

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

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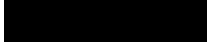
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PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Apremilast (CC-10004) in Subjects with Mild to Moderate Plaque Psoriasis

Indication

The indication is mild to moderate plaque psoriasis.

Objectives

Primary Objective

- 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

- 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)

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 static Physician Global Assessment (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:

- 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

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 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.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Approximately 574 adult subjects ≥ 18 years of age with mild to moderate plaque psoriasis will be randomized. Only subjects who don't have prior exposure to biologics for the treatment of psoriatic arthritis, psoriasis, or any other indication that could impact the assessment of psoriasis and who are inadequately controlled with or intolerant of topical therapies (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 will be eligible for the study.

Length of Study

The study is designed as a 32-week study with a Four-week Post-treatment Observational Follow-up Visit and consists of 4 phases as described above. Please refer to [Section 1.3.2](#) for details.

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.

Study Treatments

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].

All study medication will be provided in blister cards throughout the entire study. Apremilast will be provided as 10, 20, or 30 mg tablets by the study Sponsor, Celgene Corporation. Placebo will be provided as identically appearing 10, 20, or 30 mg tablets.

Investigational product will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. As in the prior Phase 3 studies, dose titration will be implemented in order to mitigate potential gastrointestinal-related adverse events (AEs). 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 for the dose titration. 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 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 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.

Dose modifications are not permitted in this study.

Overview of Key Efficacy Assessments

Primary Efficacy Assessment

- sPGA

Additional Efficacy Assessments

- Body Surface Area (BSA)
- Psoriasis Area Severity Index (PASI)
- Whole Body Itch Numeric Rating Scale (NRS)
- Scalp PGA (ScPGA)
- Dermatological Life Quality Index (DLQI)
- Nail Psoriasis Severity Index (NAPSI)

Overview of Key Safety Assessments

Safety assessments will include:

- Adverse events (AE)
- Vital signs
- Pregnancy tests for females of childbearing potential (FCBP)
- Clinical laboratory tests
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Methods

The sample size estimation is based on the results of the Phase 3 and 4 studies with apremilast. With a total of approximately 574 subjects and a randomization ratio of 1:1, the study will randomize approximately 287 subjects to apremilast 30 mg BID and 287 subjects to placebo.

This sample size will provide more than 90% power to detect a 15% difference between the two treatment groups for the primary endpoint at a two-sided significance level of 0.05. The calculation is based on a chi-square test assuming 15% response rate for placebo and adjusting for a 20% dropout rate.

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.

The treatment difference for the primary endpoint will be compared between apremilast 30 mg BID and placebo using a Cochran Mantel-Haenszel (CMH) test adjusting for the stratification factor. 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 stratification factor 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 multiple imputation (MI) as the primary method, with sensitivity analysis using the non-responder imputation (NRI) method and the tipping point analysis.

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 other binary endpoints will be analyzed similarly as the primary endpoint using the CMH test.

To control the overall type I error rate, a fixed-sequence testing procedure will be used to test the primary and secondary endpoints in a predefined order. The test will be performed in sequence and significance of all preceding endpoints is required in order to proceed to the next one. The proposed sequence of testing for the primary and secondary efficacy endpoints is listed below.

- Proportion of subjects with sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects who improved $\geq 75\%$ 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



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.

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 serious adverse events (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 comparing with the normal reference ranges pre-treatment 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.

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1. INTRODUCTION

1.1. Disease Background

Psoriasis is a chronic, immune-mediated disorder. Plaque psoriasis, the most common form of psoriasis, is typically characterized by raised, demarcated erythematous plaques covered by a silvery scale ([Lebwohl, 2003a](#)). Psoriasis affects 2-3% of the population, with approximately 80% of patients experiencing mild to moderate disease ([Menter, 2009](#)). Psoriasis is associated with a range of comorbidities that have been demonstrated in subjects regardless of psoriatic disease severity ([Ahlehoff, 2011, 2013](#)).

Treatment guidelines categorize therapy by extent of psoriatic disease based on the amount of affected body surface area (BSA). Limited involvement or mild disease, defined as 0-3% BSA (National Psoriasis Foundation [NPF]) or $\leq 5\%$ (American Academy of Dermatology [AAD], [[Menter, 2008](#)]) can be treated with topical therapies. However, treatment satisfaction remains low in patient using topical therapies compared to systemic or phototherapy ([Cranenburgh, 2013](#)). In a recently published comparison of combination calcipotriene and betamethasone (Enstilar[®]) with the individual component therapies in a 4-week treatment period, about half of the subjects in this treatment group did not achieve a meaningful reduction of their plaque psoriasis, and even higher numbers of subjects failed to achieve response with calcipotriene or betamethasone treatment alone ([Stein Gold, 2016](#)). Additionally, topical therapies may not be adequate for subjects with less than 5% BSA affected with psoriasis in vulnerable areas such as the face, genitals, hands and feet, scalp, or intertriginous areas ([Menter, 2011](#)). Treatment of nail psoriasis with topical therapies also poses a clinical challenge and may not be adequate for subject with significant skin and nail disease ([Crowley, 2015; Pasch, 2016](#)).

Extensive disease or moderate to severe disease, established by health authorities as $BSA \geq 10\%$, Psoriasis Area Severity Index (PASI) ≥ 12 and static Physician Global Assessment (sPGA) ≥ 3 (moderate or greater) can be treated with systemic therapies, but biologics and oral therapies such as methotrexate may be limited by safety concerns and the need for careful laboratory monitoring. Consequently, subjects with mild to moderate psoriasis, represent an underserved population. There remains an unmet medical need for an effective, convenient treatment of mild to moderate psoriasis that is well tolerated compared to the currently available treatment options ([Armstrong, 2013](#)).

1.2. Compound Background

Apremilast (CC-10004) is a specific phosphodiesterase type 4 (PDE4) inhibitor under development for use in the treatment of inflammatory conditions. The PDE4 is one of the major phosphodiesterases expressed in leukocytes. PDE4 inhibition by apremilast elevates cyclic adenosine monophosphate (cAMP) levels in immune cells, which in turn down-regulates the inflammatory response by reducing the expression of pro-inflammatory mediators such as tumor necrosis factor (TNF)- α , interleukin (IL)-23, IL-17, and other inflammatory cytokines, and increasing the production of anti-inflammatory mediators.

In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies,

apremilast (OTEZLA®) is approved in approximately 50 countries worldwide for the treatment of adult patients with active psoriatic arthritis and the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Apremilast remains under further clinical development for the treatment of inflammatory/autoimmune disorders including Behçet's disease, and ulcerative colitis. Further studies within the approved indications of plaque psoriasis and psoriatic arthritis are also ongoing.

Please refer to the current Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational product (IP).

1.3. Rationale

1.3.1. Study Rationale and Purpose

Treatment of mild to moderate plaque psoriasis can be challenging, and patient satisfaction and compliance with current treatment modalities are often low, particularly with topical therapies (Cranenburgh, 2013; Duffin, 2014). Low satisfaction with treatment options can lead to poor adherence and suboptimal response.

There remains an unmet medical need for an effective, convenient treatment of mild to moderate psoriasis that is well tolerated compared to the currently available treatment options (Armstrong, 2013). Currently approved topical corticosteroids and vitamin D analogues may be limited by short treatment durations, poor treatment compliance and significant adverse effects such as tachyphylaxis, skin atrophy, striae, telangiectasia, and hypothalamic-pituitary-adrenal (HPA) axis suppression (Chan, 2009; Kragballe, 2013). Other topical therapies, such as coal tar and anthralin preparations have cosmetically unappealing formulations, foul odor, limited efficacy, and potential carcinogenic risk (Chan, 2009). Systemic therapies including conventional therapies such as methotrexate, retinoids and cyclosporine or the biologics, have been approved for moderate to severe plaque psoriasis, and are associated with dose limiting effects such as hepatotoxicity, teratogenicity, nephrotoxicity and increased risk of malignancy or severe infection. In addition, careful laboratory monitoring for infections, reactivation of latent tuberculosis, hypersensitivity reactions and malignancies (Menter, 2009; Nast, 2012) may be required with these agents.

Apremilast (APR, OTEZLA®) is a drug that is taken orally (by mouth [PO]). Apremilast inhibits the enzyme PDE4, which is a cAMP-specific PDE and the dominant PDE in inflammatory cells. By inhibiting PDE4, apremilast elevates intracellular cAMP levels, which in turn modulates a network of pro- and anti-inflammatory mediators and reduces the inflammatory response.

The proposed Phase 3 study is intended to assess the safety and efficacy of apremilast 30 mg twice daily (BID) in the treatment of subjects with mild to moderate plaque psoriasis who are not adequately controlled by topical therapies.

1.3.2. Rationale for the Study Design

Study CC-10004-PSOR-012 was a randomized, double-blind, placebo-controlled Phase 4 trial, in which the efficacy and safety of apremilast was evaluated in 221 subjects with moderate plaque psoriasis defined as BSA of 5-10% and sPGA of 3 (moderate). In addition, eligible subjects had

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 ≥ 4 -point reduction (improvement) in the whole body itch numeric rating scale (NRS) score among subjects with baseline whole body itch NRS ≥ 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 ≥ 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

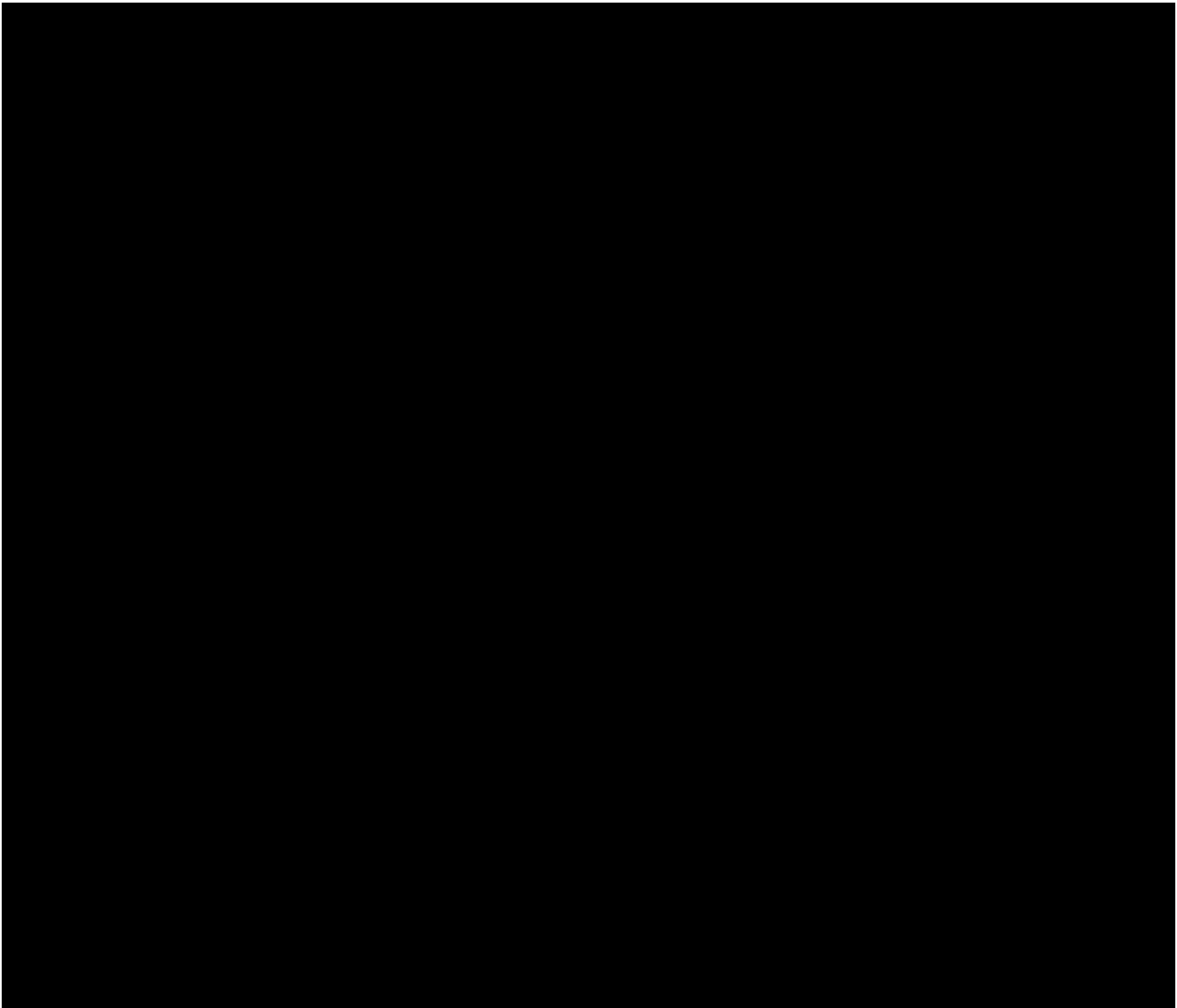
30% of subjects randomized will have baseline sPGA score of mild (2) and approximately 70% of subjects will have a baseline sPGA score of moderate (3).

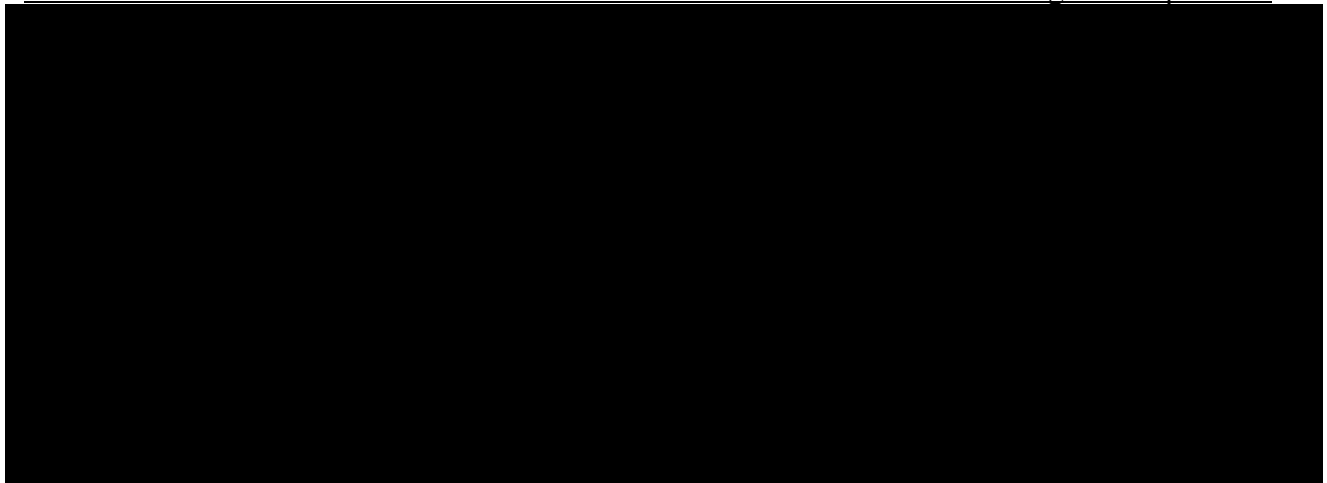
1.3.3. Rationale for Dose, Schedule and Regimen Selection

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

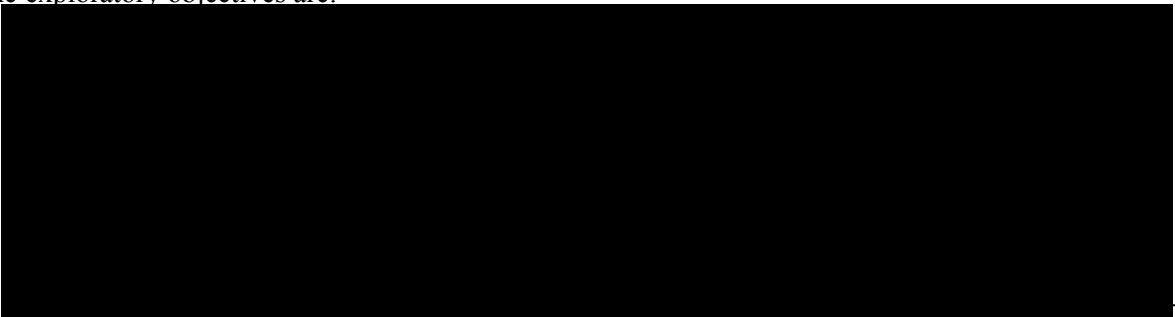
Primary Objective
The primary objective of the study is to evaluate the clinical efficacy of oral apremilast 30 mg twice daily (BID), compared to placebo, in subjects with mild to moderate plaque psoriasis during the 16-week Placebo-controlled Phase.
Secondary Objectives
<p>The secondary objectives are:</p> <ul style="list-style-type: none">• 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)
<p>The exploratory objectives are:</p> 

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 $\geq 75\%$ 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 $BSA \leq 3\%$ 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 $NRS \geq 4$	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			

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):

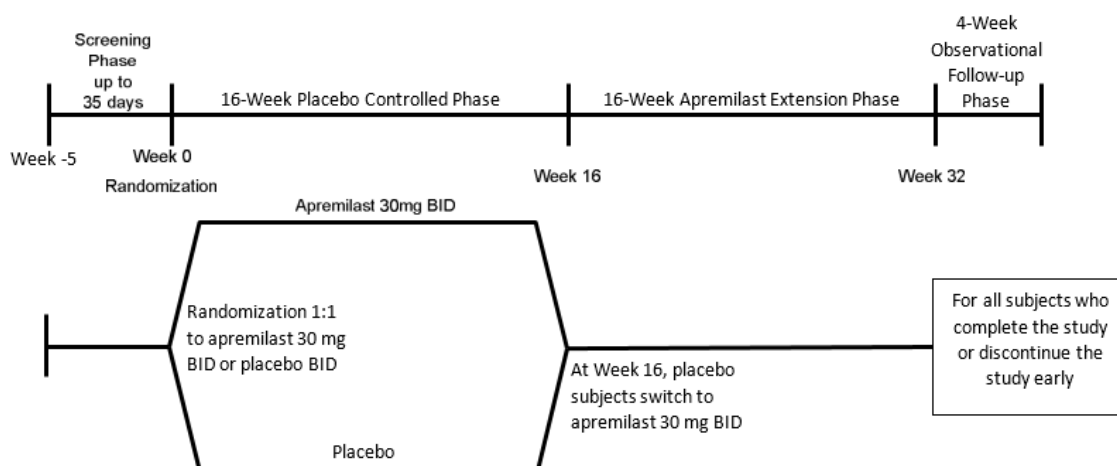
- Screening Phase – up to 35 days
- Double-blind Placebo-controlled Phase – Weeks 0 to 16
 - Subjects will be randomly assigned in a 1:1 ratio to either apremilast 30 mg BID or placebo.
- Apremilast Extension Phase – Weeks 16 to 32
 - All subjects will be switched to (or continue with) apremilast 30 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

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.

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 $\geq 3000/\text{mm}^3$ ($\geq 3.0 \times 10^9/\text{L}$) and $< 14,000/\text{mm}^3$ ($< 14 \times 10^9/\text{L}$)
 - b. Platelet count $\geq 100,000/\mu\text{L}$ ($\geq 100 \times 10^9/\text{L}$)
 - c. Serum creatinine $\leq 1.5 \text{ mg/dL}$ ($\leq 132.6 \mu\text{mol/L}$)
 - d. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) $\leq 2 \times$ upper limit of normal (ULN)
 - e. Total bilirubin $\leq 2 \text{ mg/dL}$ ($34 \mu\text{mol/L}$)

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 contraceptive² 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).

- b. treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence.
11. Subject has prior history of suicide attempt at any time in the subject's life time prior to signing the informed consent and randomization, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent.
 12. Subject has psoriasis flare/rebound (defined as a sudden worsening of psoriasis which requires administration of prohibited medications) within 4 weeks of signing the ICF or between the Screening and Baseline Visit.
 13. Subject has current or planned concurrent use of the following therapies that may have a possible effect on psoriasis during the course of the treatment phase of the trial:
 - a. Topical therapy within 2 weeks of randomization (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). An unmedicated skin moisturizer (eg, Eucerin[®]) will be also permitted for body lesions only. Subjects should not use these topical treatments within 24 hours prior to the clinic visit.
 - b. Conventional systemic therapy for psoriasis within 4 weeks prior to randomization (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, or fumaric acid esters).
 - c. Phototherapy treatment of body within 4 weeks prior to randomization (ie, ultraviolet B [UVB], psoralen and ultraviolet A [PUVA] radiation).
 - d. Use of any investigational drug beginning 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
 14. Subject has evidence of skin conditions that would interfere with clinical assessments.
 15. Subject has prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources.
 16. Subject had prior treatment with apremilast.
 17. Subject has history of allergy or hypersensitivity to any components of the investigational product (IP).

5. TABLE OF EVENTS

Table 3: Table of Events

Visit Number	Screening	Placebo-controlled Treatment Phase						Apremilast Extension Phase			Observational Follow-up
	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
Administrative/Demographics											
Informed consent ^d	X	-	-	-	-	-	-	-	-	-	-
Optional consent for research ^d	X	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion criteria	X	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-
Prior psoriasis medication	X	-	-	-	-	-	-	-	-	-	-
Prior / concomitant medications or therapies	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments											
Height	X	-	-	-	-	-	-	-	-	-	-
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	-	-	-	-	-	-	-	-	X	-
Pregnancy Test for FCBP and Contraception Education ^e	X	X	-	X	X	X	X	X	X	X	-
Hepatitis B and C ^f	X	-	-	-	-	-	-	-	-	-	-
Clinical Laboratory Evaluations ^g	X	X	-	-	X	-	X	-	X	X	-

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 ^k	-	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)											
Inflammatory Protein Biomarkers	-	X	-	-	-	-	X	-	-	-	-

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.

6. PROCEDURES

The following administrative/demographic procedures will be conducted as outlined in the Table of Events, [Table 3](#).

Informed Consent

An informed consent form (ICF) must be signed by the subject before any study-related assessments are performed. Details of the informed consent process may be found in [Section 13.3](#).

The appropriate optional consent form(s) for research must be signed by the subject before any sub-study sampling takes place.

Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria ([Section 4.2](#)) and must not have any of the conditions specified in the exclusion criteria ([Section 4.3](#)) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study (eg, if a female subject does not require pregnancy testing and birth control because of a hysterectomy, the date of the hysterectomy must be included in the medical history).

Medical and Disease History

Relevant medical history, as defined in the electronic Case Report Form (eCRF) Completion Guidelines, should be recorded, including smoking and alcohol history, as well as previous relevant surgeries (please refer to the eCRF Completion Guidelines for further details). Disease history includes history of psoriasis.

Prior/Concomitant Medications and Therapies

All medications and therapies being taken/used by the subject at the time of consent or at any time during the study should be recorded. Other key medications and therapies, such as previous treatment for TB or relevant diseases, should be recorded. Please refer to the eCRF Completion Guidelines and the Study Manual for additional instructions and for further details.

All medications and therapies for psoriasis, including topicals (used within the last 5 years prior to randomization), systemics, and all medications and therapies for psoriatic arthritis, should be recorded. The stop dates for all medications and therapies prohibited in the study should be recorded. Responses to prior psoriasis therapies should also be recorded. Please refer to the eCRF Completion Guidelines for additional instructions.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 35 days of screening unless noted otherwise below.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses and all assessments will be performed by the central laboratory. Screening laboratory values must demonstrate subject eligibility, but exclusionary results may be re-tested one time within the screening window, without Celgene Medical Monitor approval.

Subjects who fail initial screening may re-screen one additional time for the study.

Efficacy assessments may be performed by the investigator or qualified designee at any time during the Screening Visit. However, when conducting the efficacy assessments, the investigator must complete these assessments in the following order: 1) sPGA; 2) BSA; 3) PASI; 4) ScPGA.

The following assessments will be performed at screening as specified in the Table of Events, [Table 3](#), after informed consent has been obtained:

- Optional consents for research sub-studies
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Demographics (initials, date of birth, sex, race, and ethnicity-if allowed by local regulations)
- Prior disease therapies: includes topical, systemic, and phototherapies
- Complete medical history (all relevant medical conditions diagnosed/ occurring prior to screening should also be included)
- Height
- Weight
- Complete physical examination
- Vital signs (including blood pressure, temperature, and heart rate)
- Efficacy assessments (see [Section 6.4](#))
- Hematology panel
- Chemistry panel (including [REDACTED])
- Urinalysis
- Hepatitis B and C screening
- Serum pregnancy test is required for all female subjects of childbearing potential. Counseling about pregnancy precautions and the potential risks of fetal exposure
- Adverse event assessment (begins when the subject signs the informed consent form)
- Prior/concomitant medications

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. For visits within the Placebo-controlled Phase and Apremilast Extension Phase, an administrative window of ± 4 days is permitted.

During the treatment period, subjects must complete the itch NRS and subject questionnaires prior to any other study procedure being performed. The subject should complete the questionnaires in the following order when applicable: 1) whole body itch NRS; 2) DLQI.

During the treatment period, efficacy assessments may be performed by the investigator or qualified designee at any time during a study visit. The investigator performing efficacy assessments shall make independent observations at a given study visit and shall not review previous assessments or subject-derived data in advance of conducting the assessments. When conducting the efficacy assessments, the investigator must complete these assessments in the following order: 1) sPGA; 2) BSA; 3) PASI; 4) ScPGA; 5) NAPSI.

The following evaluations/assessments will be performed at the frequency specified in the Table of Events, [Table 3](#):

- Subject reported outcomes or health-related quality of life (HRQoL)
- Concomitant medications or therapies evaluation
- Vital signs
- Weight
- Biomarker and Pharmacodynamic sampling
- Hematology panel
- Chemistry panel (including [REDACTED])
- Urinalysis
- C-SSRS
- Adverse event evaluation (continuously)
- Efficacy assessments (see [Section 6.4](#))
- Urine pregnancy test and contraception education (prior to dosing on Day 1)
- IP dispense, return, and IP tablets count

6.2.1. End of Treatment

An end of treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. The end of treatment (Visit 10) assessments will also be performed for subjects who complete the study.

Subjects must complete the itch NRS and subject questionnaires prior to any other study procedure being performed. The subject should complete the questionnaires in the following order when applicable: 1) whole body itch NRS; 2) DLQI.

The investigator performing efficacy assessments shall make independent observations at a given study visit and shall not review previous assessments or subject-derived data in advance of conducting the assessments. When conducting the efficacy assessments, the investigator must

complete these assessments in the following order: 1) sPGA; 2) BSA; 3) PASI; 4) ScPGA; 5) NAPSI.

The following evaluations will be performed as specified in the Table of Events, [Table 3](#):

- Subject reported outcomes or health-related quality of life (HRQoL)
- Concomitant medications or therapies evaluation
- Complete physical exam
- Vital signs
- Weight
- Hematology panel
- Chemistry panel (including [REDACTED])
- Urinalysis
- C-SSRS
- Adverse event evaluation (continuously)
- Efficacy assessments (see [Section 6.4](#))
- Serum pregnancy test
- IP return and IP tablets count

6.3. Observational Follow-up Period

For visits within the Observational Follow-up Phase, an administrative window of ± 2 weeks from the last dose of IP is permitted.

6.3.1. Safety Follow-up

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in [Section 10.1](#).

The following evaluations will be performed at the Follow-up Visit as specified in the Table of Events, [Table 3](#).

- Concomitant medications or therapies evaluation
- Weight
- Vital signs
- Adverse event evaluation
- C-SSRS

6.3.2. Efficacy Follow-up

During the follow-up period, efficacy assessments may be performed by the investigator or qualified designee at any time during a study visit. The investigator performing efficacy assessments shall make independent observations at a given study visit and shall not review previous assessments in advance of conducting the assessments. When conducting the efficacy assessments, the investigator must complete these assessments in the following order: 1) sPGA; 2) BSA; 3) PASI; 4) ScPGA.

6.4. Efficacy Assessments

The following assessments will be conducted as outlined in the Table of Events, [Table 3](#)

- **static Physician Global Assessment**

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. The sPGA 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 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 disease signs, the sign that is the predominant feature of the disease should be used to help determine the sPGA score. See ([Appendix B](#)) grading criteria.

- **Body Surface Area**

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

- **Psoriasis Area and Severity Index**

The PASI will be determined for all subjects throughout the study. The PASI calculation is described in [Appendix C](#).

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI is a validated instrument that has become standard in clinical trials for psoriasis.

Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity ([Fredriksson, 1978](#)). Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then

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 ≤ 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

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, CO₂], 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**

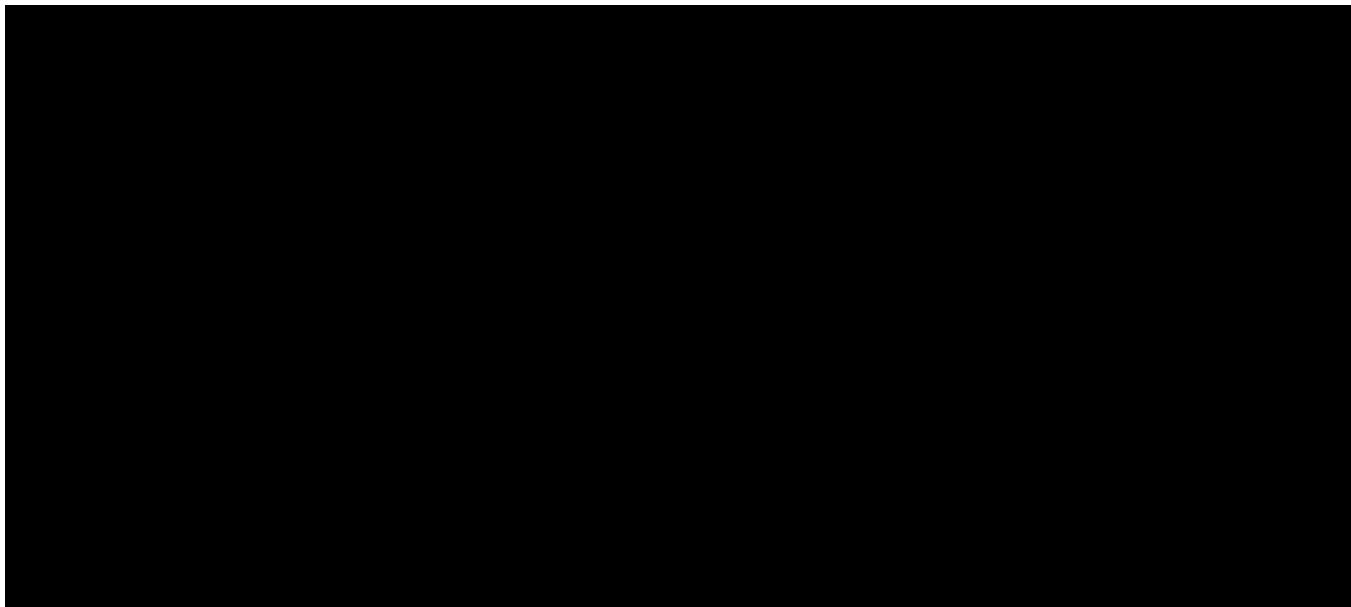
Psoriasis flare represents an atypical or unusual worsening of disease during treatment ([Carey, 2006](#)). It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. A more typical, gradual worsening of plaque psoriasis would not be recorded as an AE.

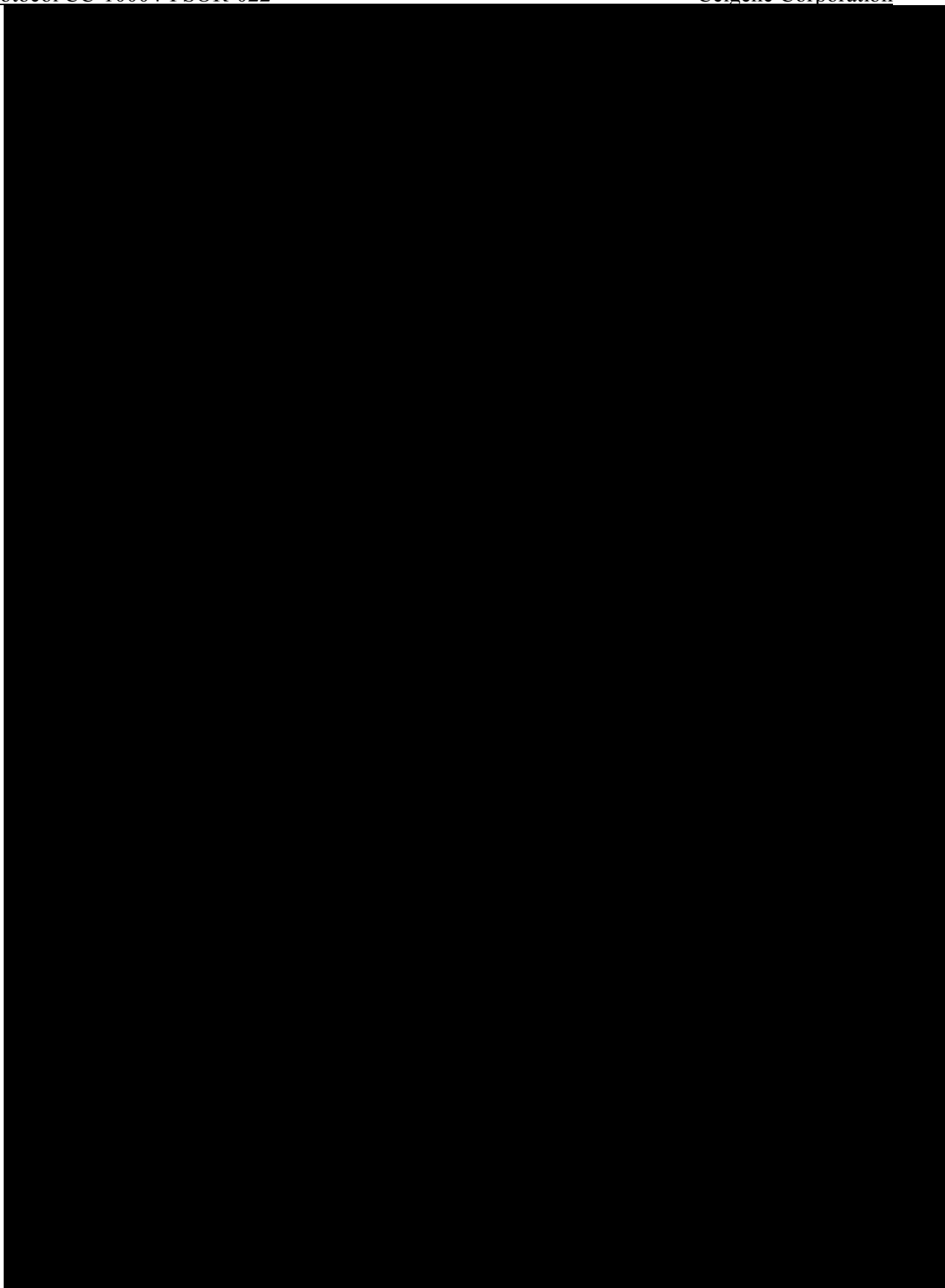
- **Adverse Events**

Details of AE reporting may be found in [Section 10.1](#).

6.6. Pharmacokinetics

Not Applicable.





6.8. Subject Reported Outcomes or Health-related Quality of Life Assessment

6.8.1. Whole Body Itch Numeric Rating Scale Assessment

Prior to any other procedures or assessments being performed during the treatment period, the subject will be asked to assess whole body itch and select a number on a scale of 0-10, where “0” represents no itch, and “10” represents the worst imaginable itch. The number selected by the subject will be recorded in the database. See [Appendix G](#).

The Whole Body Itch NRS scale has been validated among patients with moderate to severe plaque psoriasis, and a 4-point change from baseline was shown to be optimal for demonstrating a level of clinically meaningful improvement in itch severity ([Kimball, 2016](#)).

6.8.2. Dermatology Life Quality Index

The DLQI was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease ([Finlay, 1994](#)). The instrument contains 10 items dealing with the subject’s skin. With the exception of Item Number 7, the subject responds on a four-point scale, ranging from “Very Much” to “Not at All.” Item Number 7 is a multi-part item, the first part of which ascertains whether the subject’s skin prevented them from working or studying (Yes or No), and if “No,” then the subject is asked how much of a problem the skin has been at work or study over the past week, with response alternatives being “A lot,” “A little,” or “Not at all.”

The DLQI Total score has a possible range from 0 to 30, with 30 corresponding to the worst health-related quality of life, and 0 corresponding to the best score. The developers suggest that the DLQI can be grouped into six subscales: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores correspond to poorer health-related quality of life. See [Appendix H](#).

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.

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](#).

Table 5: Treatment Schema for Dose Titration at Visit 7 (Week 16)

	Week 16											
	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 P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	30 mg A	30 mg A
Placebo to APR 30 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

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

7.2. Treatment Administration and Schedule

Investigational product 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 this study. During Week 0 (Days 1 to 7) and Week 16 (when placebo subjects are switched to receive apremilast 30 mg BID), subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo tablets for the dose titration. At all other visits where IP is dispensed, apremilast will be provided in blister cards as 10, 20, and 30 mg tablets or identically appearing placebo tablets. The treatment schema for dose titration at baseline and Week 16 is shown in [Table 4](#) and [Table 5](#). Blister card configurations are pictured in [Appendix I](#), [Appendix J](#), and [Appendix K](#).

7.3. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the investigational product(s) only. Therefore, for a drug to be subject to the overdose definition it must be *both required* and an *investigational drug*. In this study the only required and investigational drug is apremilast and the control arm drug (ie, placebo), hence the overdose definition will apply to only apremilast (or matching placebo). Other required or optional non-IP intended for prophylaxis of certain side effects are excluded from this definition.

Overdose for this protocol, on a per dose basis, is defined as ingestion of 4 or more 30 mg apremilast (or matching placebo) tablets in any 24-hour period whether by accident or intentionally. On a schedule or frequency basis, an overdose is defined as dosing more than 4 times during any 24-hour period.

7.4. Method of Treatment Assignment

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). Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to enter the IRT to randomize subjects.

The system will present a menu of questions by which the research center personnel will identify the subject and confirm eligibility. When all questions have been answered and the subject deemed eligible, the IRT will assign a randomization identification number.

Confirmation of the randomization will be sent to the investigational site, Celgene, and/or its representative. The confirmation reports should be maintained as source documents. During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization number assigned by the IRT.

7.5. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or 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 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.

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

- Phototherapy
 - UVB or PUVA
- Biologic agents, including:
 - TNF or IL-17 blockers, anti-IL-12 or anti-IL-23 monoclonal antibodies or biosimilars for each
- Use of any investigational drug or device
- Prolonged sun exposure or any use of tanning booths or other ultraviolet light sources

8.3. Required Concomitant Medications and Procedures

Not Applicable

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 3, multicenter, randomized, placebo-controlled, double-blind study of the efficacy and safety of apremilast (CC-10004) in subjects with mild to moderate plaque psoriasis. 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 objective of the statistical analysis will be to evaluate the efficacy and safety of apremilast 30 mg BID versus placebo for 16 weeks, and to evaluate the effects of apremilast 30 mg BID as a treatment for up to 32 weeks in subjects with mild to moderate plaque psoriasis.

After all subjects have completed the Placebo-controlled Phase (Weeks 0 to 16), the primary analysis will be performed. At the study completion, ie, when all subjects have also completed the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final analysis will be performed. To maintain the blind at the site and subject level, the individual subject treatment assignments will not be revealed to the investigators until after the final database lock following the study completion.

9.2. Study Population Definitions

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

The safety population will consist of all subjects who are randomized and receive at least one dose of IP (IP). Subjects will be included in the treatment group corresponding to the IP they actually receive.

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

9.3. Sample Size and Power Considerations

The sample size estimation is based on the results of the Phase 3 and 4 studies with apremilast. With a total of approximately 574 subjects and a randomization ratio of 1:1, the study will randomize approximately 287 subjects to apremilast 30 mg BID and 287 subjects to placebo. This sample size will provide more than 90% power to detect a 15% difference between the two treatment groups for the primary endpoint at a two-sided significance level of 0.05. The calculation is based on a chi-square test assuming 15% response rate for placebo and adjusting for a 20% dropout rate.

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)

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 $\geq 75\%$ 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 $\leq 3\%$ 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

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



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.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in [Section 10.3](#)), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See [Section 7.3](#) for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF. The overdose itself should not be reported as an AE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. All adverse events (serious/non-serious) will be recorded on the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by recording on the CRF and transmitting the data electronically. 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.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;

- 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.

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.

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 AE 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 AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the AE. |

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of each AE, as applicable (eg, discontinuation, interruption, or dose modification, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or

- 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 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 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/m² at baseline who lose $\geq 5\%$ 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

- 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.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblended dose information.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/package breach, product missing/short/overage, contamination, suspected falsified,

tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing customercomplaints@celgene.com or by contacting the Celgene Customer Care Center (1-888-423-5436).

16. PUBLICATIONS

As described in [Section 13.2](#), all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADLs	Activities of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BMI	Body mass index
BSA	Body Surface Area
cAMP	cyclic adenosine monophosphate
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
CMH	Cochran-Mantel-Haenzel
CO ₂	Carbon dioxide
CRO	Contract Research Organization
CRF	Case report form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
EC	Ethics Committee
eCRF	Electronic case report form
EMA	European Medicines Agency
EOT	End of treatment
FAS	Full analysis set
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice

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

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

Appendix B: Static Physician Global Assessment (sPGA) of Whole Body Psoriasis

Score	Category	Description
0	Clear	Plaque Elevation = 0 (no elevation over normal skin) Scaling = 0 (no evidence of scaling) Erythema = 0 (except for residual hyperpigmentation/hypopigmentation)
1	Almost Clear	Plaque Elevation = \pm (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = \pm (surface dryness with some desquamation) Erythema = \pm (faint, diffuse pink or slight red coloration)
2	Mild	Plaque Elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = mild (light red coloration)
3	Moderate	Plaque Elevation = marked (marked definite elevation with rough or sloped edges) Scaling = coarser (coarser scale covering most or all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque Elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarser (coarse, non tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)

Appendix C: Psoriasis Area and Severity Index (PASI)

* Round all calculations to 1 decimal place

STEP A. Please write in the appropriate number for rows 1 - 3 using the scale below:				
0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe				
	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
1. Erythema				
2. Thickness				
3. Scaling				
4. TOTAL Each Column				
STEP B. Enter the number of hands the psoriasis covers on each body area				
	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
5. Number of Hands				
6. Area (% of total BSA)	10	30	20	40
STEP C. Calculate % of involvement:				
7. % of each region involved [(Row 5 ÷ Row 6) x 100*]				
8. TOTAL BSA (sum of # of hands from row 5)				
STEP D. Select Degree of Involvement using value in Row 7:				
0 = No involvement				
1 = <10%				
2 = 10 < 30%				
3 = 30 < 50%				
4 = 50 < 70%				
5 = 70 < 90%				
6 = 90 < 100%				
9. Degree of Involvement (0-6) of each region				
STEP E. Calculate PASI (Row 4 x Row 6 x Row 9) ÷ 100*				
10. PASI for each body region				
11. TOTAL PASI (sum of Row 10 subscores)				

Appendix D: Scalp Physician Global Assessment (ScPGA)

Score	Category	Description
0	Clear	Scalp Plaque Elevation = 0 (no elevation over normal skin) Scalp Scaling = 0 (no evidence of scaling) Scalp Erythema = 0 (except for residual hyperpigmentation/hypopigmentation)
1	Almost Clear	Scalp Plaque Elevation = \pm (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scalp Scaling = \pm (surface dryness with some desquamation) Scalp Erythema = \pm (faint, diffuse pink or slight red coloration)
2	Mild	Scalp Plaque Elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scalp Scaling = fine (fine scale partially or mostly covering lesions) Scalp Erythema = mild (light red coloration)
3	Moderate	Scalp Plaque Elevation = marked (marked definite elevation with rough or sloped edges) Scalp Scaling = coarser (coarser scale covering most or all of the lesions) Scalp Erythema = moderate (definite red coloration)
4	Severe	Scalp Plaque Elevation = marked (marked elevation typically with hard or sharp edges) Scalp Scaling = coarser (coarse, non tenacious scale predominates covering most or all of the lesions) Scalp Erythema = severe (very bright red coloration)

Appendix E: Nail Psoriasis Severity Index (NAPSI)

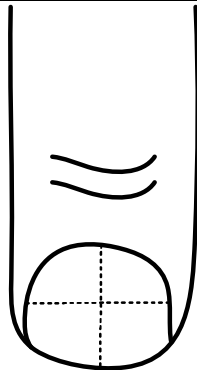
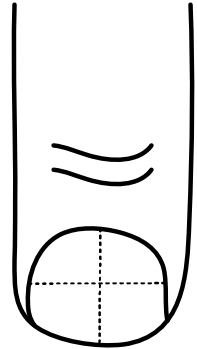
Nail Psoriasis Severity Index (NAPSI) (Version 1.00)

Complete at VISIT 2 only: Circle the number of the thumb or fingernail that will be used as the target nail (i.e. the nail that has the worst nail psoriasis) for the NAPSI calculation for this subject during the study:

- 1 = Right Thumb
- 2 = Right Index Finger
- 3 = Right 3rd Finger
- 4 = Right 4th Finger
- 5 = Right 5th Finger
- 6 = Left Thumb
- 7 = Left Index Finger
- 8 = Left 3rd Finger
- 9 = Left 4th Finger
- 10 = Left 5th Finger
- 11 = No Nail Psoriasis

Complete at EVERY VISIT: Enter the number of nails that have nail psoriasis.

Number of thumb and fingernails with psoriasis: _____

<p>The target thumb or finger nail which represents the worst nail psoriasis is graded for nail matrix psoriasis and nail bed psoriasis. The sum of these two scores is the total score for that nail.</p>	
<p>Evaluation 1: <u>Nail matrix</u>. In each quadrant of the nail, nail matrix psoriasis is evaluated by presence of any of the nail matrix features (pitting, leukonychia red spots in the lunula, crumbling):</p>	
<p>Score for nail matrix psoriasis _____</p> <p>0 = none 1 = present in 1/4 nail 2 = present in 2/4 nail 3 = present in 3/4 nail 4 = present in 4/4 nail</p>	
<p>Evaluation 2: <u>Nail bed</u>. Nail bed psoriasis is evaluated by the presence of any of the nail bed features (onycholysis, splinter hemorrhages, subungual hyperkeratosis, “oil drop” (salmon patch dyschroma):</p>	
<p>Score for nail bed psoriasis _____</p> <p>0 = none 1 = present in 1/4 nail 2 = present in 2/4 nail 3 = present in 3/4 nail 4 = present in 4/4 nail</p>	
<p>TOTAL FOR NAIL _____ (0-8)</p>	

[Rich, 2003.](#)

Appendix F: Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline Version 1/14/09

**Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.;
Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.**

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. Have you wished you were dead or wished you could go to sleep and not wake up? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan. Have you actually had any thoughts of killing yourself? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it". Have you been thinking about how you might do this? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them". Have you had these thoughts and had some intention of acting on them? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <hr/> Most Severe Ideation: Type # (1-5) Description of Ideation	Most Severe
Frequency How many times have you had these thoughts? (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____
Duration When you have the thoughts, how long do they last? (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	_____
Controllability Could /can you stop thinking about killing yourself or wanting to die if you want to? (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	_____

<p>Deterrents <i>Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply</p>	<p>_____</p>
<p>Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (2) Mostly to get attention, revenge or a reaction from others. (5) Completely to end or stop the pain and to end/stop the pain. (you couldn't go on living with the pain or how you were feeling). (3) Equally to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply</p>	<p>_____</p>

<p>SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)</p>	<p>Lifetime</p>
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe: Has subject engaged in Non-Suicidal Self-Injurious Behavior?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of Attempts _____ Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of interrupted _____</p>

Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. <i>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</i> If yes, describe:			Yes No <input type="checkbox"/> <input type="checkbox"/> Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). <i>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</i> If yes, describe:			Yes No <input type="checkbox"/> <input type="checkbox"/>
Suicidal Behavior: Suicidal behavior was present during the assessment period?			Yes No <input type="checkbox"/> <input type="checkbox"/>
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	<i>Enter Code</i> _____	<i>Enter Code</i> _____	<i>Enter Code</i> _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	<i>Enter Code</i> _____	<i>Enter Code</i> _____	<i>Enter Code</i> _____

Appendix G: Whole Body Itch Numeric Rating Scale (NRS)

ITCH NUMERIC RATING SCALE

Please rate the itching severity due to your psoriasis by circling the number that best describes your worst level of itching in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

0 = No itching

10 = Worst itch imaginable

[Naegeli, 2015.](#)

Appendix H: The Dermatology Life Quality Index (DLQI)



The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or yard ?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant
4.	Over the last week, how much has your skin influenced the clothes you wear?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant
5.	Over the last week, how much has your skin affected any social or leisure activities?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant
6.	Over the last week, how much has your skin made it difficult for you to do any sport ?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant
7.	Over the last week, has your skin prevented you from working or studying ?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not relevant
	If "No", over the last week how much has your skin been a problem at work or studying ?	<input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives ?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant
9.	Over the last week, how much has your skin caused any sexual difficulties ?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant
10.	Over the last week, how much of a problem has the treatment for your skin been, for example, by making your home messy, or by taking up time?	<input type="checkbox"/> Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all	<input type="checkbox"/> Not relevant

Finlay, 1994.



Appendix I: Titration Blister Card Configuration

30mg BID Titration and Treatment Card (28 day +5 Extra)

	1	10p		20p	30p		1	10p		20p	30p
	2	10p		20p	30p		2	10p		20p	30p
	3	10p		20p	30p		3	10p		20p	30p
	4	10p		20p	30p		4	10p		20p	30p
	5	10p		20p	30p		5	10p		20p	30p
	6				30p		6				30p
	7				30p		7				30p
	8				30p		8				30p
	9				30p		9				30p
	10				30p		10				30p
	11				30p		11				30p
	12				30p		12				30p
	13				30p		13				30p
	14				30p		14				30p
	15				30p		15				30p
	16				30p		16				30p
	17				30p		17				30p
	18				30p		18				30p
	19				30p		19				30p
	20				30p		20				30p
	21				30p		21				30p
	22				30p		22				30p
	23				30p		23				30p
	24				30p		24				30p
	25				30p		25				30p
	26				30p		26				30p
	27				30p		27				30p
	28				30p		28				30p
	29				30p		29				30p
	30				30p		30				30p
	31				30p		31				30p
	32				30p		32				30p
	33				30p		33				30p



Appendix J: Active Treatment Dummy Titration Blister Card Configuration

30mg BID Dummy Titration Card (28 day +5 Extra)

	1	10p		20p	30		1	10p		20p	30
	2	10p		20p	30		2	10p		20p	30
	3	10p		20p	30		3	10p		20p	30
	4	10p		20p	30		4	10p		20p	30
	5	10p		20p	30		5	10p		20p	30
	6				30		6				30
	7				30		7				30
	8				30		8				30
	9				30		9				30
	10				30		10				30
	11				30		11				30
	12				30		12				30
	13				30		13				30
	14				30		14				30
	15				30		15				30
	16				30		16				30
	17				30		17				30
	18				30		18				30
	19				30		19				30
	20				30		20				30
	21				30		21				30
	22				30		22				30
	23				30		23				30
	24				30		24				30
	25				30		25				30
	26				30		26				30
	27				30		27				30
	28				30		28				30
	29				30		29				30
	30				30		30				30
	31				30		31				30
	32				30		32				30
	33				30		33				30

Appendix K: Placebo Treatment Blister Card Configuration

Placebo Titration and Treatment Card (28 day +5 Extra)

	1	10p 	20p	30p		1	10p 	20p	30p
	2	10p	20p	30p		2	10p	20p	30p
	3	10p	20p	30p		3	10p	20p	30p
	4	10p	20p	30p		4	10p	20p	30p
	5	10p	20p	30p		5	10p	20p	30p
	6			30p		6			30p
	7			30p		7			30p
	8			30p		8			30p
	9			30p		9			30p
	10			30p		10			30p
	11			30p		11			30p
	12			30p		12			30p
	13			30p		13			30p
	14			30p		14			30p
	15			30p		15			30p
	16			30p		16			30p
	17			30p		17			30p
	18			30p		18			30p
	19			30p		19			30p
	20			30p		20			30p
	21			30p		21			30p
	22			30p		22			30p
	23			30p		23			30p
	24			30p		24			30p
	25			30p		25			30p
	26			30p		26			30p
	27			30p		27			30p
	28			30p		28			30p
	29			30p		29			30p
	30			30p		30			30p
	31			30p		31			30p
	32			30p		32			30p
	33			30p		33			30p



Celgene Signing Page

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**This page is the manifestation of the electronic signature(s) used in compliance with
the organizations electronic signature policies and procedures.**

UserName: [REDACTED]

Title: VP, Clinical R&D

Date: Sunday, 25 November 2018, 05:40 PM Eastern Daylight Time

Meaning: Approved, no changes necessary.

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1. JUSTIFICATION FOR AMENDMENT

Changes included in this amendment are summarized below:

- Provided clarification to Sections 6.1, 6.2 and 6.5 [REDACTED]
- Provided clarification to Sections 5 and 6.5 Safety Assessments, Serum and Urine Pregnancy Tests for Females of Childbearing Potential to further specify that an unscheduled serum pregnancy test should be performed if the FCBP subject has missed a menstrual period or has a positive urine dipstick test.
- Modified Sections 4.3, 5, 6.1, and 6.5 to include hepatitis C testing to be consistent with apremilast historical studies.
- Modified Section 10 Adverse Events to reflect the process by which adverse events are to be reported.

1. JUSTIFICATION FOR AMENDMENT

Changes included in this amendment are summarized below:

- In the Protocol Summary, provided clarifications regarding the approximate enrollment limits in Study Design and topical psoriasis preparations in Study Population; included Columbia Suicide Severity Rating Scale (C-SSRS) in Overview of Key Safety Assessment and tipping point analysis in Statistical Method based on FDA recommendation.
- Provided clarification in Section 3.1 regarding the approximate enrollment limits as determined by baseline sPGA scores of mild (2) or moderate (3).
- Provided clarification in Section 4.2 Inclusion Criteria #6 to define topical psoriasis preparations.
- Modified Section 5 Table of Events to include Optional Consent for Research based on new protocol template; to include C-SSRS, additional body weight measures, additional clinical laboratory evaluations, and urine pregnancy tests based on FDA recommendations; and to include clarifications on the footnotes.
- Modified Sections 5, 6.1, and 6.3.2 to update the NPSI assessment schedule.
- Provided clarification in Section 6 Procedures under Medical and Disease History to remove psoriatic arthritis. Clarified the need for subjects to sign optional consents for research before any sub-study sampling may be performed.
- Modified Section 6.1 to include options consents for research being presented to subjects, and to review prior/concomitant medications during the screening period.
- Modified Sections 6.1, 6.2, 6.3, 6.5, 17, Appendix A, and Appendix F to reflect the addition of C-SSRS based on FDA recommendation.
- Modified Section 6.5 with additional time points for urine pregnancy testing for FCBP subjects.
- Provided clarification in Section 6.7 to reflect the sub-studies are optional.
- Modified reference in Sections 6.8, 7.2 to reflect the addition of C-SSRS as an appendix.
- Provided modification in Section 7.7 investigational Product Compliance to include upper range of > 120% compliance between visits as meeting definition of a gross compliance problem.
- Provided clarification in Section 9.6.1.1 Primary Efficacy Endpoint where reference to LOCF was replaced with “tipping point analysis” based on FDA recommendation.
- Provided clarification in Section 11.1 Treatment Discontinuation to include the following reason: “Subjects with BMI < 18.5 kg/m² at baseline who lose ≥ 5% of their baseline weight, based on FDA recommendation.
- Provided clarification to Appendix E to include a count of the number of nails with psoriasis involvement.
- Appendices F, G, H, I, J were modified to reflect the addition of C-SSRS as an appendix.