studies. This modified 5-point ScPGA scale is static, limited in the number of categories, and has categorical descriptions that are distinct and non-overlapping.

The primary endpoint will be assessed at Week 16 as results from prior studies suggest that a treatment effect over placebo can be demonstrated by this time point. The use of placebo for 16 weeks has been acceptable in moderate to severe plaque psoriasis clinical trials. A total treatment duration of 32 weeks was selected in order to assess longer term effect of apremilast in the treatment of moderate to severe scalp psoriasis.

The study will also investigate the efficacy of apremilast 30 mg BID, compared with placebo, in the improvement of itch. The data from the two pivotal Phase 3 studies of apremilast in subjects with moderate to severe plaque psoriasis (Study PSOR-008 and Study PSOR-009) demonstrated improvement in itch severity using a Visual Analog Scale (VAS). In this study, improvement of itch will be assessed using Numeric Rating Scales (NRS) as these are considered to have better reliability and precision, and lesser potential for missing values, than the VAS (Phan, 2012). The first secondary endpoint will be the proportion of subjects with ≥4-point reduction (improvement) from baseline in the Whole Body Itch NRS score at Week 16. It is anticipated that approximately 80% of the subjects would be evaluable for this analysis, based on prior experience in Studies PSOR-008 and PSOR-009 as well as other clinical trials in moderate to severe plaque psoriasis (Griffiths, 2015).

Eligible subjects will be randomized 2:1 to receive either apremilast 30 mg BID or placebo in order to reduce exposure to placebo without greatly increasing numbers of subjects exposed to IP, while maintaining the statistical power of the study. Randomization will be stratified by baseline ScPGA score in order to ensure balance between treatment arms with respect to baseline severity of scalp psoriasis.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

Exploratory analyses from the two pivotal Phase 3 studies (PSOR-008 and PSOR-009) demonstrated that apremilast 30 mg BID provided a treatment benefit in subjects with plaque psoriasis of the scalp of moderate or greater severity. This study will directly investigate the safety and efficacy of this dosing regimen in the treatment of subjects with moderate to severe plaque psoriasis of the scalp.

1.3.4. Rationale for Choice of Comparator

A randomized, double-blind placebo-controlled design was chosen in order to measure the absolute treatment effect of apremilast 30 mg BID in moderate to severe plaque psoriasis of the scalp. 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).

CCI [redacted]

CCI [redacted]

Table 2: Study Endpoints

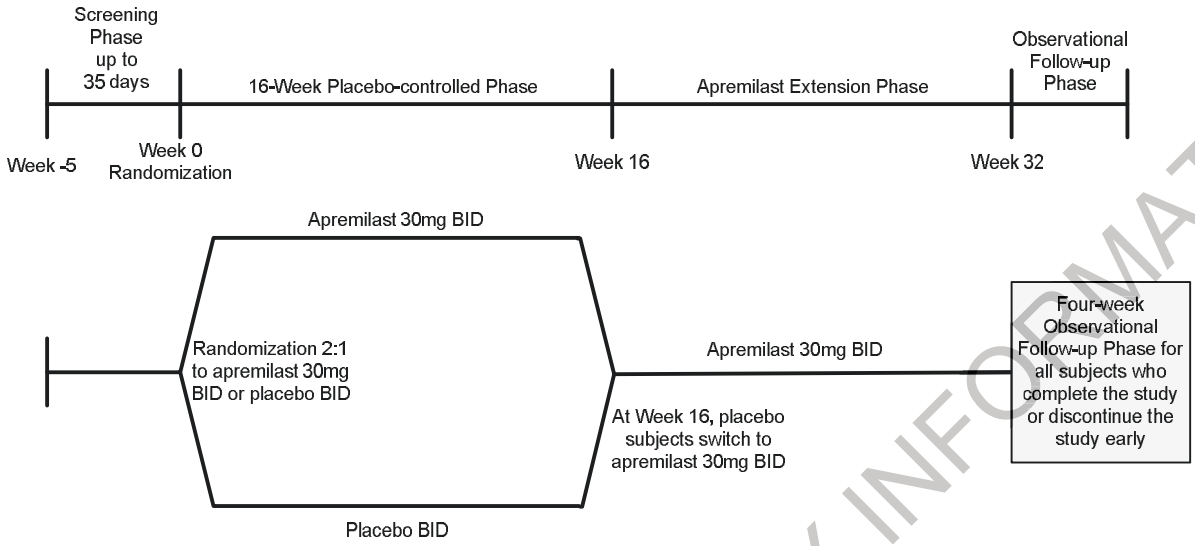
Endpoint	Name	Description	Timeframe
Primary	Scalp Physician Global Assessment (ScPGA)	Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16.	Week 16
Secondary	Itch Numeric Rating Scale (NRS) [whole body]	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score	Week 16
	Itch NRS (Scalp)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the scalp itch NRS score	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)
	Dermatological Life Quality Index (DLQI)	Change from baseline in DLQI total score	Week 16
Exploratory	CCI [redacted]	[redacted]	[redacted]
	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
	CCI [redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	CCI [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	DLQI	Change from baseline in DLQI total score	Weeks 4, 8, 16 and 32
	CCI [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
Safety	Type, frequency, severity, and relationship of adverse events to IP	Day 0 through end of Observational Follow-Up	Study duration

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.

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 pre-specified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 300 subjects with moderate to severe plaque psoriasis of the scalp will be enrolled and randomized from investigator sites in Canada and the USA.

4.2. Inclusion Criteria

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

1. Males or females, ≥ 18 years of age at the time of signing the informed consent document
2. Understand and voluntarily sign an informed consent form (ICF) prior to any study-related assessments/procedures being conducted.
3. Be willing and able to adhere to the study visit schedule and other protocol requirements.
4. Have a diagnosis of moderate to severe plaque psoriasis of the scalp at screening and baseline as defined by:
    a. ScPGA (See Appendix B) score of ≥ 3 (moderate or severe) and,
    b. Scalp Surface Area (SSA) involvement of ≥ 20% and,
    c. Inadequate response or intolerance to at least one topical therapy (for example, potent or super potent topical corticosteroids, vitamin D analogs, and combination products) for plaque psoriasis of the scalp.
5. Must be a candidate for phototherapy and/or systemic therapy for either body or scalp psoriasis lesions.
6. Have moderate to severe plaque psoriasis at screening and baseline as defined by:
    a. Psoriasis Area and Severity Index (PASI) (CCI [redacted]) score ≥ 12 and,
    b. Body Surface Area (BSA) ≥ 10% and,
    c. Static Physician Global Assessment (sPGA) (CCI [redacted]) ≥ 3 (moderate)
7. Must be in good health (except for psoriasis) as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), clinical laboratories, and urinalysis
8. 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)
    f. Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)

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]**
Vasculitis Assessment [i]	-	-	-	-	-	-	-	-	-	-	-
Psychiatric Evaluation [j]	-	-	-	-	-	-	-	-	-	-	-
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Psoriasis Flare Assessment [k]	-	-	-	-	-	-	-	-	-	-	-
Clinical Efficacy Assessment(s)[l]											
Whole Body Itch NRS[m]	-	X	X	X	X	X	X	X	X	X	-
Scalp Itch NRS[m]	-	X	X	X	X	X	X	X	X	X	-
ScPGA	X	X	X	X	X	X	X	X	X	X	X
CCI											
Patient Reported Outcomes											
CCI											
DLQI	-	X	-	X	X	-	X	-	-	X	-
CCI											

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 B for grading criteria.

- CCI [redacted]

- **TB Testing**

  The QuantiFERON®-TB Gold test should be used in lieu of the tuberculin skin test (TST) or purified protein derivative (PPD) skin test if possible. This test result must be negative within one month prior to first administration of IP or prior completed treatment was documented.

- **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).

- **Vasculitis Assessment**

  The PDE4 inhibitors, including apremilast, have been shown to produce inflammatory perivascular histopathological changes in animal studies (eg, rodent toxicology studies). The Investigator should be watchful for any signs and symptoms of vasculitis at all times. Any suspicion of vasculitis must be thoroughly investigated by taking pertinent patient history, doing a physical examination, reviewing adverse events, and performing diagnostic procedures, as clinically indicated. A subject with signs and symptoms of possible vasculitis should receive a thorough evaluation as described above, be managed as medically appropriate, and continued with follow-up until the signs and symptoms of vasculitis have resolved.

- **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 (post-randomization), 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, 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.

[redacted]

6.8. Photography

Photographic assessments will be done at selected sites to provide supportive evidence of efficacy as scheduled in Table 3. The procedure for taking the photographs and processing and shipping photographs will be described in a separate procedure manual distributed to investigational sites performing photographic assessments.

Photographic assessments are an optional part of this study. Subjects enrolled at the selected photography sites will be asked to provide separate consent prior to being photographed.

regulatory statements as 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 IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6.1. Record of Administration

Accurate recording of all IP administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

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% 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.

proportion of subjects with ≥4-point improvement from baseline in the whole body itch NRS score.

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency 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)

Statistical comparisons will be made between apremilast 30 mg BID and placebo. All statistical tests will be at the 2-sided 0.05 significance level and the corresponding p-values will be reported. Data summaries will be provided for the two randomized treatment arms (apremilast 30 mg BID and placebo).

9.6.1.1. 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). It 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 (Cochran–Mantel–Haenszel) 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. Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc. 2008) 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 assessments in the Placebo-controlled Phase (Weeks 0-16) 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 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.

9.6.1.2. Secondary Efficacy Endpoints

For the binary endpoints defined as ≥4-point reduction (improvement) from the baseline visit in either the whole body pruritus NRS score or the scalp pruritus NRS score at post-baseline visits, the analyses will be based on subjects in the ITT population with baseline whole body pruritus NRS score ≥4 or baseline scalp pruritus NRS score ≥4, respectively. For the continuous secondary endpoint (ie, 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) will be reported.

In order to evaluate the onset of effect of apremilast 30 mg BID compared to placebo for itch, the following secondary endpoints are specified (Section 2):

- 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 overall body itch NRS score at Week 12, Week 8, Week 4, and Week 2
- 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 ten endpoints will be performed one by one downward from Week 16 to Week 2. Multiplicity adjustment is specified in Section 9.6.1.3.

The binary endpoints will be analyzed similarly as the primary endpoint. The treatment difference at each time point between apremilast 30 mg BID and placebo will be compared using CMH (Cochran–Mantel–Haenszel) 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. Missing values will be imputed using the similar MI method as the primary endpoint, with sensitivity analysis using the LOCF method and NRI method.

The continuous endpoint (ie, 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. Missing values at Week 16 will be imputed using the MI method, with sensitivity analysis using the LOCF 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 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

events leading to death or to IP withdrawal and serious AEs will also 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 compared with the normal reference ranges pre-treatment versus post-treatment will be provided.

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

By-subject listings will be provided for all relevant safety data.

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 lock will be performed, the primary data analysis will be conducted CCI CCI. 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 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.

9.9. Other Topics

9.9.1. Investigational Product Compliance (Tablets)

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.

9.9.2. 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.

9.9.3. Steering Committee

Guidance in protocol development and interpretation of data analysis will be provided by a scientific steering committee (SSC). Details for the SSC are pre-specified in a separate SSC charter.

- 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.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

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

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 β-subunit of human chorionic gonadotropin [β-hCG] 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 female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

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 an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug

Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent 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 information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

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 (eg, 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 Celgene and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

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
- 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
- Protocol deviation

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GI	Gastrointestinal
CCI [redacted]	[redacted]
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
LLN	Lower level of normal
LOCF	Last observation carried forward
LS	Least squares
CCI [redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NRI	Non-responder imputation
NRS	Numeric Rating Scale
PA	Posterior to anterior
CCI [redacted]	[redacted]
PDE4	Phosphodiesterase type 4
PP	Per protocol

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is 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.
Secondary Objective(s)
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
Exploratory Objective(s)
The exploratory objectives are: CCI [redacted] • To evaluate the effect of apremilast 30 mg BID compared to placebo on Dermatological Life Quality Index (DLQI) CCI [redacted]

3. OVERALL STUDY DESIGN

3.1. Overall Study Design

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 database lock 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]. 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

g. Hemoglobin A1c ≤ 9.0%

9. Females of childbearing potential (FCBP)[†] 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[§] 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. Other than psoriasis, history of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease.
2. 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. Any condition that confounds the ability to interpret data from the study.
4. Pregnant or breast feeding
5. Hepatitis B surface antigen positive at Screening
6. Anti-hepatitis C antibody positive at Screening
7. AST (SGOT) and/or ALT (SGPT) > 1.5 X ULN **and** total bilirubin > ULN and/or albumin < lower limit of normal (LLN)
8. Active tuberculosis (TB) or a history of incompletely treated TB

[†] 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).

[§] 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).

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]**
Optional Assessment(s) at Selected Investigative Sites											
Photographs[o]	-	X	-	-	X	-	X	-	-	X	-
Dosing											
Dispense IP	-	X	-	X	X	X	X	X	X	-	-
Return and count IP tablets	-	-	-	X	X	X	X	X	X	X	-

Abbreviations: BMI = body mass index; CCI ; CXR = Chest Radiograph; DLQI = The Dermatology Life Quality Index; ECG = Electrocardiogram; ET = Early Termination Visit; FCBP = females of childbearing potential; CCI IP = Investigational Product; NRS = Numeric Rating Scale; CCI ; ScPGA = Scalp Physician Global Assessment; CCI TB = tuberculosis testing; CCI

[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.
[e] CXRs taken within 12 weeks prior to screening will be accepted. CXRs should be performed as indicated by local treatment guidelines or practice for monitoring while on immunosuppressive/immunomodulatory therapy. If such guidelines are not available/applicable, routine CXRs should be performed as per the Table of Events or when clinically indicated.
[f] The QuantiFERON® Gold test should be used for TB testing in lieu of the tuberculin skin test (TST) or purified protein derivative (PPD) test, if possible.
[g] FCBP: Serum pregnancy tests will be performed at the Screening and Early Termination/Last Treatment Visit. Urine dipstick pregnancy test(s) will be performed at baseline, prior to dosing. An unscheduled pregnancy test should be administered if the subject has missed a menstrual period. 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.
[h] Refer to Section 6.5, Procedures, for details regarding hematology, clinical chemistries, and urinalysis parameters to be tested.
[i] At any time vasculitis is suspected. See Section 6.5, Procedures
[j] At any time when suicidal thoughts or a suicide attempt is identified. See Section 6.5, Procedures
[k] At any time, a psoriasis flare may be reported as an adverse event, provided it meets the protocol definition. See Section 6.5, Procedures
[l] Clinician assessments are to be performed after subject completes numeric rating scales and patient reported outcomes questionnaires as scheduled in the Table of Events. Clinician assessments must be done in the following order: ScPGA, CCI .
[m] Subject assessment of whole body itch must be performed prior to scalp itch assessment.
[n] Subject assessments must be completed in the following order: whole body itch NRS, scalp itch NRS, CCI DLQI, CCI as scheduled in the Table of Events.
[o] Photographs will be obtained from subjects who provide separate consent to be photographed and at select sites only.

CCI [redacted]

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 IB.

  All females of childbearing potential (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 (FCBP)**

  A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP subjects at screening and at the Early Termination or Last Treatment Visit. 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. An unscheduled pregnancy test should be performed if the FCBP subject has missed a menstrual period.

- **Chest Radiograph (CXR)**

  A CXR is required during Screening. A PA view is required; an additional lateral view is strongly recommended but not required. Alternatively, PA or PA/lateral radiographs that were taken within the 12 weeks prior to screening will be accepted. Chest radiographs should be performed as indicated by local treatment guidelines or practice for monitoring while on immunosuppressive/immunomodulatory therapy. If such guidelines are not available/applicable, routine CXRs should be performed when clinically indicated.

- **Hepatitis B and C**

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

- **Twelve-lead Electrocardiogram**

  A 12-lead ECG will be performed after the subject has been supine for approximately 3 minutes. ECGs will be performed at screening as indicated in Table 3. ECGs will be evaluated by a central reader.

- **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 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], adiponectin, 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 Hemoglobin A1C at the Screening Visit, 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 re-test 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 adverse event (AE).

- **Adverse Events**

  Details of AE reporting may be found in Section 10.1.

CCI [redacted]

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 1-7), subjects will be dispensed dose titration 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 2:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). 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. Dose titration 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.

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.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics (PK), or excretion, please see the Investigator's 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
- Phototherapy
  - UVB or PUVA

- 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 Dermatology Life Quality Index total score at Week 16

9.6.1.4. Exploratory 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.

9.6.1.5. 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 (age, gender, race, etc.) or baseline disease characteristics will be provided to determine the robustness of the treatment effect.

CCI [redacted]

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. 2-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 as defined in Section 9.2. Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, and ECG measurements; no inferential testing for statistical significance will be performed.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. Adverse events will be tabulated for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast Exposure Phase in the study. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. Adverse

9.9.4. Internal Celgene Safety Monitoring During the Apremilast Program: Role of the Safety Management Team

In addition to daily safety monitoring conducted by investigators and individual study personnel, cumulative and interval blinded adverse events (AEs), serious adverse events (SAEs), discontinuations, and laboratory findings are reviewed internally by a Safety Management Team (SMT) at Celgene. The review follows the Council for International Organizations for Medical Sciences, Working Group VI (CIOMS VI) recommendations. The SMT is comprised of lead representatives from multiple Celgene functions engaged in the apremilast development program. The scope, conduct, processes, and accountabilities of the SMT are specified in the SMT charter.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event based on the descriptions listed below.

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 obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there

- 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.

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PUVA	Psoralens ultraviolet A
RBC	Red blood cell
CCI [redacted]	[redacted]
SAE	Serious adverse event
ScPGA	Scalp Physician Global Assessment
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMT	Safety Management Team
SOP	Standard Operating Procedure
CCI [redacted]	[redacted]
[redacted]	[redacted]
SSC	Scientific steering committee
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosing factor
CCI [redacted]	[redacted]
TST (PPD)	Tuberculin sensitivity test (purified protein derivative)
ULN	Upper limit of normal
USA	United States of America
UV	Ultraviolet
UVB	Ultraviolet B
WBC	White blood cell
WHO	World Health Organization