Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Static Physician Global Assessment (sPGA) 0/1	Proportion of subjects with an sPGA score of clear (0) or almost clear (1) and with at least a 2-point reduction from baseline	Week 16
Secondary	Body Surface Area (BSA)	Proportion of subjects who improved ≥ 75% in BSA from baseline	Week 16
	BSA	Change from baseline in affected BSA.	Week 16
	Psoriasis Area and Severity Index (PASI)	Change from baseline in total PASI score	Week 16
	BSA	Proportion of subjects who achieved BSA ≤ 3% for subjects with baseline BSA > 3%	Week 16
	Whole body itch numeric rating scale (NRS)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score among subjects with baseline whole body itch NRS ≥ 4	Week 16
	Scalp Physician Global Assessment (ScPGA)	Proportion of subjects with a ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline among subjects with baseline ScPGA score ≥ 2	Week 16
	Dermatology Life Quality Index (DLQI)	Change from baseline in DLQI total score	Week 16
	Safety	Type, frequency, severity and relationship of adverse events to investigational product (IP)	Throughout study (Day 0 to end of Observational Follow-up Phase)

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory	[redacted]		

Table 3: Table of Events (Continued)

	Screening	Placebo-controlled Treatment Phase						Apremilast Extension Phase			Observational Follow-up
Visit Number	**1**	**Baseline[a] 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10/ET[b]**	**11**
Week	**-5 to 0**	**0 (Day 1)**	**2 (± 4 days)**	**4 (± 4 days)**	**8 (± 4 days)**	**12 (± 4 days)**	**16 (± 4 days)**	**20 (± 4 days)**	**24 (± 4 days)**	**32 (± 4 days)**	**4 Weeks After Last Dose (± 2 weeks)[c]**
C-SSRS screening	X	-	-	-	-	-	-	-	-	-	-
C-SSRS since last visit	-	X	X	X	X	X	X	X	X	X	X
Psychiatric evaluation[h]	-	-	-	-	-	-	-	-	-	-	-
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Psoriasis Flare Assessment[i]	-	-	-	-	-	-	-	-	-	-	-
Clinical Efficacy Assessments											
sPGA	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X	X	X	X
ScPGA[j]	X	X	X	X	X	X	X	X	X	X	X
NAPSI[j]	-	X	-	-	X	-	X	-	-	X	-
Subject Rated Outcomes or Health-related Quality of Life Assessment											
Whole body itch NRS	-	X	X	X	X	X	X	X	X	X	-
DLQI	-	X	X	X	X	X	X	-	-	X	-
Pharmacodynamic Assessments (optional for subjects)											
[redacted]											
Inflammatory Protein Biomarkers	-	X	-	-	-	-	X	-	-	-	-
[redacted]											

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
GI	Gastrointestinal
HDL	High-density lipoproteins
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect model for repeated measures
NAPSI	Nail psoriasis severity index
NPF	National Psoriasis Foundation
NRI	Non-responder imputation
NRS	Numeric rating scale
PASI	Psoriasis Area and Severity Index
PDE4	Phosphodiesterase type 4
PP	Per protocol
PQC	Product Quality Complaint
PUVA	Psoralen and ultraviolet A

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 574 subjects with mild to moderate plaque psoriasis will be enrolled and randomized from investigator sites in Canada and the United States of America (USA).

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject must be male or female, ≥18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments / procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have a diagnosis of chronic plaque psoriasis for at least 6 months prior to signing the ICF.
5. Subject must have a diagnosis of mild to moderate plaque psoriasis at both Screening and Baseline as defined by:
    a. sPGA score of 2-3 (mild to moderate)
    b. BSA 2-15%
    c. PASI score 2-15
6. Subject must be inadequately controlled with, or intolerant of at least one topical therapy (including topical corticosteroids, topical retinoids or vitamin D analog preparations, calcipotriene and betamethasone dipropionate ointment or foam, tacrolimus, pimecrolimus, or anthralin/dithranol) for the treatment of psoriasis at both Screening and Baseline.
7. Subject has not had prior exposure to biologics for the treatment of psoriatic arthritis, psoriasis, or any other indication that could impact the assessment of psoriasis.
8. Subject must be in good health (except for psoriasis) as judged by the investigator, based on medical history, physical examination, clinical laboratories, and urinalysis.
9. Subject must meet the following laboratory criteria:
    a. White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L)
    b. Platelet count ≥ 100,000/μL (≥ 100 x 10^9/L)
    c. Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
    d. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤ 2 x upper limit of normal (ULN)
    e. Total bilirubin ≤ 2 mg/dL (34 μmol/L)

no prior exposure to systemic therapy (conventional or biologic), and no concurrent topical therapy for psoriasis was permitted during the study, with the exception of an unmedicated moisturizer such as Eucerin®. Subjects were treated with APR 30 BID or placebo for 16 weeks during the Placebo-controlled Phase. At the end of the Placebo-controlled Phase at Week 16, subjects entered the Apremilast Extension Phase and received APR 30 BID up to study Week 52.

Analyses of the proportion of subjects who achieved an sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16, demonstrated statistically significant benefit with APR 30 BID compared to placebo in the treatment of subjects with plaque psoriasis of moderate severity. These results from the CC-10004-PSOR-12 study are consistent with results from the pivotal Phase 3 studies CC-10004-PSOR-008 and CC-10004-PSOR 009, which were conducted in subjects with moderate to severe psoriasis.

This study will directly investigate the safety and efficacy of apremilast 30 mg BID, compared with placebo, in the treatment of subjects with mild to moderate plaque psoriasis. While PASI-75 has been the standard primary efficacy endpoint to measure disease severity in subjects with moderate to severe plaque psoriasis (BSA $\geq$ 10%), the utility of PASI is limited by its decreased sensitivity in moderate disease (BSA < 10%) where the general degree of improvement is underestimated (Spuls, 2010; Menter, 2008). The PASI scoring system combines the severity of the psoriatic lesion and BSA involvement into a single score of 0-72. Assessment of PASI includes the scoring of affected skin based on categories of involved BSA, with the lowest score covering a BSA of < 10%. As the extent of the psoriatic lesion decreases, the score is increasingly dependent on plaque severity. Consequently, in subjects with a baseline BSA of < 10%, the PASI score can no longer account for changes in affected skin surface area, but only plaque severity.

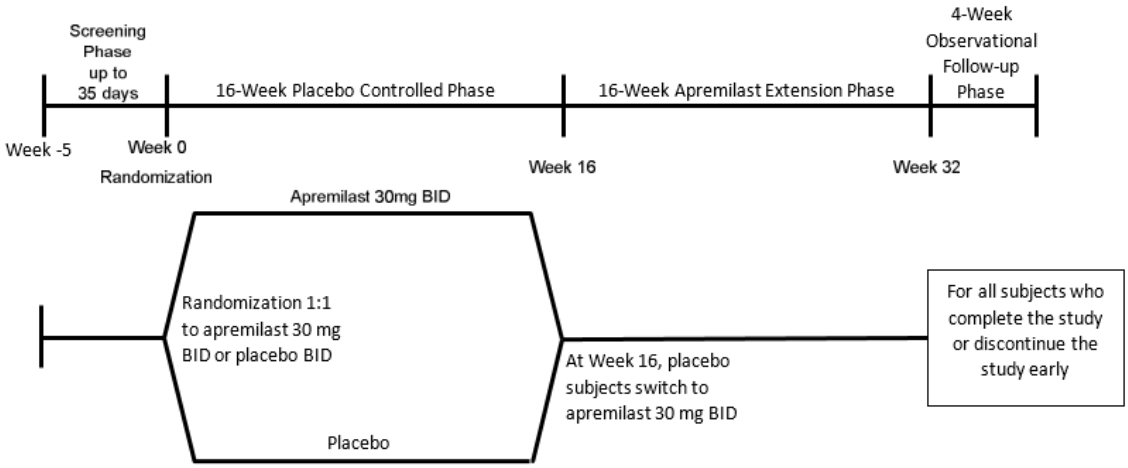
The primary endpoint will be the proportion of subjects with an sPGA score of 0 (clear) or 1 (almost clear) at Week 16 with at least a 2-point reduction from baseline. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the 3 primary signs of the disease: erythema, scaling and plaque elevation (Feldman, 2005). This assessment has been used routinely in pivotal studies evaluating response to investigational psoriasis therapies and has been used in all clinical psoriasis trials with apremilast. In the proposed study population of subjects with a baseline of sPGA of mild (2) or moderate (3), in whom topicals are inadequate, inappropriate or contraindicated, Celgene believes that achieving an sPGA score of clear (0) or almost clear (1) with at least a 2-point at Week 16 will represent a clinically meaningful benefit in patients with limited treatment options.

Secondary endpoints of response will include, at Week 16, proportion of subjects who improved $\geq$ 75% in BSA, change from baseline in affected BSA, PASI score, proportion of subjects who achieved BSA $\leq$ 3%, proportion of subjects with $\geq$4-point reduction (improvement) in the whole body itch numeric rating scale (NRS) score among subjects with baseline whole body itch NRS $\geq$ 4, proportion of subjects with Scalp Physician Global Assessment (ScPGA) score of clear (0) or almost clear (1) and with at least a 2-point reduction among subjects with baseline ScPGA score $\geq$ 2, and Dermatology Life Quality Index (DLQI) total score.

Eligible subjects will be randomized 1:1 to receive either apremilast 30 mg BID or placebo. Randomization will be stratified by baseline sPGA score (mild [2] or moderate [3]) to ensure balance between treatment arms with respect to baseline severity of psoriasis. Approximately

available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Week 16 CSR. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

Figure 1: Study Design



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.

3.2. Study Duration for Subjects

Subjects who complete the entire study will spend a total of approximately 41 weeks in this clinical trial:

- Up to 35 days (5 weeks) in the Screening Phase
- Weeks 0 to 16 (16 weeks) in the Double-blind Placebo-controlled Phase
- Weeks 16 to 32 (16 weeks) in the Apremilast Extension Phase
- Four-week (4 weeks) Post-treatment Observational Follow-up Phase

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

- **Scalp Physician Global Assessment**

  The ScPGA is a measurement of overall scalp involvement by the Investigator at the time of evaluation. The ScPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. When making the assessment of overall scalp severity, the Investigator should factor in areas that have already been cleared (ie, have scores of 0) and not just evaluate remaining lesions for severity, ie, the severity of each sign is averaged across all areas of involvement, including cleared lesions.

  In the event of different severities across signs of psoriasis, the sign that is the predominant feature of psoriasis should be used to help determine the ScPGA score. See Appendix D for grading criteria.

- **Nail Assessments/Nail Psoriasis Severity Index**

  The number of fingers with psoriasis nail involvement will be counted. The NAPSI will assess one target thumb nail or fingernail representing the worst nail psoriasis involvement at baseline. See Appendix E for grading criteria.

6.5. Safety Assessments

- **Contraception Education**

  The risks to a fetus or to a nursing child from apremilast are not known at this time. Results of animal and in vitro studies can be found in the current IB.

  All FCBP must use one of the approved contraceptive options as described in Section 4.2 while on IP and for at least 28 days after administration of the last dose of the IP. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

  At screening and at baseline, and at any time during the study when a female subject of childbearing potential's contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding contraception options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

- **Serum and Urine Pregnancy Tests for Females of Childbearing Potential**

  A serum pregnancy test with a sensitivity of $\leq$ 25 mIU/mL will be required for FCBP subjects at screening and at the Early Termination Visit or Visit 10. In addition, a local urine pregnancy test kit will be provided by the central laboratory and will be performed at the site on all FCBP subjects at the Baseline Visit, prior to dosing, and at Visits 4, 5, 6, 7, 8, and 9. An unscheduled serum pregnancy test should be performed if the FCBP subject has missed a menstrual period or has a positive urine dipstick test.

- **Hepatitis B and C**

  Hepatitis testing will include hepatitis B surface antigen and anti-hepatitis C antibody.

- **Vital Signs, Height, and Weight**

  Vital signs, including temperature, pulse, and seated blood pressure, will be taken during the visits indicated in Table 3. Height will be measured and recorded at Screening; weight will also be measured and recorded at screening and then as indicated in Table 3. Body mass index (BMI) will be calculated at Screening.

- **Complete 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).

- **Columbia Suicide Severity Rating Scale (C-SSRS)**

  The C-SSRS (Posner, 2007) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period (Appendix F). The C-SSRS must be administered by appropriately trained site personnel. The C-SSRS will be completed at all study visits. At Visit 1 (Screening) the C-SSRS will be completed for the subject's lifetime history of suicidal ideation and behavior. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit.

- **Psychiatric Evaluation**

  Apremilast prescriber information (eg, Summary of Product Characteristics, Package Insert) includes a warning regarding depression and suicidal thoughts. Patients with chronic diseases may be prone to depression. The risks and benefits of starting or continuing treatment with apremilast should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. At any time during the study, subjects who have suicidal thoughts or behavior should be evaluated. If the psychiatrist deems the subject not to be a risk for suicide, the subject may remain in the study, but if a risk of suicide is confirmed, the subject must be discontinued from the study. If the subject is discontinued during the treatment phase of the study, the subject should return for the Observational Follow-up Visit.

  A copy of the psychiatric evaluation report must be in the subject's source documentation, especially if the subject is confirmed not to be at risk for suicide and is continuing in the study.

- **Clinical Laboratory Evaluations**

  Clinical laboratory evaluations will be performed by a central laboratory and as indicated in Table 3. Clinical laboratory evaluations include complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count); serum chemistries (total

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

The chemical name of apremilast (CC-10004) is acetamide, N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl].

Apremilast will be supplied by the Sponsor, Celgene Corporation, and labeled appropriately as investigational product for this study.

All IP will be provided in blister cards throughout the entire study. Apremilast will be provided as 10, 20, or 30 mg tablets. Placebo will be provided as identically appearing 10, 20, or 30 mg tablets. Apremilast, the investigational product (IP), will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To mitigate potential gastrointestinal (GI) side effects, dose titration will be implemented in the first week of this study (see Table 4).

During Week 0 (Days 1 to 7), subjects will be dispensed placebo or 30 mg BID titration and treatment blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo tablets. The blister cards will contain all IP required for 4 weeks of treatment, with the first 7 days containing the titration supplies or matching placebo (see Table 4 Treatment Schema for Dose Titration at Visit 2 [Week 0] which details the titration supplies from Day 1 to Day 7).

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 1:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). Treatment assignment will be stratified by baseline sPGA score [mild (2), or moderate (3)]. Approximately 30% of subjects randomized will have baseline sPGA score of mild (2) and approximately 70% of subjects will have a baseline sPGA score of moderate (3). The IRT system will monitor the total enrollment of each strata and screening will close once the approximate percentages are reached. IP will be dispensed as indicated below.

- Weeks 0 to 16: Double-blind, Placebo-controlled Treatment Phase: Apremilast 30 mg BID or placebo BID.
  - Week 0 to 1: subjects will be dose titrated as described above and detailed in Table 4.
- Weeks 16 to 32: Apremilast Extension Phase: Apremilast 30 mg BID.
  - Week 16 to 17: subjects will be dose titrated as described below and detailed in Table 5.

Starting at Week 16, all subjects will be switched to, or will continue with apremilast. Subjects originally randomized to placebo at Week 0 will be switched to apremilast 30 mg BID at Week 16. The 30 mg BID titration and treatment blister cards will be used for subjects switching from placebo to apremilast; dummy titration blister cards (dosing at 30 mg BID directly) will be used for subjects initially randomized to receive apremilast 30 mg BID. At all other visits during the Apremilast Extension Phase, all subjects will receive apremilast 30 mg tablets which are to be taken twice daily.

applicable. Additional information may be included on the label as applicable per local regulations.

7.6. Investigational Product Accountability and Disposal

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study.

The Investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP accountability form. The Investigator(s) or Pharmacist(s) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

The IP should be stored as directed on the package label.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.7. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. Investigational product will be dispensed as noted in the Table of Events, Table 3. The subjects will be instructed to return the IP containers, including any unused medication, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their IP as instructed at each study visit. Any problems with IP compliance will be reviewed with the subject. If a subject misses 4 or more consecutive days of dosing, Celgene should be contacted to decide whether dosing should resume or whether the subject should be terminated from the Treatment Phase of the study, and enter into the Observational Follow-up Phase.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% or more than 120% of the doses between study visits) are protocol deviations and should be discussed with Celgene. Overall compliance with the study treatment regimen is defined as taking between 75% and 120% of the expected doses during a subject's participation while in the treatment phases (Placebo-controlled Phase and Apremilast Extension Phases) of the study.

tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency tabulations and percent for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast Extension Phase (Weeks 16 to 32). A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency distributions.

9.6. Efficacy Analysis

9.6.1. Efficacy Evaluation for the Placebo-controlled Phase (Weeks 0 to 16)

For the Placebo-controlled Phase (Weeks 0 to 16), the analyses for efficacy endpoints will be based on the intent-to-treat (ITT) population, defined as all subjects who are randomized. Statistical comparisons will be made between apremilast 30 mg BID and placebo. All statistical tests will be at the two-sided 0.05 significance level and the corresponding p-values and 95% confidence intervals (CIs) will be reported.

9.6.1.1. Primary Efficacy Endpoint

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

The primary endpoint will be analyzed using the Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factor at randomization. The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided.

Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc., 2011) based on similar subjects who remained in the study as the primary method. Sensitivity analysis will be conducted to account for missing data using the non-responder imputation (NRI) method and the tipping point analysis. Details of the NRI method and the tipping point analysis will be provided in the Statistical Analysis Plan (SAP).

For the multiple imputation method, the SAS procedure MI will be used to impute missing sPGA scores at the scheduled analysis visits in the Placebo-controlled Phase (Weeks 0 to 16) to create M=50 complete data sets. The missing data patterns will be checked at the scheduled analysis visits, ie, Baseline (Week 0), and Weeks 2, 4, 8, 12 and 16. If there are non-monotone missing patterns, two steps will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used with a single chain to impute missing scores by treatment and stratification factor to create M=50 imputed data sets with monotone missing patterns. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both

treatment and stratification factor in imputation model if necessary. The seed will be set to 17813721. The imputed scores will be rounded to the nearest integer. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest sPGA scores.

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

After the completion of imputation, sPGA response at Week 16 will be derived based on both observed and imputed scores. The same CMH method will be used to analyze the 50 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

9.6.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on the ITT population. The two-sided p-values and two-sided 95% confidence intervals (CIs) will be reported for treatment difference between apremilast and placebo arms. Multiplicity adjustment will be specified in the next section.

The continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM) as the primary method. The MMRM model will use the change from baseline as the response variable and include treatment group, visit time, treatment-by-time interaction, and stratification factor as fixed effects, and the baseline value as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted maximum likelihood (REML) to make proper statistical inference. Within-group least-squares (LS) means and the associated standard errors (SEs) and two-sided 95% CIs, treatment differences in LS means and the associated two-sided 95% CIs and two-sided p-values will be derived from the MMRM model. A sensitivity analysis will be conducted using the analysis of covariance (ANCOVA) model with treatment and stratification factor as the fixed effects, the baseline value as the covariate and the LOCF method to impute the missing data.

The binary endpoints will be analyzed similarly as the primary endpoint using the CMH test adjusting for the stratification factor at randomization. The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided. Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc., 2011) based on similar subjects who remained in the study as the primary method. Sensitivity analysis will be conducted to account for missing data using the last observation carried forward (LOCF) method and the non-responder imputation (NRI) method.

9.6.1.3. 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 two-sided 0.05

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

- Proportion of subjects with sPGA score of clear (0) or almost clear (1) and with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects who improved ≥ 75% in BSA from baseline
- Change from baseline in affected BSA at Week 16
- Change from baseline in total PASI score at Week 16
- In subjects with BSA > 3% at baseline, proportion of subjects who achieved BSA ≤ 3% at Week 16
- In subjects with whole body Itch NRS score ≥ 4 at baseline, proportion of subjects with ≥ 4-point reduction (improvement) from baseline in the whole body itch NRS score at Week 16
- In subjects with ScPGA score ≥ 2 at baseline, 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
- Change from baseline in DLQI total score at Week 16

9.6.1.4. Exploratory Endpoints

[redacted]

9.6.1.5. Subgroup Analysis

Subgroup analyses for sPGA response at Week 16 based upon baseline demographic (age, gender, race, etc.) or baseline disease characteristics will be provided to determine the robustness of the treatment effect.

9.6.2. Efficacy Evaluation – Apremilast Extension Phase (Weeks 16 to 32)

Efficacy endpoints for time points beyond Week 16 will be summarized according to the treatment assigned at randomization. For all subjects, changes in measurements will be calculated relative to measurements obtained at baseline (Week 0). Descriptive summary statistics or proportion of subjects achieving specified criteria will be summarized by treatment group. For continuous variables, descriptive statistics for baseline and changes or percent changes from baseline will be provided. Categorical variables will be summarized with frequency tabulations. Two-sided 95% confidence intervals will be provided for changes or percent changes and response rates.

9.7. Safety Analysis

The safety analyses will be performed using the safety population, defined as all subjects who are randomized and receive at least one dose of investigational product. Safety will be assessed by clinical review of all relevant parameters including treatment emergent adverse events (TEAEs), laboratory tests, and vital signs; no inferential testing for statistical significance will be performed. Data from safety assessments will be summarized descriptively for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast Exposure Period when subjects receive apremilast treatment. For safety analyses in the Placebo-controlled Phase, baseline will be relative to the first dose date following randomization at Week 0. For safety analyses in Apremilast Exposure Period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the Apremilast Extension Phase (Weeks 16 to 32).

Adverse events will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity and relationship to investigational product. TEAEs leading to death or to discontinuation from treatment and SAEs will be summarized and listed separately.

Data from other safety assessments will be summarized descriptively. Shift tables for laboratory parameters showing the number of subjects with values low, normal, and high compare to the normal reference ranges pretreatment versus post treatment will be provided.

To account for the different exposure to the investigational product, AEs or marked laboratory abnormalities will also be summarized using the exposure adjusted incidence rate, in addition to the simple incidence rates.

9.8. 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 database restriction will be performed, the primary data analysis will be conducted and a Week 16 CSR will be generated. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Week 16 CSR. 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 CSR will be generated.

9.9. Other Topics

9.9.1. Pharmacodynamic Analysis

[redacted]

- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by recording them on the CRF, or other appropriate method as directed.

- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE on the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in a female subject of childbearing potential are immediately reportable events.

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of the relevant CRFs. All SAEs must be reported to Celgene Drug Safety by recording them on the CRF and transmitting the data electronically within 24 hours of the Investigator's knowledge of the event. In the event the CRF is not available for transmission, a paper SAE Report Form will be sent directly to Celgene Drug Safety. The event must also be reported on the CRF once available. This

instruction pertains to the initial reporting of an SAE as well as reporting any follow-up information.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured within the CRF but will not be transmitted electronically to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE source documents and all correspondence with the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be generated from Celgene Drug Safety to the site via the CRF.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to apremilast based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC. (See Section 14.3 for record retention information).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event
- Lack of efficacy
- Withdrawal by subject
- Death
- Lost to follow-up
- Non-compliance with IP
- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Subjects with a BMI < 18.5 kg/m^2 at baseline who lose ≥ 5% of their baseline weight
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

When a subject is discontinued from treatment, the Investigator should make every attempt possible to have the subject evaluated at the Early Termination Visit within 4 days of the last intake of IP.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up

3. OVERALL STUDY DESIGN

3.1. Study Design

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

Approximately 574 subjects will be enrolled and randomized 1:1 to receive either apremilast 30 mg BID or placebo for the first 16 weeks. Subjects will be randomized based on a permuted block randomization using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline sPGA score (mild [2] or moderate [3]). Approximately 30% of subjects randomized will have a baseline sPGA score of mild (2) and approximately 70% of subjects will have a baseline sPGA score of moderate (3).

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

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

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

The blind should be maintained for persons responsible for the ongoing conduct of the study. Blinded persons may include but are not limited to: Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, Clinical Research Associates.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed; the primary data analysis will be conducted and a Week 16 Clinical Study Report (CSR) will be generated. However, unblinded data will only be made

Table 3: Table of Events (Continued)

	Screening	Placebo-controlled Treatment Phase						Apremilast Extension Phase			Observational Follow-up
Visit Number	**1**	**Baseline[a] 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10/ET[b]**	**11**
Week	**-5 to 0**	**0 (Day 1)**	**2 (± 4 days)**	**4 (± 4 days)**	**8 (± 4 days)**	**12 (± 4 days)**	**16 (± 4 days)**	**20 (± 4 days)**	**24 (± 4 days)**	**32 (± 4 days)**	**4 Weeks After Last Dose (± 2 weeks)[c]**
Dosing											
Dispense IP	-	X	-	X	X	X	X	X	X	-	-
Return and count IP tablets	-	-	-	X	X	X	X	X	X	X	-

BSA = body surface area; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; ET = Early Termination Visit; FCBP = females of childbearing potential; IP = investigational product; NAPSI = Nail Psoriasis Severity Index; NRS = Numeric Rating Scale; ScPGA = Scalp Physician Global Assessment; RNA = ribonucleic acid; sPGA = Static Physician Global Assessment.

[a] All baseline assessments must be completed prior to randomization and dispensing of IP.

[b] Visit 10 will serve as the Early Termination Visit for any subject who prematurely discontinues from the study.

[c] All subjects who complete the study or discontinue the study early will be asked to enter the Four-week Post-Treatment Observational Follow-up Phase.

[d] Written informed consent will be obtained by the Principal Investigator or designee prior to performing any study assessments. Optional consents for research include: RNA Gene Expression, [redacted] sub-studies.

[e] FCBP: Serum pregnancy tests will be performed at the Screening and Early Termination/Visit 10. Urine dipstick pregnancy test will be performed at baseline, prior to dosing and at Visits 4, 5, 6, 7, 8, and 9. An unscheduled serum pregnancy test should be administered if the subject has missed a menstrual period or has a positive urine dipstick test. The investigator will educate all FCBP about the options for and correct use of contraceptive methods at the Screening and Baseline Visits and at any time when a FCBP's contraceptive measures or ability to become pregnant changes.

[f] Hepatitis B surface antigen and anti-hepatitis C antibody.

[g] Refer to Section 6.5, Clinical Laboratory Evaluations for details regarding hematology, clinical chemistries, and urinalysis parameters to be tested.

[h] Should be performed at any time during the study when suicidal thoughts or a suicide attempt is identified. See Section 6.5, Psychiatric Evaluation.

[i] At any time during the study, a psoriasis flare may be reported as an adverse event, provided it meets the protocol definition. See Section 6.5, Psoriasis Flare Assessments.

[j] Post-baseline NAPSI and ScPGA assessments will only be performed for subjects with nail and/or scalp involvement, respectively, at Baseline.

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RBC	Red blood cell
REML	restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
ScPGA	Scalp Physician Global Assessment
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
sPGA	Static Physician Global Assessment
SUSAR	Suspected unexpected serious adverse reaction
SE	Standard error
TB	Tuberculosis
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosing factor
ULN	Upper limit of normal
USA	United States of America
UV	Ultraviolet
UVB	Ultraviolet B
WBC	White blood cell
WHO	World Health Organization

10. Females of childbearing potential (FCBP)[1] must have a negative pregnancy test at Screening and Baseline. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive[2] options described below:

    Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

    OR

    Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subjects has any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject is pregnant or breast feeding.
5. Subject has hepatitis B surface antigen or anti-hepatitis C antibody positive at Screening.
6. Subject has active tuberculosis (TB) or a history of incompletely treated TB.
7. Subject has history of positive human immunodeficiency virus (HIV), or has congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
8. Subject has active substance abuse or a history of substance abuse within 6 months prior to signing the ICF.
9. Subject has bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of signing the ICF. Any treatment for such infections must have been completed at least 4 weeks prior to randomization.
10. Subject has malignancy or history of malignancy except for:
    a. treated (ie, cured) basal cell or squamous cell in situ skin carcinomas;

[1] A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).
[2] The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

30% of subjects randomized will have baseline sPGA score of mild (2) and approximately 70% of subjects will have a baseline sPGA score of moderate (3).

1.3.3. Rationale for Dose, Schedule and Regimen Selection

In addition to subgroup analysis of Phase 3 pivotal studies of CC-10004-PSOR-008 and CC-10004-PSOR-009, Study CC-10004-PSOR-012, a randomized, double-blind, placebo-controlled Phase 4 study, demonstrated that apremilast 30 mg BID provided a treatment benefit in subjects with moderate plaque psoriasis. This study will directly investigate the safety and efficacy of this dosing regimen in the treatment of subjects with mild to moderate plaque psoriasis.

1.3.4. Rationale for Choice of Comparator Compounds

A randomized, double-blind placebo-controlled design was chosen in order to measure the absolute treatment effect of apremilast 30 mg BID in mild to moderate plaque psoriasis. The placebo-controlled design also minimizes subject and investigator bias in evaluating the efficacy and safety of apremilast in the selected patient population (Food and Drug Administration [FDA] Guidance for Industry E10 [FDA, 2016]).

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the clinical efficacy of oral apremilast 30 mg twice daily (BID), compared to placebo, in subjects with mild to moderate plaque psoriasis during the 16-week Placebo-controlled Phase.
Secondary Objectives
The secondary objectives are: • To evaluate the safety and tolerability of apremilast 30 mg BID, compared with placebo, in subjects with mild to moderate plaque psoriasis • 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 Health-related Quality of Life (HRQoL)
Exploratory Objective(s)
The exploratory objectives are: [redacted]

protein, albumin, calcium, phosphorous, glucose, total cholesterol [TC], triglycerides, high-density lipoprotein [HDL], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST; serum glutamic-oxaloacetic transaminase, SGOT], alanine aminotransferase [ALT; serum glutamic pyruvic transaminase, SGPT], sodium, potassium, chloride, bicarbonate [carbon dioxide, CO_2], blood urea nitrogen, creatinine, lactate dehydrogenase [LDH], and magnesium); as well as [redacted] and dipstick urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen). Dipstick urinalysis will be performed by the central laboratory; microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the dipstick urinalysis is abnormal.

Fasting is not required. However, if significant elevation of serum lipid(s) is observed, a fasting retest should be requested to determine whether or not elevation was caused by eating.

- **Psoriasis Flare Assessments**

  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. A more typical, gradual worsening of plaque psoriasis would not be recorded as an AE.

- **Adverse Events**

  Details of AE reporting may be found in Section 10.1.

6.6. Pharmacokinetics

Not Applicable.

[redacted]

The treatment schema for dose titration at baseline is shown in Table 4.

Table 4: Treatment Schema for Dose Titration at Visit 2 (Week 0)

	Week 0											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6-7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Apremilast 30 mg BID	10 mg A 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg P 30 mg A	30 mg A	30 mg A
Placebo	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	30 mg P	30 mg P

A = Apremilast; BID = twice daily; P = Placebo.

During Weeks 16 to 32, the IP will remain blinded, to prevent study personnel and subjects from knowing the IP assignment in the Placebo-controlled Treatment Phase and to maintain the blind regarding the initial treatment assignment, all subjects will receive dose titration cards at Visit 7 (Week 16). Although only subjects initially randomized to placebo will be dose titrated during their first week of the Apremilast Extension Phase, all subjects entering the Apremilast Extension Phase will receive identically-appearing titration/treatment cards as shown in Table 5.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the Investigator.

All concomitant treatments, including blood and blood products, used from 28 days prior to first dose of IP until 28 days after the last dose of IP, must be reported on the CRF.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics, or excretion, please see the current Investigators Brochure and/or local package insert.

8.1. Permitted Concomitant Medications and Procedures

Subjects may take any medication that is not restricted by the protocol and would not be expected to interfere with the conduct of the study or affect assessments. Chronic medication should be dosed on a stable regimen.

All medications (prescription and non-prescription), treatments and therapies taken by the subject from screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, the date the medication was started and the date the medication was stopped (if not ongoing) must be recorded. The recording of any permitted topical medications taken for psoriasis should also include the area of the body to which they are applied and the frequency of application.

The following topical therapies will be permitted during the study:

- For body lesions: unmedicated emollients
- For scalp lesions: non-medicated shampoos

8.2. Prohibited Concomitant Medications and Procedures

The following psoriasis medications cannot be administered for the duration of the study:

- Topical therapy
  - Topical therapy, including, but not limited to, topical corticosteroids, retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol for body lesions; coal tar, salicylic acid preparations, or medicated shampoos for scalp lesions, or as specified in Section 8.1.
- Intralesional corticosteroid injections for psoriasis lesions
- Conventional systemic therapy
  - Systemic therapy including but not limited to cyclosporine, corticosteroids, methotrexate, retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, or fumaric acid esters

9.9.2. Investigational Product Compliance

Investigational product record information will be summarized. Overall compliance will be estimated by the proportion of subjects who take between 75% and 120% of the intended quantity of IP.

9.9.3. Concomitant Therapy

All concomitant treatments documented during the study period will be summarized in frequency tabulations. The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For all AEs, the Investigator must assess the severity/ intensity of the event.

Mild

- *Asymptomatic or mild symptoms; clinical or diagnostic observations only*
- *Intervention not indicated*
- *Activities of daily life (ADLs) minimally or not affected*
- *No or minimal intervention/therapy may be required*

Moderate

- *Symptom(s) cause moderate discomfort*
- *Local or noninvasive intervention indicated*
- *More than minimal interference with ADLs but able to carry out daily social and functional activities.*
- *Drug therapy may be required*

Severe (could be non-serious or serious)

- *Symptoms causing severe discomfort/pain*
- *Symptoms requiring medical/surgical attention/intervention*
- *Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)*
- *Drug therapy is required*

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.