

DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-10004-SPSO-001

A PHASE 3, MULTI-CENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS OF THE SCALP

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STATISTICAL ANALYSIS PLAN

A PHASE 3, MULTI-CENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS OF THE SCALP

INVESTIGATIONAL PRODUCT (IP):	Apremilast (CC-10004)
PROTOCOL NUMBER:	CC-10004-SPSO-001
DATE FINAL:	29 Mar 2017

Prepared by:

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STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	Statistical Analysis Plan for a Phase 3, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Apremilast (CC-10004) in Subjects with Moderate To Severe Plaque Psoriasis of the Scalp
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INVESTIGATIONAL PRODUCT	Apremilast (CC-10004)
PROTOCOL NUMBER	CC-10004-SPSO-001
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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse Event
ANCOVA	Analysis of Covariance (model)
ATC	Anatomical-Therapeutic-Chemical
BID	Twice Daily
BMI	Body Mass Index
CCI	[REDACTED]
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF or eCRF	(electronic) Case Report Form
CRO	Contract Research Organization
CRP	Clinical Research Physician
DLQI	Dermatology Life Quality Index
FCBP	Female of Childbearing Potential
CCI	[REDACTED]
[REDACTED]	[REDACTED]
HRQoL	Health-Related Quality of Life
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
LS Mean	Least Square Mean
CCI	[REDACTED]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NRI	Non-responder Imputation

NRS	Numeric Rating Scale
CCI	[REDACTED]
CCI	[REDACTED]
PP	Per-Protocol (population)
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ScPGA	Scalp Physician Global Assessment
SD or STDEV	Standard Deviation
SE	Standard Error
SI	Standard International (unit)
CCI	[REDACTED]
SOC	System Organ Class
CCI	[REDACTED]
TEAE	Treatment-emergent Adverse Event
CCI	[REDACTED]
US	United States
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-10004-SPSO-001, "A Phase 3, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Apremilast (CC-10004) in Subjects with Moderate to Severe Plaque Psoriasis of the Scalp".

An interim analysis is not planned. After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 data restriction will be performed, the primary data analysis will be conducted **CCI** [REDACTED]. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data **CCI** [REDACTED] **CCI** [REDACTED]. 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 data base lock and analysis will be performed and a final Clinical Study Report will be generated.

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This SAP provides a more technical and detailed elaboration of the statistical analyses as outlined and/or specified in the study protocol final version dated 29 Mar 2017 and final version of Amendment 1 dated 30 Nov 2017. 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 the responsibility of the Biostatistics & Programming department of **CCI** [REDACTED] and will be conducted using SAS® Version 9.3 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the clinical efficacy of apremilast 30 mg twice daily (BID) compared with placebo, in subjects with moderate to severe plaque psoriasis of the scalp, at Week 16

3.2. Secondary Objectives

The secondary objectives are:

- To evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo, in subjects with moderate to severe plaque psoriasis of the scalp
- To evaluate the effect of apremilast 30 mg BID compared with placebo on itch over the whole body caused by plaque psoriasis
- To evaluate the effect of apremilast 30 mg BID compared with placebo on itch associated with plaque psoriasis of the scalp
- To evaluate the onset of effect on itch over the whole body caused by plaque psoriasis with apremilast 30 mg BID compared with placebo
- To evaluate the onset of effect on itch associated with plaque psoriasis of the scalp with apremilast 30 mg BID compared with placebo
- To evaluate the effect of apremilast 30 mg BID compared with placebo on health-related quality of life (HRQoL)

3.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the effect of apremilast 30 mg BID compared to placebo on Dermatological Life Quality Index (DLQI)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, multicenter, randomized, placebo-controlled, double-blind study of the efficacy and safety of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis of the scalp.

Approximately 300 subjects with moderate to severe plaque psoriasis of the scalp will be randomized 2:1 to receive either apremilast 30 mg BID or placebo for the first 16 weeks. Randomization will be stratified by baseline Scalp Physician Global Assessment (ScPGA) score (moderate [3], severe [4]) to ensure balance between treatment arms with respect to baseline severity of scalp psoriasis.

- 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:

- Screening Phase – up to 35 days
- Double-blind Placebo-controlled Phase – Weeks 0 to 16

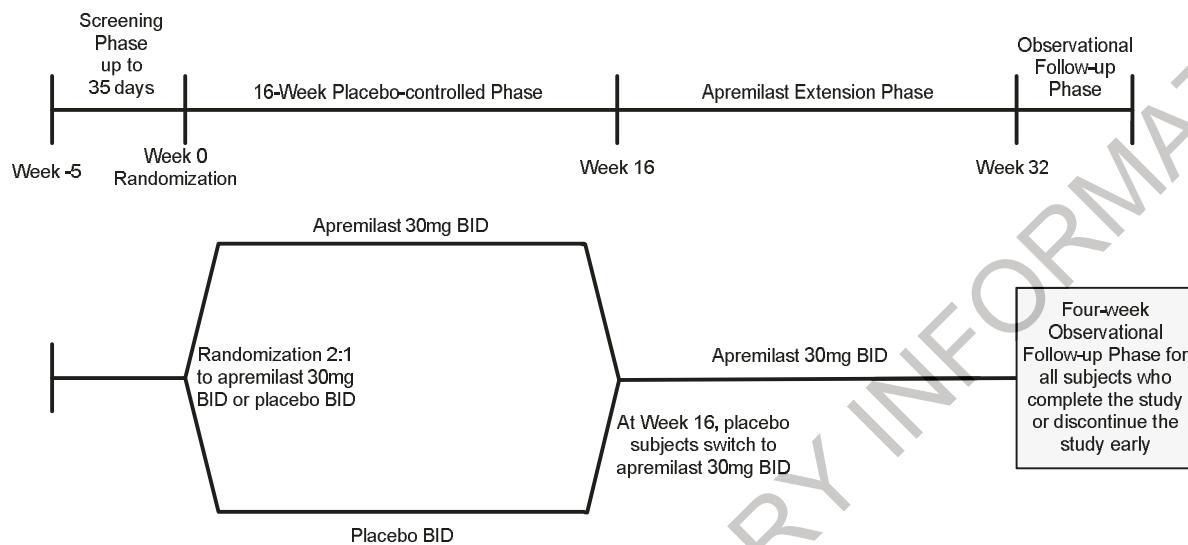
Subjects will receive treatment with one of the following:

- apremilast 30 mg tablets orally BID or
- placebo tablets (identical in appearance to apremilast 30 mg tablets) orally BID
- Apremilast Extension Phase – Weeks 16 to 32
 - All subjects will be switched to (or continue with) apremilast 30 mg BID at Week 16. All subjects will maintain this dosing through Week 32.
- Observational Follow-up Phase
 - Four-week Post-treatment Observational Follow-up Phase for all subjects who complete the study or discontinue from the study early.

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

Figure 1: Study Design



Abbreviation: BID = twice daily.

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

4.2. Study Endpoints

The endpoints of the study are listed below:

4.2.1. Primary Endpoint

- Scalp Physician Global Assessment (ScPGA): Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16

4.2.2. Secondary Endpoints

- Itch NRS (Whole Body): Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 16
- Itch NRS (Scalp): Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 16
- Onset of effect on itch NRS (Whole Body): Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score by visit in placebo-controlled phase (Week 12, Week 8, Week 4, Week 2)

- Onset of effect on itch NRS (Scalp): Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score by visit in placebo-controlled phase (Week 12, Week 8, Week 4, Week 2)
- DLQI: Change from baseline in DLQI total score at Week 16

4.2.3. Exploratory Endpoints

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- ScPGA: Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline by visit
- Itch NRS (Whole Body): Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score by visit in apremilast extension phase
- Itch NRS (Scalp): Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score by visit in apremilast extension phase

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 - DLQI: Change from baseline in DLQI total score at Weeks 4, 8, 16 and 32

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4.2.6. Safety Endpoints

Safety endpoints will include:

- Adverse Events (AEs)
 - Type, frequency, severity, seriousness, and relationship of adverse events to apremilast

- Number of subjects who prematurely discontinue investigational product (IP) due to an adverse event
- Death
- Psoriasis flare
- Clinical laboratory evaluations
- Vital signs and weight
- Physical examinations
- Pregnancy tests for females of child bearing potential (FCBP)

4.2.7. Derivations of Efficacy Endpoints

The derivation of each efficacy endpoint is described below in separate sections. Baseline definition for all efficacy endpoints is given in Section 5.3. Change from baseline is calculated as on-treatment value minus the baseline value. Percent change from baseline is defined as $100^* \text{ Change from baseline/Baseline value (\%)}$. Handling of time points is described in Section 5.4.

4.2.7.1. Scalp Physician Global Assessment (ScPGA)

The ScPGA is a measurement of overall scalp involvement. The ScPGA is a 5-point scale that assesses three dimensions (Plaque Elevation, Scaling, and Erythema) on a scale of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe). The ScPGA scores will be collected on the eCRF directly at each visit.

For a post baseline visit, the ScPGA response is defined as achieving ScPGA global assessment of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.

4.2.7.2. Whole Body Itch Numeric Rating Scale (NRS) Assessment

Prior to any other procedures or assessments being performed during the treatment period, the subject will be asked to assess their worst level whole body itch (including the scalp) over the past 24 hours and select a number on a scale of 0 to 10, where “0” represents no itching, and “10” represents the worst itch imaginable. The number selected by the subject will be recorded in the database.

The Whole Body Itch NRS scale has been validated among patients with moderate to severe plaque psoriasis, and a 4-point change from baseline was shown to be optimal for demonstrating a level of clinically meaningful improvement in itch severity.

For a post baseline visit, the whole body itch NRS response is defined as achieving ≥ 4 -point reduction (improvement) from baseline in the NRS score.

4.2.7.3. Scalp Itch Numeric Rating Scale (NRS) Assessment

After completing the Whole Body Itch NRS, the subject will be asked to assess the severity of their worst level of scalp itch over the past 24 hours and select a number on a scale of 0 to 10,

where “0” represents no scalp itch, and “10” represents the worst scalp itch imaginable. The number selected by the subject will be recorded in the database.

For a post baseline visit, the scalp itch NRS response is defined as achieving \geq 4-point reduction (improvement) from baseline in the NRS score.

4.2.7.4. Dermatology Life Quality Index (DLQI)

During the treatment phase, DLQI will be assessed by the subject upon arrival at the site, after completing the Whole Body Itch NRS, Scalp Itch NRS, **CCI** and prior to any other procedures or assessments being performed. 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.

The developers suggest that the DLQI can be grouped into 6 subscales: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores for 4 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 correspond to poorer HRQoL.

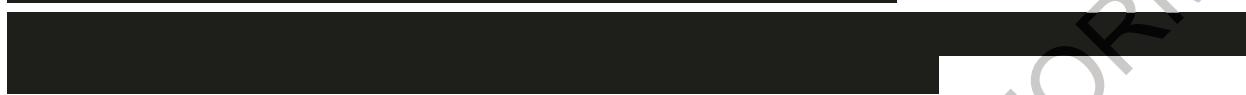
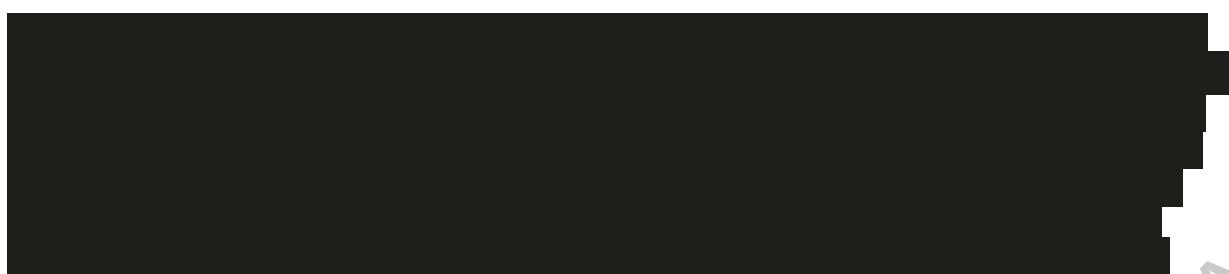
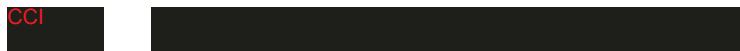
If one of the 10 items is left unanswered, it is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more of the ten items are left unanswered, DLQI total score will be left missing. When using sub-scales, if the answer to one item in a sub-scale is missing, the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

DLQI total score and change from baseline will be derived, where change = visit value – baseline value.

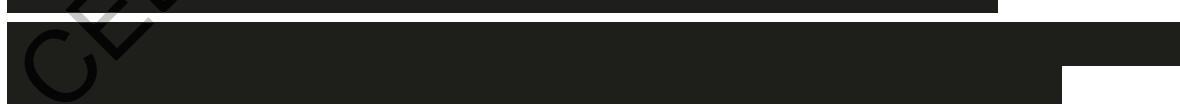
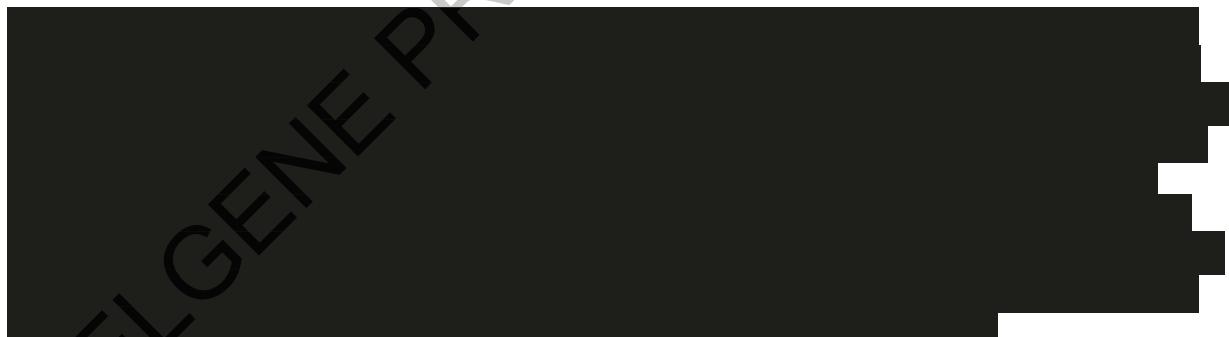
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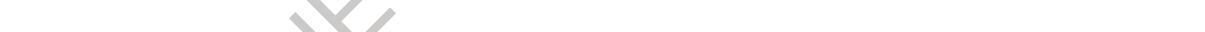


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4.2.9. Derivations of Safety Endpoints

Baseline definition for all safety endpoints is given in Section 5.3. Change from baseline is calculated as on-treatment value minus the baseline value. Handling of time points is described in Section 5.4.

4.2.9.1. 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 the study 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 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 Appendices [Appendix A1A1.1](#) .

4.2.9.2. Treatment-emergent Adverse Events Leading to Drug Withdrawal, Leading to Drug Interruption, and Leading to Death, and Drug-related Treatment-emergent Adverse Events

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.

4.3. Randomization, Stratification, and Blinding

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 2:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to enter the IRT to randomize subjects. Treatment assignment will be stratified by baseline ScPGA score [moderate (3), or severe (4)].

All subjects will receive apremilast 30 mg BID in the Apremilast Extension Phase.

The original treatment assignments (apremilast 30 mg BID or placebo) will remain blinded until all subjects have completed their Week 16 visit (or have discontinued). After Week 16 data restriction, unblinded data will only be made available to select Sponsor and CRO team members involved with analysis of the data ^{CC1} [REDACTED]. 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.

4.4. Sample Size Determination

The sample size estimation is based on the results of the Phase 3 and 3b studies, including CC-10004-PSOR-008, PSOR-009 and PSOR-010 which demonstrated positive treatment effects between apremilast 30 mg BID and placebo in the proportion of subjects achieving ScPGA response at Week 16 (range 18% to 29%). Approximately 300 subjects will be randomized in a 2:1 ratio to apremilast 30 mg BID or placebo. With this sample size, a chi-square test at the 2-sided 0.05 significance level will have 90% power to detect a minimum treatment difference of 18% (38% for apremilast 30 mg BID versus 20% for placebo) between the two arms for

proportions of subjects achieving ScPGA response at Week 16 (defined as ScPGA score of clear [0] or almost clear [1] with at least a 2 point reduction from baseline at Week 16).

If at least 60% of the approximate 300 randomized subjects would be evaluable for the whole body itch NRS analysis, the subset sample size of 180 subjects will provide 90% power to detect a treatment difference of 25% (45% for apremilast 30 mg BID and 20% for placebo) in the proportion of subjects with ≥ 4 -point improvement from baseline in the whole body itch NRS score.

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5. ANALYSIS PHASES OR PERIODS, DEFINITION OF ANALYSIS POPULATIONS, BASELINE AND TIME POINTS

5.1. Analysis Phases or Periods

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

5.1.1. Analysis Phases

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

- 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.

- Apremilast Extension Phase – Weeks 16 to 32

This phase starts on the next day that 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 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.

- Observational Follow-up Phase – 4 weeks

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

5.1.2. Apremilast-exposure Period for Safety Analysis

In addition to the above defined phases, Apremilast-exposure Period will be used for safety analyses.

- Apremilast-exposure Period:

This period starts on the date of either: (1) the first dose of IP following randomization (Week 0/Visit 2) for subjects who are treated with apremilast 30 mg BID first; or (2) the first dose of IP from the IP dispensed at Week 16/Visit 7 for subjects who were originally treated with placebo and are treated with apremilast 30 mg BID at Week 16.

This period stops on either: (1) data cut-off date; or (2) the day of the treatment discontinuation if the subject discontinued prior to or at Week 32/Visit 10; or (3) the last

known study day if the subject lost to follow-up prior to Week 32/Visit 10; or (4) Week 32/Visit 10 visit date.

5.2. Definition of analysis populations

5.2.1. Intent-to-treat Population

The intent-to-treat (ITT) population will consist of all subjects who are randomized. Subjects will be included in the treatment group to which they are randomized.

5.2.2. Per-protocol Population

The per protocol (PP) population will consist of all subjects included in the ITT population who receive at least one dose of IP, have both baseline and at least one post-treatment ScPGA evaluation, and have no important protocol deviations which may affect analyses in the Placebo-controlled Phase.

5.2.3. Safety Population

5.2.3.1. Placebo-controlled Phase (Weeks 0 to16)

Safety analyses will be based on the safety population, which will include all subjects who are randomized and receive at least one dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received (apremilast 30 mg BID or placebo) for the analyses and summaries using the safety population.

5.2.3.2. Apremilast Extension Phase (Weeks 16 to 32)

Safety analyses will be based on subjects who are treated in the phase. At Week 16, subjects will continue 30 mg BID treatment or will switch to 30 mg BID from placebo.

5.2.3.3. Apremilast-exposure Period

The safety analyses for the Apremilast-exposure Period will be based on the apremilast subjects as treated population, which includes all subjects who are randomized to (at Week 0/Visit 2) or treated with (at Week 16/Visit 7) apremilast 30 mg BID, and receive at least one dose of apremilast after randomization or Week 16. All subjects will be included in apremilast 30 mg BID dose group.

5.3. 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 visit.

For safety analysis, baseline is defined as the last value measured prior to or on the day of the first dose of IP in the summaries for the Placebo-controlled Phase, and defined as the last value measured prior to or on the start day (defined in Section 5.1, ie, the first apremilast dose date) of the Apremilast-exposure Period in the summaries for the Apremilast-exposure Period. For subjects who are randomized but do not take any study medication, baseline for the Placebo-controlled Phase is defined as the last value measured prior to or on the day of the randomization.

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 or may not be the same as the visits/study weeks as recorded in the database.

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

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

Analysis Visit	Target Day	Visit Window
Baseline	1	≤ 1
Placebo-controlled Phase		
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) for randomization. Definitions for baseline and start or end of the phases are specified in Section 5.1 and 5.3 for both efficacy and safety analysis.

Time points in the analyses or summaries of efficacy data over time include the scheduled study weeks per protocol, the end of a study phase, and the observational follow-up visit. Appropriate dates (e.g., date of measurement or date of specimen collection) will first be used to ensure only data (including data from scheduled, unscheduled, discontinuation, and observational follow-up visits) measured or collected within the specific analysis phase (as defined in Section 5.1) 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.

The time points for summaries of safety data (laboratory parameters, vital signs and weight) are based on study week/visit for the Placebo-controlled Phase. For the Apremilast-exposure Period, the scheduled study weeks for placebo subjects who are treated with apremilast 30 mg BID at Week 16/Visit 7 will be mapped to reflect the study weeks relative to the first dose of apremilast (see table below).

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

Original Visit	Re-Mapped Visit for subjects initially randomized to placebo
Week 16 (Visit 7)	Week 0 (Baseline)
Week 20 (Visit 8)	Week 4
Week 24 (Visit 9)	Week 8
Week 32 (Visit 10)	Week 16

6. STATISTICAL METHODOLOGY FOR EFFICACY

6.1. General Approaches to Efficacy Analysis

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

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

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

For discrete variables, the response rate and its 95% confidence interval (CI) will be calculated by treatment. Treatment difference will be tested using the Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor at randomization (baseline ScPGA score moderate (3) or severe (4)) for the Double-blind Placebo-controlled Phase. The difference of response rate (apremilast 30 mg BID - placebo) and its 95% CI as well as the p-value will be produced using CMH method.

The continuous endpoints will be analyzed using the analysis of covariance (ANCOVA) model with treatment group and stratification factor as independent variables and the baseline value as a covariate variable. SAS Proc Mixed will be used for the analysis. The least square means (LS mean) with 95% CI for each treatment and difference of LS mean (apremilast 30 mg BID - placebo) with 95% CI as well as the p-value will be provided.

For the primary and the secondary efficacy endpoints, the primary approach in handling missing data will be the multiple imputation (MI) methods. Statistical outputs from the imputed complete data sets will be combined in making statistical inferences.

Efficacy results will be considered statistically significant after consideration of the strategy for controlling the Type I error rate that is described in Section 6.2. All statistical tests will be two-sided and be conducted at the 0.05 significance level, and p-values will be reported.

6.2. Multiplicity Adjustment

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

- Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 16
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 16
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 12
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 12
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 8
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 8
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 4
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 4
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 2
- Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 2
- Change from baseline in DLQI total score at Week 16

6.3. Analyses of Primary Efficacy Endpoint

The primary endpoint is the proportions of subjects who achieving ScPGA response at Week 16 (defined as ScPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline at Week 16). The primary endpoint will be analyzed using the ITT population. A sensitivity analysis will be performed using the PP population.

The treatment difference between apremilast 30 mg BID and placebo will be compared using CMH test adjusting for the stratification factor at randomization. The 2-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 2-sided 95% CIs using a normal approximation to the weighted average will be provided ([Mehrotra and Railkar, 2000](#)). Missing values at Week 16 will be imputed using the multiple imputation (MI) method ([SAS Institute Inc. 2011](#)) as the primary analysis, with sensitivity analysis using the last observation carried forward (LOCF) method and the non-responder imputation (NRI) method.

The SAS procedure MI will be used to impute missing ScPGA scores at the scheduled analysis visits in the Placebo-controlled Phase (Weeks 0 to 16) to create M=25 complete data sets. The missing data patterns will be checked by treatment and stratification factor at 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 to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest ScPGA scores. The seed will be set to 804529, the imputed values will be rounded to integers and a single chain will be used to produce imputations. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary.

In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 25 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with seed 447159. The missing values at each visit will be imputed based on treatment, stratification factor, and ScPGA scores at baseline 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 CMH method will be used to analyze the 25 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

In summary, the primary analysis will be performed for ITT population using the MI method for treating missing values. Supportive analyses will be performed for: (1) ITT population treating missing values using the LOCF method, (2) ITT population treating missing values using the NRI method, (3) PP population using the MI method for treating missing values. In addition, analyses using CMH test adjusting for the stratification factor at randomization and pooled site will be performed for ITT population using MI method for imputing missing values.

6.4. Analyses of Secondary Efficacy Endpoint

For the binary endpoints defined as ≥ 4 -point reduction (improvement) from the baseline visit in either the whole body itch NRS score or the scalp itch NRS score at post-baseline visits, the analyses will be based on subjects in the ITT population with baseline whole body itch NRS score ≥ 4 or baseline scalp itch NRS score ≥ 4 , respectively. For the continuous secondary endpoint (i.e. change from baseline in DLQI total score at Week 16), the analyses will be based on ITT population. Unadjusted 2-sided p-values and 2-sided 95% confidence intervals (CIs) (ie, without multiplicity adjustment) will be reported.

6.4.1. Whole Body Itch Numeric Rating Scale (NRS) and Scalp Itch Numeric Rating Scale (NRS) Assessments

In order to evaluate the onset of effect of apremilast 30 mg BID compared to placebo for itch, the following secondary endpoints are specified.

- Whole Body Itch NRS Response: Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 16
- Scalp Itch NRS Response: Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 16
- Whole Body Itch NRS Response: Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 12, Week 8, Week 4, and Week 2
- Scalp Itch NRS Response: Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 12, Week 8, Week 4, and Week 2

Statistical analyses for the 10 endpoints will be performed 1 by 1 downward from Week 16 to Week 2. Multiplicity adjustment is specified in Section 6.2.

These binary endpoints will be analyzed similarly as the primary endpoint. The treatment difference between apremilast 30 mg BID and placebo will be compared using CMH test adjusting for the stratification factor at randomization. The 2-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 2-sided 95% CIs using a normal approximation to the weighted average will be provided.

The SAS procedure MI will be used to impute missing whole body itch NRS score (or scalp itch NRS score) at the scheduled analysis visits in the Placebo-controlled Phase (Weeks 0 to 16) to create M=25 complete data sets. The missing data patterns will be checked by treatment and stratification factor at 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 to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. The minimum and the maximum values for imputation will be 0 and 10, which correspond to the lowest and the highest whole body itch NRS score (or scalp itch NRS score). The seed will be set to 804529, the imputed values will be rounded to integers and a single chain will be used to produce imputations. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary.

In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 25 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with seed 447159. The missing values at each visit will be imputed based on treatment, stratification factor, and whole body itch NRS score (or scalp itch

NRS score) at baseline and previous visits. The number of closest observations to be used in the selection will be K=5.

After the completion of imputation, the same CMH method will be used to analyze the 25 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

In summary, the primary analysis of whole body Itch NRS response (or scalp Itch NRS response) will be performed separately for each post baseline visit in the Placebo-controlled Phase for ITT population using MI method for treating missing values. Supportive analyses will be performed at Week 16 visit for: (1) ITT population treating missing values using the LOCF method, (2) ITT population treating missing values using NRI method. In addition, analyses using CMH test adjusting for the stratification factor at randomization and pooled site will be performed at Week 16 for ITT population using MI method for imputing missing values.

6.4.2. Change from Baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 16

Change from baseline in DLQI total score at Week 16 will be analyzed based on the ITT population using the analysis of covariance (ANCOVA) model. The ANCOVA model will use the change from baseline as the dependent variable and will include treatment group and stratification factor as independent variables and the baseline value as a covariate variable. Within-group least-squares (LS) mean changes from baseline at Week 16, the associated standard errors (SEs) and 2-sided 95% CIs, treatment differences in LS mean changes from baseline, and the associated 2-sided 95% CIs and p-values, will be derived from the ANCOVA model.

The SAS procedure MI will be used to impute missing DLQI total score at the scheduled analysis visits in the Placebo-controlled Phase (Weeks 0 to16) to create M=25 complete data sets. The missing data patterns will be checked by treatment and stratification factor at Baseline (Week 0), and Weeks 4, 8 and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. The minimum and the maximum values for imputation will be 0 and 30, which correspond to the lowest and the highest DLQI total score. The seed will be set to 804529, the imputed values will be rounded to integers and a single chain will be used to produce imputations. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary.

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

After the completion of imputation, the same ANCOVA model will be used to analyze the 25 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

In summary, the secondary analysis of change from baseline in DLQI total score at Week 16 will be performed for ITT population using MI method for treating missing values. Sensitivity analysis will be performed for ITT population treating missing values using the LOCF method,

6.5. Analyses of Exploratory Efficacy Endpoints

Descriptive summary statistics or proportion of subjects achieving specified criteria will be summarized by treatment group. When appropriate, exploratory endpoints at Week 16 will also be analyzed using CMH or ANCOVA methods similar to the primary and secondary endpoints based on ITT population with missing values imputed using LOCF method.

6.5.1. Study Phases

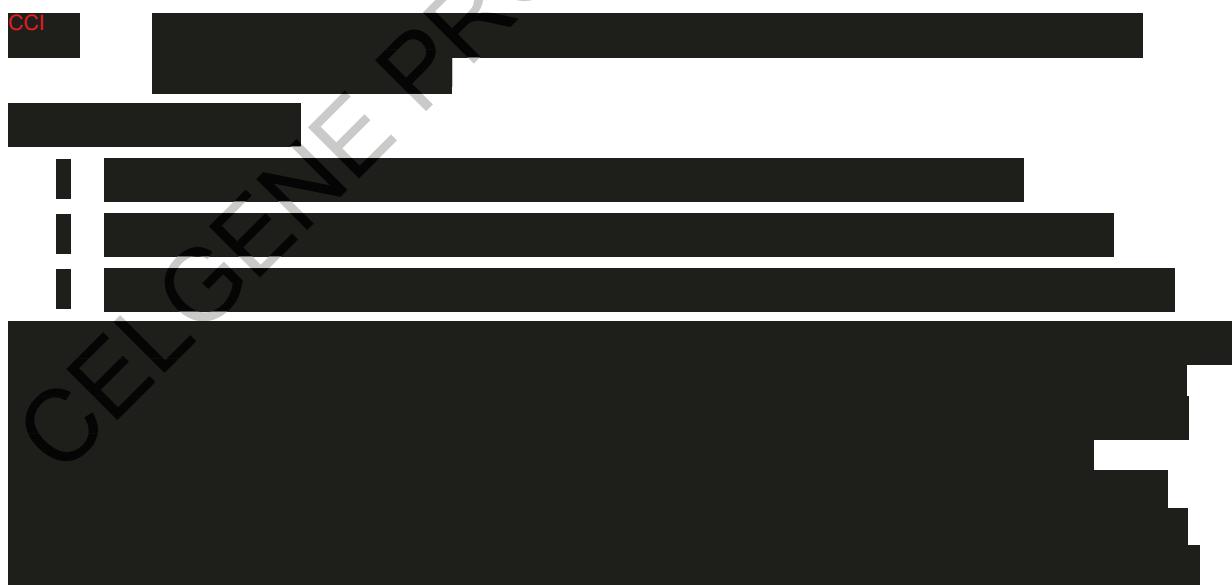
The subjects included and the treatment arms considered for statistical analyses and summaries in each phase are described below in this section. The specific summaries are discussed in the following sections.

- Placebo-controlled Phase (Weeks 0 to 16)

The two treatment arms are 30 mg BID or Placebo, all subjects in the ITT population are to be included.

- Apremilast Extension Phase (Weeks 16 to 32)

The two treatment arms are 30 mg BID/30 mg BID, and Placebo/30 mg BID. Subjects included are those in the ITT population who entered the Apremilast Extension Phase, either were initially randomized to 30 mg BID or placebo, respectively.



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6.5.3. Dermatology Life Quality Index (DLQI)

The endpoints include:

- Change from baseline in DLQI total score at Weeks 4, 8, 16 and 32
- Change from baseline in DLQI subscale scores at Weeks 4, 8, 16 and 32

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Mean change from baseline in DLQI total score and subscale scores will be summarized by treatment group and time point using descriptive statistics. Analysis for the Week 16 change from baseline in DLQI total score is presented in the secondary efficacy endpoint Section 6.4.2.

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Week 16 DLQI

response will be analyzed similarly as the primary and secondary binary endpoint. The treatment difference between apremilast 30 mg BID and placebo will be compared using CMH test adjusting for the stratification factor at randomization. The 2-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 2-sided 95% CIs using a normal approximation to the weighted average will be provided. The analysis will be based on ITT population with missing values imputed using the LOCF method.

6.5.4. Whole Body Itch and Scalp Itch Numeric Rating Scale (NRS) Assessment

The endpoints include:

- Whole body itch NRS score by visit
- Scalp itch NRS score by visit
- Change from baseline in whole body itch NRS score by visit
- Change from baseline in scalp itch NRS score by visit

All endpoints will be summarized by treatment group and time point using descriptive statistics.

Shift tables for shifts from baseline to post-baseline visits and End of Phase (LOCF) will be provided by treatment and time point for whole body itch NRS score and scalp itch NRS score.

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6.5.6. Scalp Physician Global Assessment (ScPGA) CCI

The endpoints include:

- ScPGA response defined as proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline by visit

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These endpoints will be summarized by treatment group and time point.

Analysis for the Week 16 ScPGA response is presented as the primary efficacy endpoint in Section 6.3.

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The treatment difference between apremilast 30 mg BID and placebo will be compared using CMH test adjusting for the stratification factor at randomization. The 2-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 2-sided 95% CIs using a normal approximation to the weighted average will be provided. The analysis will be based on ITT population with missing values imputed using the LOCF method.

Shift tables for CCI and ScPGA shifts from baseline to post-baseline visits and End of Phase (LOCF) will be provided by treatment and time point.

6.6. Subgroup Analysis

Subgroup analyses for ScPGA response at Week 16 and proportions of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS or scalp itch NRS scores at post baseline time points based upon baseline demographic or baseline disease characteristics. Summary and analysis will be based on ITT population and missing values will be imputed using MI method. Treatment-difference for response will be reported with 2-sided 95% CI.

The following subgroup variables will be considered and analyzed when appropriate:

- Sex (Male, Female)
- Race (White, Others)
- Age category (< 65 , ≥ 65)
- Baseline weight (< 85 , ≥ 85 to < 100 , ≥ 100 kg)
- Baseline BMI category (< 25 , ≥ 25 to < 30 , ≥ 30 to < 35 , ≥ 35 to < 40 , ≥ 40 kg/m^2)
- Geographical region (USA, Canada)
- Alcoholic beverage drinking (Yes, No)
- Tobacco use (Current user, Past user, Never used)
- Duration of plaque psoriasis categories (< 10 , ≥ 10 to < 20 , ≥ 20 years)
- Baseline ScPGA score: 3 (moderate), 4 (severe)

- Baseline whole body itch NRS score (0 to 3, 4 to 6, 7 to 10)
- Baseline scalp itch NRS score (0 to 3, 4 to 6, 7 to 10)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Number of prior conventional systemic therapies (0, ≥ 1)
- Number of prior biologic therapies (0, ≥ 1)
- Number of prior systemic therapies (0, ≥ 1)
- Number of prior topical scalp psoriasis medications or shampoo treatments (1, ≥ 2)
- Number of failed prior scalp psoriasis medications or shampoo treatments for subjects who had prior scalp psoriasis medications or shampoo treatments (0, ≥ 1)

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.9. Assessing Study Site Effect

This multicenter study has approximately 46 study sites. As site enrollment caps are imposed, no single site will have sufficient number of subjects to allow a meaningful within-site analysis of treatment effects stratified by baseline ScPGA score; therefore, study site effect will be assessed by pooling sites on geographic basis to help interpret the results should potential site effect be suspected.

In pooling sites for analysis purposes, a minimum of 5 randomized subjects per treatment group (apremilast 30 mg BID or placebo) per stratum of baseline ScPGA score (moderate [3], or severe [4]) will be used. The pooling strategy is described as follows: 1) Sites will be pooled within

each country (USA or Canada) according to their rank based on site-specific sample size, starting with the smallest sites; i.e., within a country, 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 country with the smallest pooled site. 3) In the rare case that all site pooled together in a country does not satisfy the above condition (a minimum cell size of 5 for each of the four cells), all sites in the country will be pooled together with the smallest pooled site of the other country.

Sites will be pooled together as described above in order to assess the site effect and site by treatment interaction on the primary and major secondary efficacy endpoints as below:

- ScPGA Response: Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Whole Body Itch NRS Response: Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the whole body itch NRS score at Week 16
- Scalp Itch NRS Response: Proportion of subjects with ≥ 4 -point reduction (improvement) from baseline in the scalp itch NRS score at Week 16

For the pooled sites, summary and analyses will be based on ITT population using MI imputation for missing values. Study site effect will be assessed for the primary and the major secondary 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 also be assessed by performing a subgroup-type analysis with respect to the endpoints, with individual study sites (or pooled sites) treated as subgroups (see Section 6.6). 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).

6.10. Interim Analysis

No interim analysis will be conducted.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 data restriction will be performed, the primary data analysis will be conducted **CC1** **CC1** **CC1**. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data **CC1**. 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. SUMMARY OF SUBJECT DISPOSITION

The number of subjects screened, the number and percentage of subjects randomized (as recorded in the IVRS database) 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 above percentages will be based on the number of subjects screened.

The number and percentage of subjects included in the ITT population, safety population, and PP population will be summarized by treatment arm; the percentages will be based on the number of subjects randomized.

For the Double-blind Placebo-controlled Phase, the number and percentage of subjects who entered, completed, and discontinued, as well as the number and percentage of primary reasons for discontinuation will be summarized.

All subjects who terminated early or completed the study treatment will be asked to continue into the Post-treatment Observational Follow-up Phase. The primary reasons for discontinuation are collected in the screening disposition, treatment disposition and follow-up disposition eCRF and will be summarized with the following categories:

- Screen failure (screening only)
- Death
- Adverse event(s)
- Pregnancy
- Lack of efficacy (treatment disposition only)
- Withdrawal by subject
- Non-compliance with study drug (treatment disposition only)
- Lost to follow-up
- Study terminated by sponsor
- Protocol deviation
- Physician decision
- Other
- Site terminated by sponsor (treatment disposition only)

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

Subject disposition will be provided by treatment arm and protocol phase:

- Placebo-controlled Phase – Weeks 0 to 16: in addition to the tabulation of subjects who are randomized, or included in the ITT, PP, and Safety populations, the number and percent of subjects who completed and entered the next phase (Weeks 16 to 32), completed but did not enter the next phase, and discontinued early will be provided. The

primary reasons for early discontinuation will also be tabulated. Subjects who complete and entered the next phase include subjects who have IP dispensed at Week 16/Visit 7, subjects who completed but did not enter the next phase include subjects who have either a Week 16 visit or a termination visit no earlier than the Week 16 visit window, and discontinued early subjects include those who discontinued prior to the Week 16 visit window.

- Apremilast Extension Phase – Weeks 16 to 32: The number and percent of subjects who entered the phase, took at least one dose of IP, completed the phase, discontinued early, and primary reason for discontinuation will be provided.
- Observational Follow-up Phase (4 weeks): Summary will include all subjects who entered Follow-up phase and whether completed Follow-up following the above phases.

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

CELGENE PROPRIETARY INFORMATION

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics, baseline characteristics, prior medication/procedure, and concomitant medications/procedure will be presented for the ITT population by treatment group and overall. Individual subject listings will also be provided.

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/m²)

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

- Age category (< 65, ≥ 65)
- Age category (< 40, ≥ 40 to < 65, ≥ 65 to < 75, ≥ 75 to < 85, ≥ 85 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Geographical region (USA, Canada)
- Alcohol History (Yes, No)
- Tobacco use (Never Smoked, Past Smoker, Current Smoker)
- Baseline BMI category (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, ≥ 40 kg/m²)

BMI will be calculated as follows: BMI (kg/m²) = Weight (kg)/ Height (m²). Other variables (i.e., age, weight, height, sex, race, ethnicity, geographical region, alcohol history and tobacco use history) will be summarized as recorded from the eCRF.

8.2. Baseline or Disease Characteristics

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

- Duration of plaque psoriasis (from date of diagnosis to the date of informed consent; year, presented one digit after the decimal point)
- Duration of plaque psoriasis categories (< 10, ≥ 10 to < 20, ≥ 20 years)
- Baseline ScPGA score

- Baseline whole body itch NRS score
- Baseline scalp itch NRS score
- Baseline DLQI total score
- Baseline DLQI total score category (0 to 3, 4 to 10, 11 to 20, 21 to 30)

- Number of prior phototherapies (0, 1, 2, ≥ 3)
- Number of failed prior phototherapies for subjects who had prior phototherapies (0, 1, 2, ≥ 3)
- Number of prior conventional systemic therapies (0, 1, 2, ≥ 3)
- Number of failed prior conventional systemic therapies for subjects who had prior conventional systemic therapies (0, 1, 2, ≥ 3)
- Number of prior biologic therapies (0, 1, 2, ≥ 3)
- Number of failed prior biologic therapies for subjects who had prior biologic therapies (0, 1, 2, ≥ 3)
- Number of prior systemic therapies (0, 1, 2, ≥ 3)
- Number of failed prior systemic therapies for subjects who had prior systemic therapies (0, 1, 2, ≥ 3)
- Number of prior topical scalp psoriasis medications or shampoo treatments (0, 1, 2, ≥ 3)
- Number of failed prior scalp psoriasis medications or shampoo treatments for subjects who had prior scalp psoriasis medications or shampoo treatments (0, 1, 2, ≥ 3)

8.3. Medical History

A summary of relevant medical history and concomitant diseases will be presented by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Affairs (MedDRA) version 20.0 or higher, using frequency distributions (counts and percentages). A similar summary will be generated for the currently active diagnosis only.

8.4. Prior and Concomitant Procedures

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

For a study phase, concomitant procedures are defined as those started during the phase. Study phases are defined in Section 5.1.1. Prior procedures and concomitant procedures will be coded using the MedDRA dictionary Version 20.0 or higher.

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

A frequency summary of concomitant procedures will be provided for the safety population by treatment group, SOC, and PT.

8.5. 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.

For a study phase, concomitant medications are defined as non-study medications started during the phase, or started before the phase and ended or remain ongoing during the phase. Study phases are defined in Section 5.1.1. The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version DDE B2 March 2017 or higher) will be used to group medications into relevant categories. A frequency summary of prior medications will be provided by treatment group, ATC2 level, and standardized medication name for the safety population.

Prior psoriasis medications will be summarized with baseline characteristics.

Concomitant medications documented during the study will be summarized. The frequency tabulation will display the number (%) of subjects receiving at least one concomitant medication, the number (%) of subjects receiving at least one medication within a relevant category, and each concomitant medication by treatment group. The summaries will be provided for (1) Placebo-controlled Phase (Weeks 0 to 16), (2) Apremilast Extension Phase (Weeks 16 to 32), and (3) Observational Follow-up Phase (4 weeks).

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

Treatment duration will be summarized by treatment group for the analysis phases (Section 5.1.1) and for the Apremilast-exposure Period (Section 5.1.2). Subjects who are treated in the corresponding phases or period will be used, i.e., the safety population for Placebo-controlled Phase (Weeks 0 to 16), and the apremilast subjects as treated population for the Apremilast-exposure Period, etc.

Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories (e.g., < 4, \geq 4 - < 8 weeks, etc.), will be provided.

9.1.1. Placebo-controlled Phase – Weeks 0 to 16

Treatment duration (in weeks) is calculated from the date of the first dose of IP at Week 0/Visit 2 to either the date one day prior to the first dose date in the Apremilast Extension phase for the IP dispense at Week 16/Visit 7, or the date of the last dose of IP in the study for subjects who discontinue in the phase. Imputation rule for partially or completely missing last dose date is specified in [Appendix A1A1.1.4](#)

Treatment duration will be summarized by actual treatment (placebo vs. apremilast 30 mg BID) for the safety population.

9.1.2. Apremilast Extension Phase – Weeks 16 to 32

Treatment duration is calculated from the first dose date in the Apremilast Extension phase for the IP dispense at Week 16/Visit 7 to the date of the last dose of IP in the study for subjects who discontinue in the phase or who complete the study at Week 32/Visit 10. Imputation rule for partially or completely missing last dose date is specified in [Appendix A1A1.1.4](#)

9.1.3. Apremilast-exposure Period

Treatment duration for Apremilast-exposure Period (Section 5.1.2) is calculated from the date of the first dose of apremilast 30 mg BID, which is the date of the first dose of apremilast after randomization at Week 0/Visit 2 or switched to apremilast at Week 16/Visit 7, to the last apremilast dose date for subjects who discontinue in the first 32 weeks or who complete the study at Week 32/Visit 10. Imputation rule for partially or completely missing last dose date is specified in [Appendix A1A1.1.4](#)

9.2. Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the numbers of tablets dispensed and/or returned will be recorded at each visit (except Week 3/ Visit 1). These records will be used to calculate treatment compliance.

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 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.

9.2.1. Placebo-controlled Phase – Weeks 0 to16

Treatment compliance will be calculated for the treatment duration in the phase specified in Section 9.1.1 and will be summarized by treatment group for ITT population.

9.2.2. Apremilast Extension Phase – Weeks 16 to 32

Treatment compliance will be calculated for the treatment duration in the phase specified in Section 9.1.2 and will be summarized by treatment group for the subset of ITT population who entered the phase.

9.2.3. Apremilast-exposure Period

Treatment compliance will be calculated for the treatment duration in the period specified in Section 9.1.3.

Treatment compliance will be summarized for apremilast 30 mg BID treatment for apremilast as treated population.

10. PROTOCOL DEVIATIONS AND IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations and important protocol deviations will be categorized by 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 removed from the per-protocol population.

Protocol deviations and important protocol deviations will be summarized by treatment. Summary tables showing the number and percent of subjects with at least one protocol deviation/important protocol deviation and by each protocol deviation/important protocol deviation will be provided. Listings of subjects with protocol deviations and important protocol deviations will also be provided.

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11. SAFETY ANALYSIS

Safety will be assessed via descriptive statistics and point estimates. 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, and apremilast 30 mg BID), and the safety analyses for the Apremilast-exposure Period will be based on the apremilast subjects as treated population and presented by apremilast dose group (i.e., apremilast 30 mg BID) irrespective of the start time of apremilast exposure (at Week 0 or 16).

For the analyses of AEs and marked abnormalities, the following point estimates are distinguished:

- 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 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) will be presented.

Descriptive statistics will be provided for vital signs, weight, 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.

11.1. Adverse Events

AEs will be coded according to the MedDRA version 18.0 or higher. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs presented in the standard international order and PTs within SOCs will be presented in descending order of subject incidence.

11.1.1. Overall Summary of TEAEs

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

- 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 Extension Phase (Weeks 16 to 32), Observational Follow-up Phase (4 weeks) and Apremilast Exposure Period overall summary of TEAEs will also be provided.

11.1.2. All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence). In addition to the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast-exposure Period, summaries will also be provided for the Apremilast Extension Phase (Weeks 16 to 32).

New events of all TEAEs by exposure interval (≤ 1 , > 1 to ≤ 4 , > 4 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 Weeks) will be summarized for the Apremilast-exposure Period.

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

All TEAEs occurring after the date of the last dose of IP and up to 28 days after the last dose of IP will also be summarized by SOC and PT for subjects who enter the observational follow-up phase. The EAIR will not be provided in this summary.

11.1.3. Common TEAEs

TEAEs with subject incidence $\geq 5\%$ (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.

11.1.4. Drug-related TEAEs

Drug-related TEAEs will be summarized and new events of drug-related TEAEs by exposure interval (see Section 11.1.2) will be summarized.

11.1.5. TEAEs by Maximum Severity

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

11.1.6. 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.

11.1.7. TEAEs Leading to Drug Interruption and TEAEs Leading to 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.

11.1.8. Deaths

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

11.2. Psoriasis Flare

Psoriasis flare represents an atypical or unusual worsening of disease during treatment (Carey, 2006). It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. At any time, a psoriasis flare may be reported as an adverse event, provided it meets the protocol definition.

TEAEs in their coded terms containing psoriasis will be summarized. A subject data listing of all those adverse events will be provided.

11.3. Clinical Laboratory Evaluations

The endpoints for clinical laboratory evaluations include:

- Laboratory marked abnormalities (see [Appendix A2](#))
- Observed value and change from baseline over time in the following laboratory parameters
 - Hematology: hemoglobin, hematocrit, platelet, erythrocytes, leukocytes, basophils/leukocytes, eosinophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes, neutrophils/leukocytes, basophils, eosinophils, lymphocytes, monocytes, and neutrophils
 - Serum chemistry: glucose, lactate dehydrogenase (LDH), bicarbonate, calcium, chloride, potassium, magnesium, phosphate, sodium, blood urea nitrogen, creatinine, urate, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, albumin, and total protein
- 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.

Laboratory marked abnormalities will be summarized; subject incidence and EAIR for each abnormality will be calculated based on subjects with a baseline value and at least one post-baseline value for criteria requiring baseline or subjects with at least one post-baseline value for criteria not requiring baseline. A subject data listing of laboratory marked abnormalities will be provided. Laboratory marked abnormalities will also be summarized for subjects with normal values at baseline and for subjects with abnormal values at baseline separately. For the purposes of these summaries, subjects with abnormal (normal) values at baseline are defined as those whose baseline value is low (not low) for criteria concerning low values and those whose baseline value is high (not high) for criteria concerning high values; both low and high are relative to the laboratory normal range.

A subject data listing of all laboratory data, including urinalysis, will be provided.

11.4. Vital Signs and Weight

The endpoints for vital signs and weight 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

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

Frequency summaries of 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/m²) and by baseline weight category (< 70 , ≥ 70 to < 85 , ≥ 85 to < 100 , and ≥ 100 kg). The categories of weight change (kg) and percent change (%) are < -20 , ≥ -20 to < -10 , ≥ -10 to < -5 , ≥ -5 to < 0 , 0 , > 0 to ≤ 5 , > 5 to ≤ 10 , > 10 to ≤ 20 , and > 20 . 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.

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

11.5. Physical Examination

A complete physical examination includes evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems. The complete physical examination is done at screening and at the Early Termination or Last Treatment Visit (Visit 10).

The protocol specified that physical examination findings of clinical significance (as defined by the investigator) are to be reported as AEs. No summary of physical examination findings will be provided.

REFERENCES

CCI



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. 2015. SAS/STAT® 14.1 User's Guide. Cary, NC: SAS Institute Inc.

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

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.

Appendix A1 – Conventions related to dates

Following are the general conventions for various computations and imputations for references. Users may need to consult with study team for specific study practices or regulatory guidelines.

A1.1 Guideline of Partially Missing Date Imputation

A1.1.1 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, 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 4: 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 5: 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., $Y_{IP} \leq Y_{Event} < Y_{APR}$	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 Week 16
4	Otherwise, i.e., $Y_{IP} < Y_{Event} < Y_{APR}$, 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})

A1.1.2 Prior/Concomitant Medications/Procedures

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

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

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

A1.1.3 Medical History

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

A1.1.4 Treatment Duration

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

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

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

Last known date in database is defined as maximum of (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).

Appendix A2 –Laboratory Marked Abnormalities Criteria

Table 6: Imputation Rules for Partially Missing AE Start Dates for Subjects who were Treated with Placebo Initially Laboratory Marked Abnormalities Criteria

Category / Analyte	SI Units	Criteria
<i>Chemistry/</i>		
Alanine Aminotransferase (SGPT)	U/L	> 3*ULN
Albumin	Kg/m3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 3*ULN
Total Bilirubin	µmol/L	> 1.8*ULN
Blood Urea Nitrogen	mmol/L	> 15
Calcium	mmol/L	1. < 1.8 2. > 3.0
Creatinine	µmol/L	> 1.7*ULN
Glucose	mmol/L	< 2.8 > 13.9
Hemoglobin A1C	%	> 9
Lactate Dehydrogenase	U/L	> 3*ULN
Magnesium	mmol/L	>1.2
Phosphate	mmol/L	1. < 0.64 2. >1.60
Potassium	mmol/L	< 3.0 > 5.5
Sodium	mmol/L	< 130 > 150
Triglycerides	mmol/L	> 3.4

Category / Analyte	SI Units	Criteria
Urate	umol/L	Male: > 590; Female: > 480
<i>Hematology/</i> Hemoglobin	g/L	Female < 8.5, Male < 10.5 Female > 17, Male > 18.5
Leukocytes	$10^9/L$	< 1.5
Lymphocytes	$10^9/L$	< 0.8
Neutrophils	$10^9/L$	< 1.0
Platelets	$10^9/L$	1. < 75 2. > 600
Total cholesterol	mmol/L	> 7.8

Appendix A3 –Reporting conventions

- Summary tabulation will be provided by treatment (e.g., placebo vs. apremilast 30 mg BID for Double-blind Placebo-controlled Phase; placebo/ apremilast 30 mg BID vs. apremilast 30 mg BID/30 mg BID for Apremilast Extension Phase; apremilast 30 mg BID for Apremilast-exposure Period);
- All statistical tests of the treatment effect will preserve a significance level of 0.05 for 2-sided tests;
- P-values will be rounded to 4 decimal places. p-values that round to 0.0000 will be presented as ‘<0.0001’ and p-values that round to 1.000 will be presented as ‘>0.9999’;
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, the sample size, mean, median, standard deviation (SD), minimum, and maximum for continuous variables, the 25th (Q1) and 75th (Q3) percentiles will also be applied to efficacy continuous variables;
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value;
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses;
- All analysis and summary tables will have the analysis population sample size (i.e., number of subjects) in the column header;
- The day of the first dose of any study drug (i.e., apremilast or placebo) will be defined as Day 1;
- Subject data listings will be provided to support the tables and graphs. All listings will be sorted for presentation in order of treatment, subject, and date of procedure or event.