first day of the month will be assigned to the missing day.

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed.

- **Incomplete Stop Date:** If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is after the year of the last dosing date, then January 1st will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is not equal to the year of the last dosing date or the year of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then that last day of the month will be assigned to the missing day.

17.2.3. 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 Palmoplantar Pustulosis). 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. If the above imputation inappropriately results in a diagnosis date on or after the informed consent date, then the incomplete date will be assigned to the day prior to the informed consent date.

17.2.4. 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 discontinuation 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 discontinuation visit date)

Last known date in database is defined as maximum of (last visit date, lab, vital signs, ECG assessment date, 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).

17.3. Laboratory Marked Abnormalities Criteria

Table 7: Laboratory Marked Abnormalities Criteria

Category	Analyte	Units	Criteria
Chemistry	Hemoglobin A1C	%	> 6.5
	Magnesium	mmol/L	> 1.2
	Sodium	mmol/L	>150, <130
	Potassium	mmol/L	>5.5, <3.0
	Total Bilirubin	umol/L	>1.8×ULN
	Glucose	mmol/L	>13.9, <2.8
	Lactate Dehydrogenase	U/L	> 2xULN
	Calcium	mmol/L	>3.0, <1.8
	Albumin	g/L	<25
	Creatinine	umol/L	>1.5×ULN
	Alanine Aminotransferase	U/L	>3.0×ULN
	Alkaline Phosphatase	U/L	>400
	Aspartate Aminotransferase	U/L	>3.0×ULN
	Blood Urea Nitrogen	mmol/L	> 24
	Urate	umol/L	> 480
	Phosphate	mmol/L	>1.60, <0.64
	Triglycerides	mmol/L	> 3.4
	Cholesterol	mmol/L	> 7.8
Hematology	Platelets	10^9/L	>600, <75
	Hemoglobin	g/L	>150, <110
	Leukocytes	10^9/L	< 2.0
	Neutrophils, Segmented	10^9/L	< 1.5
	Lymphocytes	10^9/L	<0.8

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