Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ADaM	Analysis Data Model
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance (model)
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical-Therapeutic-Chemical
BID	Twice Daily
BMI	Body Mass Index
BSA	Body Surface Area (%) Affected by Psoriasis
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Corona Virus Disease 2019
CRO	Contract Research Organization
CRP	Clinical Research Physician
CSR	Clinical Study Report
DAO	Data As Observed
DLQI	Dermatological Life Quality Index
EAIR	Exposure-adjusted incidence rate
ET	Early Termination
EU	Europe
GPI-NRS	Genital Psoriasis Itch Numeric Rating Scale
GPSS	Genital Psoriasis Symptoms Scale
GSO-DM	Global Study Operations-Data Management
HRQoL	Health-Related Quality of Life
IL	Interleukin
IP	Investigational Product

IPD	Important Protocol Deviation
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LS Mean	Least Squares Mean
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
[redacted]	
PK	Pharmacokinetic
PP	Per-Protocol (population)
PsA	Psoriatic arthritis
PT	Preferred Term
REML	Restricted Maximum Likelihood
[redacted]	
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	Standard International (unit)
sPGA	static Physician Global Assessment
sPGA-G	static Physician Global Assessment of Genitalia
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal

USA	United States of America
WHODD	World Health Organization Drug Dictionary

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 amendment 3 for study 20200063, AMG407 dated 03 Mar 2021. The scope of this plan includes the primary analysis and final analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

The SAP will be finalized and signed prior to the unblinding of the Week 16 database. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the clinical efficacy of oral apremilast 30 mg twice daily (BID), compared to placebo, in subjects with moderate to severe genital psoriasis during the 16-week Placebo-controlled Phase.	• Modified static Physician Global Assessment of Genitalia (sPGA-G) 0/1 : Proportion of subjects with a modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
Secondary	
• To evaluate the safety and tolerability of apremilast 30 mg BID, compared with placebo, in subjects with moderate to severe genital psoriasis during the 16-week Placebo-controlled Phase.	• static Physician Global Assessment (sPGA) 0/1: Proportion of subjects achieving an overall sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
• To evaluate the effect of apremilast 30 mg BID compared with placebo on genital psoriasis symptoms during the 16-week Placebo-controlled Phase.	• Genital Psoriasis Itch Numeric Rating Scale (GPI-NRS): Proportion of subjects with at least a 4-point improvement in GPI-NRS item score within the Genital Psoriasis Symptoms Scale (GPSS) for subjects with a baseline score of ≥ 4 at Week 16 • BSA: Change from baseline in affected BSA at Week 16 • GPSS: Change from baseline in GPSS total score and individual items scores at Week 16

• To evaluate the effect of apremilast 30 mg BID compared with placebo on Health-related Quality of Life (HRQoL) during the 16-week Placebo-controlled Phase.	• Dermatology Life Quality Index (DLQI): Change from baseline in DLQI total score at Week 16

Exploratory
[redacted]

[redacted]

2.2 Hypotheses and/or Estimations

The primary hypothesis for this study is: Apremilast monotherapy is superior to placebo in subjects with moderate to severe genital psoriasis as measured by proportion of subjects with a modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16.

H_0: the difference in proportion of subjects who achieved a modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16 in apremilast and in that of placebo = 0.

H_1: the difference in proportion of subjects who achieved a modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16 in apremilast and in that of placebo ≠ 0.

3. Study Overview

3.1 Study Design

This Phase 3 multicenter, randomized, placebo-controlled, double-blind study is designed to evaluate the efficacy and safety of apremilast over 32 weeks of treatment in approximately 286 subjects with moderate to severe genital psoriasis (modified sPGA-G ≥ 3, moderate or severe). Subjects will be randomized 1:1 based on a permuted block randomization using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline psoriasis-involved body surface area (BSA) (< 10% or ≥ 10%). No more than 60% of subjects with BSA < 10% will be enrolled.

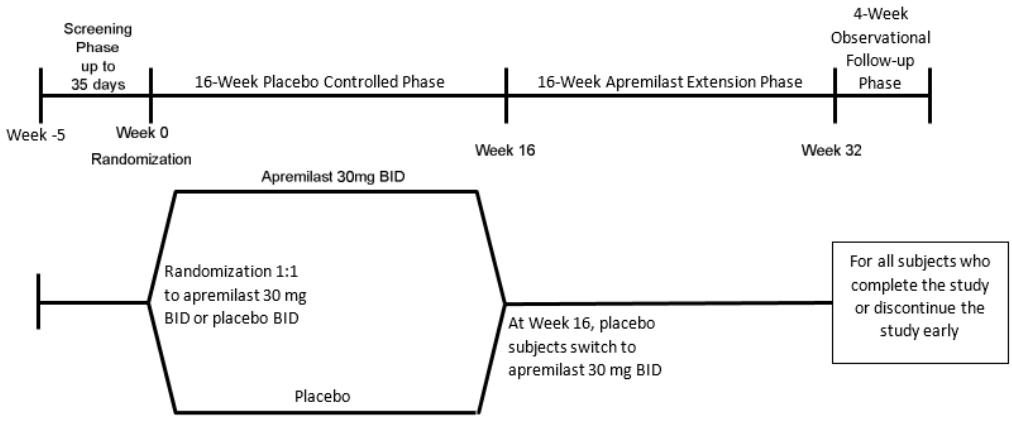
- Subjects randomized to the apremilast 30 mg BID treatment group will receive apremilast 30 mg tablets orally twice daily for the first 16 weeks
- Subjects randomized to the placebo treatment group will receive placebo tablets (identical in appearance to apremilast 30 mg tablets) orally twice daily for the first 16 weeks
- All subjects will receive apremilast 30 mg tablets orally twice daily after the Week 16 Visit through the end of the Apremilast Extension Phase of the study

The study will consist of four phases (Figure 1):

1. Screening Phase – up to 35 days
2. Double-blind Placebo-controlled Phase – Weeks 0 to 16
    - Subjects will be randomly assigned in a 1:1 ratio to either apremilast 30 mg BID or placebo.
3. Apremilast Extension Phase – Weeks 16 to 32
    - All subjects will be switched to (or continue with) apremilast 30 mg BID. All subjects will maintain this dosing through Week 32.
4. Observational Follow-up Phase – 4 weeks
    - Four-week Post-Treatment Observational Follow-up Phase for all subjects who complete the study or discontinue the study early

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed; the primary data analysis will be conducted. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the regulatory submission activities. 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 conclusion of the study.

Figure 1. Study Design



3.2 Sample Size

[redacted] It is assumed that modified sPGA-G response will be similar to historic sPGA response. With a total of approximately 286 subjects and a randomization ratio of 1:1, this study will randomize approximately 143 subjects to the apremilast 30 BID group and 143 subjects to the placebo group. This sample size will provide 85% power to detect a minimum treatment difference of 15% at Week 16 (25% for apremilast 30 BID and 10% for placebo) for the primary endpoint using a chi-square test at a 2-sided significance level of 0.05 after adjusting for a 20% dropout rate. The sample size calculation was done using nQuery.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Covariates includes but not be limited to baseline value for each measured endpoint.

4.2 Subgroups

Subgroup analysis will be carried out for modified sPGA-G response at Week 16 based upon baseline demographics and disease characteristics. Summary and analysis will be based on ITT population and missing values will be imputed using MI method.

The following subgroup variables will be used:

- Baseline BSA (%) category (<10%, ≥10%)
- Baseline modified sPGA-G score (moderate [3] or severe [4])
- Sex (Male, Female)
- Race (White, Non-white)
- Age category (<65 years, ≥ 65 years)
- Alcohol usage (Yes, No)
- Tobacco usage (Current user, Past user, Never used)
- Geographical region (USA/Canada, EU)
- Baseline weight category (< 50, ≥ 50 to < 60, ≥ 60 to < 70, ≥ 70 to < 85, ≥ 85 kg)

- Baseline BMI category (< 18.5, ≥ 18.5 to < 25, ≥25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, ≥ 40 kg/ m2)
- Duration of genital psoriasis categories (<2, ≥2 to <5, ≥5 to < 10, ≥ 10 to < 20, ≥ 20 years)
- Prior conventional systemic therapies (Used or Never used)
- Prior phototherapies (Used or Never used)
- Prior biologic therapy (Used or Never used)

5. Definitions

5.1 Derivations of Efficacy Endpoints

5.1.1 Modified static Physician Global Assessment of Genitalia (sPGA-G)

The modified sPGA-G is the assessment by the investigator of the subject's psoriasis lesions' overall disease severity in the genital area at the time of evaluation. The modified sPGA-G is a 5-point scale ranging from clear (0), almost clear (1), mild (2), moderate (3), to severe (4), incorporating an assessment of the severity of the three primary signs of the disease: erythema, plaque elevation, and scaling. It is not necessary that all three criteria be fulfilled. The modified sPGA-G is based on a combination of erythema and the secondary features (plaque elevation and/or scale).

The modified sPGA-G response at a post-baseline visit is defined as achieving modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline.

5.1.2 Static Physician Global Assessment (sPGA)

The sPGA is the assessment of whole body psoriasis by the investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from clear (0), almost clear (1), mild (2), moderate (3), to severe (4), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation.

The sPGA response at a post-baseline visit is defined as achieving sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline.

5.1.3 Genital Psoriasis Symptoms Scale (GPSS)

The GPSS is a patient-administered assessment of eight symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Numeric

rating scales (NRS) are used to assess the self-reported overall severity of each of the eight symptoms individually in the genital area on an 11-point horizontal scale anchored at 0 (no) and 10 (worst imaginable). The overall severity for each individual symptom from patient's genital psoriasis is indicated by selecting the number from 0 to 10 that best describes the worst level of each symptom in the genital area in the past 24 hours. Each of the eight individual items will receive a score of 0 to 10 and will be reported as item scores for itch, pain, discomfort, stinging, burning, redness, scaling, and cracking.

In addition, a total score ranging from 0 (no genital psoriasis symptoms) to 80 (worst imaginable genital psoriasis symptoms) will be reported.

5.1.4 Genital Psoriasis Itch Numeric Rating Scale (GPI-NRS)

The GPI-NRS is one of eight components of the validated GPSS which was developed to assess symptoms that are particularly burdensome to subjects with genital psoriasis. Patient self-reported severity score of itch in the genital area on an 11-point horizontal scale anchored at 0 (no) and 10 (worst imaginable) will be reported.

For a post baseline visit, the GPI-NRS response is defined as ≥ 4 points reduction (improvement) from baseline in the GPI-NRS score for subjects with baseline score of ≥ 4. Change from baseline in the GPI-NRS score will also be derived.

5.1.5 Body Surface Area (BSA)

BSA is a measurement of involved skin over the whole body. The overall BSA affected by psoriasis is estimated based on the palm area of the subject’s hand. The surface area of the whole body is made up of approximately 100 palms or “handprints” (each entire palmar surface or “handprint” equates to approximately 1% of total body surface area).

BSA scores will be presented with one digit after the decimal point. For post-baseline visits, BSA score change and percent change from baseline will be derived. BSA score percent change will be rounded to integers.

5.1.6 Dermatology Life Quality Index (DLQI)

The DLQI was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease. The instrument contains 10 items dealing with the subject’s skin. With the exception of Item Number 7, the subject responds on a four-point scale, ranging from “Very Much” (score 3) to “Not at All” or “Not relevant” (score 0). Item Number 7 is a multi-part item, the first part of which ascertains whether the subject’s skin prevented them from working or studying (Yes or No, scores 3 or 0 respectively), and if “No,” then the subject is asked

how much of a problem the skin has been at work or study over the past week, with response alternatives being “A lot,” “A little,” or “Not at all” (scores 2, 1, or 0 respectively). The DLQI total score is derived by summing all item scores, which has a possible range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best.

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

DLQI total score and change from baseline will be derived.

5.2 Derivations of Safety Endpoints

Baseline definition for all safety endpoints is given in Section 5.4. Change from baseline is calculated as post-baseline visit value minus the baseline value. Handling of time points is described in Section 5.5.

5.2.1 Treatment-emergent Adverse Event

An AE is a treatment-emergent AE (TEAE) if the AE start date is

- On or after the date of the first dose of IP and no later than 28 days after the last dose of IP for subjects who have completed study treatment or have discontinued early by the time of database cut, or
- On or after the date of the first dose of IP for subjects who are ongoing with study treatment at the time of database cut.

If the treatment-emergent status of an AE is unclear due to a missing/incomplete start date, it will always be considered treatment-emergent, unless shown otherwise by data. Date imputation rules for missing AE start dates are described in section 8.3.2.

Adverse event started more than 28 days after the last dose of IP will not be considered as a treatment-emergent AE.

5.2.2 Treatment-emergent Adverse Event Leading to Drug Withdrawal, Drug Interruption, or Death, and Drug-related Treatment-emergent Adverse Event

A TEAE leading to drug withdrawal is a TEAE for which the investigator indicates that the action taken with respect to IP is withdrawn permanently. A TEAE leading to drug interruption is a TEAE for which the investigator indicates that the action taken with respect to IP is interrupted. A TEAE leading to death is a TEAE for which the outcome is

fatal. Relationship to IP is based on the investigator's causality judgment; that is, a drug-related AE is an AE indicated by the investigator to have a suspected relationship to IP.

5.2.3 Vital Signs and Weight

Vital signs and weight endpoints include:

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

5.2.4 Clinical Laboratory Evaluations

Laboratory evaluations include:

- Observed value and change from baseline over time in hematology and serum chemistry parameters
- Laboratory marked abnormalities and by baseline laboratory category will be analyzed for selected analytes (Appendix B).
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal (low or high) in hematology and serum chemistry parameters

[redacted]

5.4 Baseline Definitions

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

For safety analyses in the Placebo-controlled Phase, baseline will be relative to the first dose date following randomization at Week 0. It is the last value measured prior to or on the day of the first dose of IP.

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 Extension Phase. It is the last value measured prior to or at the first apremilast dose date.

5.5 Time Points

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

6. Analysis Sets

6.1 Intent-to Treat Analysis Set

The intent-to-treat (ITT) analysis set will consist of all subjects who are randomized regardless of whether the subject received IP. Subjects will be included in the treatment group to which they are randomized.

6.1.1 Primary Analysis Set

The primary analysis set is the intent-to-treat analysis set, and will be based on week 16 database.

6.2 Safety Analysis Set

The safety analysis set will consist of all subjects who are randomized and received at least one dose of investigational product (IP). Subjects will be included in the treatment group corresponding to the IP they actually received (apremilast or placebo) for the analyses and summaries using the safety analysis set.

6.3 Per Protocol Set(s)

The per protocol (PP) analysis set will consist of all subjects included in the ITT analysis set who receive at least one dose of IP, have both baseline and at least one post-baseline modified sPGA-G assessment, and have no important protocol deviations which may affect efficacy assessments in the Placebo-controlled Phase.

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not applicable.

[redacted]

Not applicable.

6.6 Interim Analyses Set(s)

Not applicable.

6.7 Study-specific Analysis Sets

Not applicable.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis will be conducted.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed, the primary data analysis will be conducted. However, unblinded data will only be made available to selected Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the regulatory submission activities. 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 conclusion of the study. At the end of the study, after all subjects have completed or have been discontinued from the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final analysis will be performed, and a final Clinical Study Report will be generated.

7.2 Primary Analysis

The primary analysis will be performed after all subjects have had the opportunity to complete the week 16 visit.

The primary analysis will present data from the completed placebo-controlled phase of the study, including the primary, secondary, and exploratory endpoints, and safety results at week 16. In addition, the primary analysis will present cumulative safety data up to the report's data cutoff date for the active treatment phase, including exposure from both the completed placebo-controlled phase and the ongoing active treatment phase.

7.3 Final Analysis

The final analysis will occur after all subjects have had the opportunity to complete the study (ie, completion of the observational follow-up phase or discontinued the study).

The scope of the final analysis is the evaluation of the remaining efficacy data and final safety data.

7.4 Analysis Phases/Period

For efficacy analysis, different phases will be used; For safety analysis, Placebo-controlled Phase and Apremilast-exposure Period will be used.

7.4.1 Analysis Phases

Per protocol specification, data summary and analysis will be provided for the following phases:

7.4.1.1 Placebo-controlled Phase – Weeks 0 to 16

This phase starts on the day of randomization (Week 0/Visit 2), and stops on either: (1) the day the first IP for the next phase is dispensed at Week 16/Visit 7; or (2) the day of the discontinuation visit if the subject discontinued prior to or at Week 16/Visit 7; or (3) the last known study day if the subject is lost to follow-up prior to Week 16/Visit 7 during the phase.

For safety analysis in subjects who continued treatment in Apremilast Extension Phase (Weeks 16 to 32), the phase stopped one day prior to the first dose date in Apremilast Extension Phase.

For analysis of adverse events, TEAEs in the phase including those with start date at the first IP dose date through either: (1) one day prior to the first IP dose date in Apremilast Extension Phase (Weeks 16 to 32); or (2) 28 days after the last IP dose date for subjects who discontinue after only receiving treatment in the Placebo-controlled Phase.

For safety analysis of visit-based data (ie, laboratory parameters, vital signs, etc), the post-baseline data in the phase including those with assessments dates after the first IP dose date (exclusive) and through either: (1) the first IP dose date (inclusive) in Apremilast Extension Phase (Weeks 16 to 32); or (2) the last visit date within 28 days of the last IP dose date (prior to the first Follow-up Visit) for subjects who discontinue after only receiving treatment in the Placebo-controlled Phase.

At the time of the Week 16 analysis, if the date of the first IP dose date in Apremilast Extension Phase is not available in data base and the subject has not discontinued, the first IP dispensing date will be used instead.

7.4.1.2 Apremilast Extension Phase – Weeks 16 to 32

This phase starts on the day after the first IP is dispensed for the phase at Week 16/Visit 7, and stops on either: (1) the day of Week 32/Visit 10; or (2) the day of the discontinuation visit if the subject discontinued prior to or at Week 32/Visit 10; or (3) the last known study day if the subject is lost to follow-up prior to Week 32/Visit 10 during the phase.

For safety analysis, the phase started at the first dose date in the phase and ended at the last dose date.

For analysis of adverse events, TEAEs in the phase including those starts at the first IP dose date in the phase through 28 days after the last IP dose date for subjects who completed or discontinued treatment in the phase.

For safety analysis of visit-based data (ie, laboratory parameters, vital signs, etc), data in the phase starts at the first IP dose date (exclusive) and stops on the last visit date within 28 days of the last IP dose date (prior to the first Follow-up visit).

7.4.1.3 Observational Follow-up Phase – 4 weeks

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

TEAEs in the Follow-up Phase will include adverse events started after and within 28 days of the last dose date. Those TEAEs will also be summarized in one of the two treatment phases.

7.4.2 Apremilast-exposure Period for Safety Analysis

This period starts on the date of either: (1) the first dose of IP following randomization (Week 0/Visit 2) for subjects who are treated with apremilast from Week 0; or (2) the first dose of IP from the IP dispensed at Week16/Visit 7 for subjects who were originally treated with placebo and are treated with apremilast at Week 16.

This period stops on either: (1) 28 days after the last IP dose date for subjects completed or discontinued treatment from the study; or (2) data cut-off date for ongoing subjects.

7.5 Treatment arms

In general, the treatment arms used in the analyses and summaries in each phase are described below in this section unless otherwise specified.

7.5.1.1 Placebo-controlled Phase (Weeks 0 to 16)

- Placebo
- Apremilast 30 mg BID
- Total (optional, not for the efficacy analysis)

7.5.1.2 Apremilast Extension Phase (Weeks 16 to 32)

Subjects who entered the extension phase will be included in analysis, ie, who were initially randomized to apremilast and continued at Week 16 and who were initially randomized to placebo and switched to apremilast at Week 16.

- Placebo/30 mg BID
- 30 mg BID/30 mg BID

7.5.1.3 Apremilast-exposure Period

Subjects who are treated with at least one dose of apremilast will be included here, which includes all subjects who are randomized to (at Week 0/Visit 2) or switched to (at Week 16/Visit 7) apremilast, and receive at least one dose of apremilast after randomization or Week 16.

- 30 mg BID as Treated

7.5.1.4 Observational Follow-up Phase (4 weeks)

For subjects who entered Follow-up Phase from Placebo-controlled Phase, summaries will be provided by their initial treatment arm:

- Placebo
- 30 mg BID

For subjects who entered Follow-up Phase from Apremilast Extension Phase, summaries will be provided by their treatment sequence:

- Placebo/30 mg BID
- 30 mg BID/30 mg BID

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. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

8.3.1 Efficacy endpoints

Missing data handling methods applied to the analysis for each efficacy endpoints is summarized as below:

Table 1. Summary of missing data handling method applied to the analysis for each efficacy endpoint

Analysis Set [a]	Week	Endpoint	Imputation Method [b]
ITT, PP	0-16	Modified sPGA-G response	MI, NRI, DAO
ITT	0-16	sPGA response	MI, NRI, DAO
ITT	0-16	GPI-NRS response	MI, NRI, DAO
ITT	0-16	BSA change and percent change from baseline	MMRM
ITT	0-16	DLQI change from baseline	MMRM
ITT	0-16	GPSS total score change from baseline	MMRM
ITT	0-16	GPSS individual items scores change from baseline	MMRM
ITT	0-16	DLQI-Q#9 change from baseline	MMRM
ITT (Subjects entered extension phase)	16-32	sPGA-G response, sPGA response, GPI-NRS response	NRI, DAO
ITT (Subjects entered extension phase)	16-32	BSA change and percent change from baseline, DLQI change from baseline, GPSS total score change from baseline, GPSS individual items scores change from baseline, GPI-NRS change from baseline, DLQI-Q#9 change from baseline	DAO

Note: MI = Multiple Imputation; NRI = Non-responder imputation; DAO = Data as Observed; MMRM= Mixed-effect model for repeated measures
[a] See Section 6
[b] See Section 9.5

8.3.2 Partially Missing Date Imputation for 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, i.e., 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 2. Imputation Rules for Partially Missing AE Start Dates for Subjects Who Were Treated with Apremilast Initially

Scenario	Condition	Imputation Rule
Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{IP}$	$12/31/Y_{Event}$
2	Otherwise, i.e., $Y_{IP} \leq Y_{Event}$	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, i.e., $Y_{IP} < Y_{Event}$, 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 field of the date);

3. The partially missing AE start date is in the same year (if both month and day are missing), or the same year/month (if only day is missing) of the first dose of apremilast following Week 16: impute it by the date of the first dose of apremilast;

4. The partially missing AE start date suggests the date is no earlier than the date of the first dose of 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 3. 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	$Y_{Event} > Y_{APR}$	$1/1/Y_{Event}$
3	$Y_{Event} = Y_{APR}$	Date of first dose of apremilast following Week 16
4	Otherwise, i.e., $Y_{IP} \le Y_{Event} < Y_{APR}$	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 Week 16
4	Otherwise, i.e., $Y_{IP} < Y_{Event} < Y_{APR}$, or ($Y_{IP} = Y_{Event} < Y_{APR}$ and $M_{IP} \le M_{Event}$), or ($Y_{IP} = Y_{Event} = Y_{APR}$ and $M_{IP} \le M_{Event} < M_{APR}$), or ($Y_{IP} < Y_{Event} = Y_{APR}$ and $M_{Event} < M_{APR}$)	Max (date of first dose of IP, $1/M_{Event}/Y_{Event}$)

8.3.3 Prior Concomitant Medications/Procedures

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

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

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

8.3.4 Medical History

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

8.3.5 Treatment Duration

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

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

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

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

8.4 Detection of Bias

This study has been designed to minimize potential bias by the use of 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 final database lock and formal unblinding

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed.

Additional sensitivity analyses may be included to assess the impact of potential biases on the primary endpoint. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

8.5 Outliers

Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

8.6 Distributional Characteristics

Distributional assumptions for the primary and secondary endpoints will be assessed If the assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

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 later.

9. Statistical Methods of Analysis

9.1 General Considerations

9.1.1 General Approaches to Efficacy Analysis

The intent-to-treat principle will be used in statistical analyses for efficacy endpoints. For the Placebo-controlled Phase (Weeks 0-16), efficacy evaluations will be conducted using the intent-to-treat (ITT) analysis set defined as all randomized subjects. Statistical comparisons will be made between the two treatment arms (placebo or apremilast). For the Apremilast Extension Phase (Weeks 16-32), efficacy evaluations will be conducted using subjects who entered the phase from both treatment arms.

Descriptive statistics (n, mean, SD, SE, median, Q1, Q3, min, max) will be presented for appropriate endpoints at specified time points. Specifically, for continuous variables, descriptive statistics for assessment values and change (plus percentage change when specified) from baseline will be provided. Binary variables will be summarized with frequency tabulations; shift tables will be provided when appropriate.

Statistical comparisons will be made between placebo arm and apremilast arm; the null hypothesis is that the effects of the two treatment arms (i.e., placebo vs. apremilast) have no difference. Statistical tests will be at the two-sided 0.05 significance level and the corresponding p-values and two-sided 95% confidence intervals will be reported.

Baseline definition for all efficacy endpoints is given in Section 5.4. Change from baseline is calculated as post-baseline visit value minus the baseline value. Percent change from baseline is defined as 100* Change from baseline/Baseline value (%). Handling of time points is described in Section 5.5.

In the event that any site errors are made in specifying the stratification factor (baseline BSA <10% or BSA ≥10%) for randomization, the classification of the stratification factor in all efficacy analyses will be based on the actual classification according to the clinical database.

In the data as observed (DAO) analyses, only subjects with sufficient data at the time point under consideration will be included.

9.1.2 Multiplicity Adjustment

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

- Proportion of subjects with modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects achieving an overall sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects with at least a 4-point improvement in GPI-NRS item score within the GPSS for subjects with a baseline score of ≥ 4 at Week 16
- Change from baseline in affected BSA at Week 16
- Change from baseline in DLQI total score at Week 16
- Change from baseline in GPSS total score and individual items scores at Week 16

9.2 Subject Accountability

The number of subjects screened, randomized, receiving IP, and completing the study will be summarized. Key study dates for the first subject enrolled, last subject enrolled and last subject's end of study will be presented.

Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation.

The number and percent of subjects randomized will be tabulated by the stratification factor.

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

prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

Protocol deviations and important protocol deviations will be categorized by the Clinical Research Physician (CRP). A list of protocol deviations and important protocol deviations for all subjects for week 16 analysis will be defined prior to the Week 16 data restriction and unblinding (i.e., prior to the unblinding of double-blind placebo-controlled phase data). The list of protocol deviations and important protocol deviations for all subjects for final analysis will be finalized prior to the final database lock. This listing of important protocol deviations for week 16 analysis will also identify which subjects are to be excluded from the per-protocol population.

Protocol deviations and important protocol deviations by treatment group and overall will be provided for the placebo-controlled phase for the ITT analysis set, and for the Apremilast extension phase for subjects who receive at least one dose of IP during the phase. Summary tables showing the number and percent of subjects with at least one protocol deviation and important protocol deviations and by each category of protocol deviations and important protocol deviations will be provided. Listings of subjects with protocol deviations and important protocol deviations will also be provided.

Additionally, protocol deviations and important protocol deviations related to COVID-19 will be summarized.

9.4 Demographic and Baseline Characteristics

Summaries for the demographics, baseline characteristics, prior medication/procedure, and concomitant medications/procedure will be presented for the ITT analysis set by treatment group and overall. Subject data listings will also be provided.

9.4.1 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)

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

- Sex (Male, Female)
- Age category (< 65, ≥ 65 years; < 40, ≥ 40 to < 65, ≥ 65 to < 75, ≥ 75 to < 85, ≥ 85 years)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Not Collected or Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Baseline weight category (< 50, ≥ 50 to < 60, ≥ 60 to < 70, ≥ 70 to < 85, ≥ 85 kg)
- Baseline BMI category (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30 to <35, ≥ 35 to < 40, ≥ 40 kg/m^2)
- Geographical region (USA/Canada, EU)
- Alcohol usage (Yes, No)
- Tobacco usage (Current user, Past user, Never used)

9.4.2 Baseline or Disease Characteristics

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

- Duration of genital psoriasis (from date of diagnosis to the date of informed consent; year, presented one digit after the decimal point)
- Duration of genital psoriasis categories (<2, ≥2 to <5, ≥5 to < 10, ≥ 10 to < 20, ≥ 20 years)
- Baseline modified sPGA-G score: Moderate (3), Severe (4)
- Baseline sPGA score: Moderate (3), Severe (4)
- Baseline psoriatic involved BSA (%)
- Baseline BSA (%) category (<10%, ≥10%)
- Baseline DLQI total score
- Number of prior phototherapies
- Number of failed prior phototherapies for subjects who had prior phototherapies
- Number of prior conventional systemic therapies

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

9.4.3 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher. A frequency summary (counts and percentage) of medical history will be presented by treatment group, system organ class (SOC), and preferred term (PT).

9.4.4 Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher. Frequency summaries of prior and concomitant procedures will be provided for the safety population by treatment group, SOC, and PT.

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 will be summarized for (1) Placebo-controlled Phase (Weeks 0 to16), (2) Apremilast Extension Phase (Weeks 16 to 32), and (3) Observational Follow-up Phase (4 weeks). The concomitant procedures will be similarly analyzed as concomitant medications in the next section.

9.4.5 Prior and Concomitant Medications

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version March 2020 or higher) will be used to group prior and concomitant medications and prior psoriasis medications into relevant categories. Frequency summaries will be provided by treatment group, ATC 2 level, and standardized medication name for the safety population.

Prior medications are defined as those started before the first dose of IP (whether or not ended before the first dose of IP). Prior medications that continue after the first dose of IP will also be reported as concomitant medications.

Prior psoriasis medications will be classified as phototherapies, biologic therapies, conventional systemic therapies, or systemic therapies through manual review by Clinical Research Physician (CRP).

For each of the treatment phases, concomitant mediations are defined as non-study medications started during the phase, or non-study medications started before the phase and ended or remained ongoing during the phase. The treatment phase for concomitant medications will start on the first dose date and end one day prior to the last dose date.

Medications in the Follow-up Phase will include those medications started from the date of last dose of investigational product.

Summaries will be provided for prior psoriasis medications and prior medications, as well as for concomitant medications in: (1) Placebo-controlled Phase (Weeks 0 to16), (2) Apremilast Extension Phase (Weeks 16 to 32), and (3) Observational Follow-up Phase (4 weeks).

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)

The primary endpoint is the proportions of subjects who achieve modified sPGA-G response at Week 16 (defined as modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16). The main analysis for the primary efficacy endpoint will be based on the ITT analysis set. A sensitivity analysis using the PP analysis set will also be performed.

The primary endpoint will be analyzed using the CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization. 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.

Missing values at Week 16 for this endpoint will be imputed using the multiple imputation (MI) method (SAS Institute Inc. 2011) based on similar subjects who remained in the study as the primary method. The SAS procedure MI will be used to impute missing modified sPGA-G scores at the scheduled analysis visits in the Placebo-controlled Phase (Weeks 0-16) to create M=50 complete data sets. The missing data patterns will be checked at the scheduled analysis visits, ie, Baseline (Week 0), and Weeks 2, 4, 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 with a single chain to impute missing scores by treatment and stratification factor to create M=50 imputed data sets with monotone missing patterns. 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. The seed will be set to 17813721. The imputed scores will be rounded to the nearest integer. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest modified sPGA-G scores.

In the second step, the predictive mean matching method will be used to impute the remaining missing scores for the 50 data sets with monotone missing patterns. The imputation procedure will use monotone statement to create one complete data set for each of the monotone data set from the first step, and the variables will include treatment arm, stratification factor, and modified sPGA-G scores at scheduled analysis visits from baseline to Week 16. The seed will be set to 55218163. The number of closest observations to be used in the selection will be set to 2.

After the completion of imputation, the modified sPGA-G response at Week 16 will be derived based on both observed and imputed scores. The same CMH method 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.

Shift table for shifts from baseline to post-baseline visits and End of Phase will be provided by treatment and time point for sPGA-G score.

Additional sensitivity analysis will be conducted to account for missing data using the non-responder imputation (NRI) method and the tipping point analyses.

For the tipping point analyses, let M1 and M2 be the total number of subjects with missing data of primary endpoint in Apremilast and Placebo. There are overall (M1 + 1)*(M2 +1) possible ways for imputing missing data as responders or non-responders in statistical analysis, ranging from imputing all missing values as non-responders to imputing all missing values as responders in each of the two arms. For each of the (M1 + 1)*(M2 +1) different imputation patterns, the Chi-square test will be used for testing statistical significance and the output can be plotted in a rectangle for inspection. The

staircase region that separates significant and non-significant outcomes forms the tipping-point boundary.

9.5.1.1 Assessing Study Site Effect

The primary endpoint will be assessed for site effect.

This study is a multicenter study and planned to have approximately 50 sites to enroll and randomize 286 subjects. A single site may not have sufficient number of subjects to allow meaningful within-site analysis of treatment effects stratified by baseline BSA category; therefore, study sites effect will be assessed by pooling sites on geographic basis to help interpret the results.

In pooling sites for analysis, the minimum cell size of 5 randomized subjects per treatment arm (placebo arm or apremilast arm) per stratum of baseline BSA (%) category (< 10% or ≥ 10%) will be used. The pooling strategy is described as follows: 1) Sites will be pooled within each region (USA/Canada or EU) according to their rank based on site-specific sample size, starting with the smallest sites; i.e., within a region, the smallest sites will first be pooled until the pooled site has a minimum cell size of 5 for each of the four cells. 2) The remaining un-pooled sites will then be pooled within the region with the smallest pooled site. 3) In the rare case that all site pooled together in a region does not satisfying the above condition (a minimum cell size of 5 for each of the four cells), all sites in the region will be pooled together with the smallest pooled site of the other region.

Sites will be pooled together as described above in order to assess the site effect and site by treatment interaction on the primary efficacy endpoint.

For the pooled sites, summary and analyses will be based on ITT analysis set using MI imputation for missing values. Study site effect will be assessed for the primary endpoint by stratifying the analysis based on pooled site in addition to the stratification factor at randomization and examining whether the treatment differences adjusted for both stratification factor and pooled site are consistent with those from the primary analysis.

In addition, the consistency of the treatment effect across individual study sites (or pooled sites) will be assessed by performing a subgroup-type analysis with respect to the endpoints, with individual study sites (or pooled sites) treated as subgroups. Listings of response rates will be provided by individual study site and by pooled site. The treatment difference for each of the individual study sites (or pooled sites) will be reviewed to determine the effect among the individual study sites (or pooled sites).

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The main analysis for the secondary efficacy endpoints will be based on the ITT analysis set. The two-sided p-values and two-sided 95% confidence intervals (CIs) will be reported for treatment difference between placebo arm and apremilast arm. Details for multiplicity adjustment are described in Section 9.1.2.

9.5.2.1 Binary Variables

The binary variables for secondary endpoints include the following:

- Proportion of subjects achieving an overall sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects with at least a 4-point improvement in GPI-NRS item score within the GPSS for subjects with a baseline score of ≥ 4 at Week 16

For these binary endpoints, the treatment difference between apremilast arm and placebo arm will be compared using CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization. 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. Missing values will be imputed using the similar MI method as the primary endpoint, with sensitivity analysis using the NRI method.

9.5.2.2 Continuous Variables

The continuous variables for secondary endpoints include the following:

- Change from baseline in affected BSA at Week 16
- Change from baseline in DLQI total score at Week 16
- Change from baseline in GPSS total score and individual items scores at Week 16

The continuous efficacy endpoints will be analyzed based on the ITT analysis set using a mixed-effect model for repeated measures (MMRM) as the primary method. 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. The Kenward-Roger adjustment will be used with restricted maximum likelihood (REML) to make proper

statistical inference. Within-group least-squares (LS) means and the associated SEs and 2-sided 95% CIs, treatment difference in LS means and the associated SEs and 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model for Week 16 and other scheduled visits (Week 2, 4, 8, and 12, if applicable) in the model.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Safety will be assessed via descriptive statistics. Unless otherwise specified, all safety analyses described in this section will be performed for both the Placebo-controlled Phase and the Apremilast-exposure Period. The safety analyses for the Placebo-controlled Phase will be based on the safety population and presented by treatment group (placebo arm or apremilast arm), 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 the analyses of AEs and lab marked abnormalities, the following endpoints will also be summarized:

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

AEs and lab marked abnormalities will be summarized by subject incidence and EAIR for the Placebo-controlled Phase (Weeks 0 to 16) and for the Apremilast-exposure Period. In addition, selected summaries for the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase (4 weeks) may be presented if deemed necessary.

Descriptive statistics will be provided for vital signs, weight, height and BMI, laboratory values (continuous measurements) by treatment and visit, including the end of treatment visits. The baseline value, value at the time point, and change from baseline will be summarized for subjects who have values at baseline and at the time point.

Shift tables, that is, tables that summarize the baseline categories (normal, abnormal) versus the category at the end of the respective periods or versus the worst post-

baseline category, include subjects who have values at baseline and at least one post-baseline value. Similarly, in frequency summaries of shifts from baseline at scheduled study weeks per protocol, only subjects who have values at baseline and at the time point will be included.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher will be used to code all events categorized as adverse events to a system organ class and a preferred term with SOCs presented in the standard international order and PTs within SOCs will be presented in descending order of subject incidence.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, drug-related treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation of investigational product, fatal adverse events and adverse events of interest.

9.6.2.1 Overall Summary of TEAEs

An overall summary of the following TEAE categories will be provided for the Placebo-controlled Phase (Weeks 0 to 16) for subjects with:

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

In addition, for Apremilast Exposure Period overall summary of TEAEs will also be provided.

9.6.2.2 All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast-exposure Period.

New events of all TEAEs by exposure interval (≤ 1, > 1 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, and > 12 Weeks) will be summarized for the Placebo-controlled Phase. 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.

In addition, new events of all TEAEs by exposure interval (≤ 1, > 1 to ≤ 8, > 8 to ≤ 16, > 16 to ≤ 24, > 24 to ≤ 32, > 32 Weeks) will be summarized for the Apremilast-exposure Period.

All TEAEs will be summarized by age category (< 65, ≥ 65 years), sex, race and, if deemed necessary, by prior/concomitant psoriasis medication usage or baseline disease characteristics.

9.6.2.3 Common TEAEs

TEAEs with subject incidence ≥ 5% (or another cut-off if justified) in any treatment group will be summarized by SOC and PT as well as by PT only in descending order of subject incidence.

9.6.2.4 Drug-related TEAEs

Drug-related TEAEs will be summarized and new events of drug-related TEAEs by exposure interval will be summarized.

9.6.2.5 TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing). If a subject reports multiple occurrence of a specific event within a specific analysis phase or period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all the occurrences, the subject will be counted only once in the “missing” category of severity.

9.6.2.6 Serious TEAEs

Serious TEAEs and serious drug-related TEAEs will be summarized.

New events of serious TEAEs and serious drug-related TEAEs by exposure interval will be summarized for Placebo-controlled Phase (Weeks 0 to 16).

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

A subject data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

9.6.2.7 TEAEs Leading to Drug Interruption and Drug Withdrawal

TEAEs leading to drug interruption and TEAEs leading to drug withdrawal will be summarized.

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

A subject data listing of TEAEs leading to drug withdrawal will be provided.

9.6.2.8 Deaths

TEAEs leading to death will be summarized. A subject data listing of all deaths will be provided.

9.6.2.9 Adverse Events of Special Interests

Summary tables and listings may be provided for the AESIs if deemed necessary.

9.6.3 Laboratory Test Results

The endpoints for clinical laboratory evaluations include:

- Laboratory marked abnormalities
- Observed value and change from baseline over time in the following laboratory parameters including but not limited to
  - Complete blood count: red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count
  - Serum chemistry: total protein, albumin, calcium, phosphorous, glucose, total cholesterol [TC], triglycerides, high-density lipoprotein [HDL], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST; serum glutamic-oxaloacetic transaminase, SGOT], alanine aminotransferase [ALT; serum glutamic pyruvic transaminase, SGPT], sodium, potassium, chloride, bicarbonate [carbon dioxide, CO_2], blood urea nitrogen, creatinine, lactate dehydrogenase [LDH], and magnesium
  - Dipstick urinalysis: specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen

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

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.

9.6.4 Vital Signs

The endpoints for vital signs include:

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

Summary statistics of observed values and changes from baseline in vital signs will be provided over time. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal will be provided for pulse and blood pressure.

9.6.5 Physical Measurements

The endpoints for physical measurements are Observed value, change and percent change from baseline over time in weight. Summary statistics of will be provided over time. Frequency summaries of change and percent change in weight from baseline to the end of the period will be provided by baseline BMI category (< 25, ≥ 25 to < 30, ≥ 30 to < 35, ≥35 to < 40, and ≥40 kg/) and by baseline weight category (< 70, ≥ 70 to < 85, ≥85 to < 100, and ≥100 kg). The categories of weight change (kg) and percent change (%) are < -20, ≥-20 to < -10, ≥-10 to < -5, ≥-5 to < 0, 0, > 0 to ≤ 5, > 5 to ≤ 10, > 10 to ≤ 20, and > 20. The end-of-period or end-of-phase value is the last post-baseline value in the analysis period or phase (excluding the value obtained at the follow-up visit, if applicable) up to 28 days after the last dose of IP in the study.

9.6.6 Electrocardiogram

Not applicable.

9.6.7 Antibody Formation

Not applicable.

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. Compliance to each IP will also be summarized.

The treatment compliance (in %) for each subject will be computed as 100 times the total number of tablets taken (the total number of tablets dispensed minus the total number of tablets returned) over the analysis phase or period divided by the intended total number of tablets that should have been taken over the same phase or period.

Summary statistics for compliance (%) will be provided by treatment arm for each analysis phase or period. Frequency summary tables of compliance will also be presented with the following categories: < 75%, ≥ 75% - ≤120%, and > 120%. A subject data listing of drug accountability records will be provided.

9.6.9 Exposure to Non-investigational Product

Not applicable.

9.6.10 Exposure to Other Protocol-required Therapy

Not applicable.

9.6.11 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

9.7 Other Analyses

9.7.1 Analyses of COVID-19 impacted data

Analyses will be performed to assess the impact of COVID-19 on the amount of data collected for the study. These analyses include:

- Number and percent of subjects who are discontinued treatment/study due to COVID-19
- Number and percent of subjects with important protocol deviations and protocol deviations related to COVID-19
- Analysis of the primary endpoint and key secondary endpoints excluding COVID-19 impacted subject data

- Number and percent of subject study participation impacted by COVID-19 along with the listing
- Listing of subject efficacy related assessment impacted by COVID-19

Listing of subject safety related assessment impacted by COVID-19

[redacted]

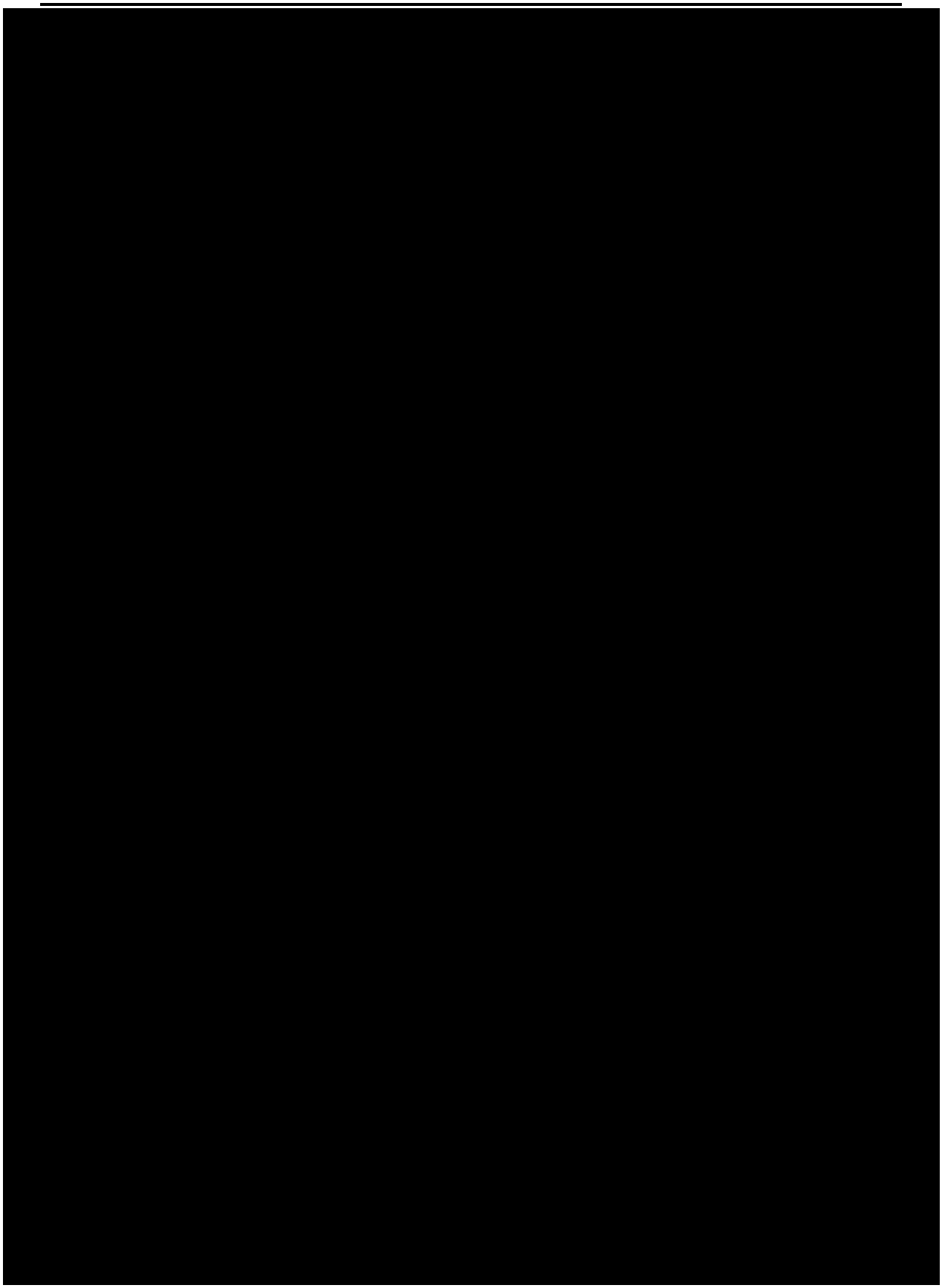
9.7.3 Analyses of Clinical Outcome Assessments

Not applicable.

9.7.4 Analyses of Health Economic Endpoints

Not applicable.

[redacted]



9.7.6 Analyses of COVID-19 impacted data

Analyses will be performed to assess the impact of COVID-19 on the amount of data collected for the study. These analyses include:

- Number and percent of subjects who are discontinued treatment/study due to COVID-19
- Number and percent of subjects with important protocol deviations and protocol deviations related to COVID-19
- Analysis of the primary endpoint and key secondary endpoints excluding COVID-19 impacted subject data
- Number and percent of subject study participation impacted by COVID-19 along with the listing
- Listing of subject efficacy related assessment impacted by COVID-19
- Listing of subject safety related assessment impacted by COVID-19

10. Changes From Protocol-specified Analyses

During the initial development of this document, it was realized that there are protocol-specified analyses that cannot be implemented/performed and the protocol is not required to be amended. The following change(s) have been made to the statistical section of the protocol:

- The last observation carried forward (LOCF) method to impute the missing data as sensitivity analysis of efficacy is removed.

These changes will also be documented in the Clinical Study Report.

11. Literature Citations / References

Cather J, Meeuwis K, Burge R, Bleakman AP, Lin CY, Ryan C. Ixekizumab provides greater improvement versus placebo on the impact of genital psoriasis on sexual activity for patients with moderate-to-severe genital psoriasis in a randomized, double-blind phase 3b clinical trial. Presented at: American Academy of Dermatology Annual Meeting; February 16-20, 2018; San Diego, CA.

Gottlieb A, Kirby B, Ryan C, Naegeli A, Burge R, Potts Bleakman A, et al. The development of a patient-reported outcome measure for assessment of genital psoriasis symptoms: The Genital Psoriasis Symptoms Scale (GPSS). Dermatol Ther (Heidelb). 2018; 8(1):45-56. Merola JF, Bleakman AP, Gottlieb AB, Menter A, Naegeli AN, Bissonnette R, et al. The static physician's global assessment of genitalia: a clinical outcome measure for the severity of genital psoriasis. J Drugs Dermatol. 2017; 16(8):793-799.

Ryan C, Menter A, Guenther L, Blauvelt A, Bissonnette R, Yang FE, et al. Efficacy and Safety of Ixekizumab in a randomized, double-blinded, placebo-controlled, Phase 3b clinical trial in patients with moderate to severe genital psoriasis. Presented at the European Academy of Dermatology and Venereal Disease: September 13-17, 2017; Geneva, Switzerland.

Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health 2005; 8 Suppl 1: S9-S24.

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

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

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

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

LaVange LM and Permutt T for the Missing Data Working Group. A regulatory perspective on missing data in the aftermath of the NRC report. Statist. Med., 2016; 35(17):2853–2864.

Permutt T. Missing Data Working Group. Sensitivity analysis for missing data in regulatory submissions. Statist. Med., 2016; 35(17): 2876–2879.

12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Not applicable.

14. Appendices

Appendix A. Analytical Windows

Post baseline time points in all analyses will be captured based on analysis visit window (range of study days) around the target day for each analysis visit, based on the actual day of evaluation relative to a reference date. Appropriate dates will be used to calculate the study day, e.g., date of measurement or date of specimen collection will first be used, and then the date of visits/study weeks as recorded in the database will be used.

Table 4. Table for Visit Mapping for by Time Point Analysis

Analysis Visit	Target Day	Visit Window (Days)
Week 0 (Baseline)	1	≤ 1
Placebo-controlled Phase		
Week 2	15	2 – 21
Week 4	29	22 – 42
Week 8	57	43 – 70
Week 12	85	71 – 98
Week 16	113	99 – End of Phase
Apremilast Extension Phase		
Week 20	141	Start of Phase – 154
Week 24	169	155 – 196
Week 32	225	197 – End of Phase

Note: Target day and visit window are relative to the date of Visit 2/Week 0 (Day 1) randomization date. For efficacy and safety analysis, definitions for start or end dates for a phase or period are specified in Section 3.1 and Baselines are specified in Section 5.4 . For endpoints that do not have week 12 assessment, the visit window for week 8 will be 43 – 98 (Days).

Time points in the analyses or summaries of efficacy data over time include the scheduled study weeks per protocol, the end of a study phase, and the observational follow-up visit when applicable. Appropriate dates (e.g., date of measurement or date of specimen collection) will first be used to ensure only data (including data from scheduled, unscheduled, discontinuation, and observational follow-up visits) measured or collected within the specific analysis phase (as defined in Section 3.1) being analyzed or summarized are included, and then the visits/study weeks as recorded in the database will be used to assign one value (possibly missing) to each time point at the

subject level. It is possible that multiple assessment values will fall into the same visit window. The following rule may be used to select the unique value for that analysis visit:

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

For the Apremilast-exposure Period, the study weeks relative to the first dose of apremilast (according to the baseline definition) for placebo subjects who are treated with apremilast 30 mg BID starting at Week 16/Visit 7 are shown below for summaries of safety data (laboratory parameters, vital signs, etc) over time.

Table 5. Analysis Visit for Placebo Subjects Who Are Treated with Apremilast 30 mg BID after Week 16 in the Apremilast-exposure Period

Original Visit	Analysis Visit for subjects initially randomized to placebo
Week 16	Week 0 (Baseline)
Week 20	Week 4
Week 24	Week 8
Week 32	Week 16

Data collected in the observational Follow-up Phase will be summarized separately when applicable.

Appendix B. Laboratory Marked Abnormalities Criteria

Category / Analyte	SI Units	Criteria
Chemistry/ Alanine Aminotransferase (SGPT)	U/L	> 2*ULN
Albumin	Kg/m3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 2*ULN
Total Bilirubin	µmol/L	> 2*ULN
Total Bilirubin and Alanine Aminotransferase /Aspartate Aminotransferase	µmol/L and U/L	Bilirubin Value > 2xULN with (ALT or AST value > 2xULN)
Blood Urea Nitrogen	mmol/L	> 24
Calcium	mmol/L	< 1.8 > 3.0
Cholesterol	mmol/L	> 7.8
Creatinine	µmol/L	> 1.5*ULN
Glucose	mmol/L	< 2.8 > 13.9
Hemoglobin A1C	%	> 6.5
Lactate Dehydrogenase (LDH)	U/L	> 2*ULN
Magnesium	mmol/L	> 1.2
Phosphate	mmol/L	<1.03 >1.94
Potassium	mmol/L	<3.0 >5.4
Sodium	mmol/L	<132 >147
Triglycerides	mmol/L	> 3.4
Urate	umol/L	Male: > 480 Female: > 480
Hematology/ Hemoglobin	g/L	Female <110, Male <110 Female >150, Male >150
Leukocytes	10^9/L	< 2.0
Lymphocytes	10^9/L	< 1.0
Neutrophils	10^9/L	< 1.5
Platelets	10^9/L	<100 >500