DISCLOSURE

REDACTED PROTOCOL AMENDMENT 1

CC-10004-SPSO-001

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

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

PROTOCOL NUMBER:	CC-10004-SPSO-001
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PPD

Printed Name of Celgene Therapeutic Area Head and Title

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PROTOCOL SUMMARY

Study Title

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

Indication

The indication is moderate to severe plaque psoriasis of the scalp.

Objectives

Primary Objective

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

Secondary Objective(s)

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

Study Design

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

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

- Subjects randomized to the apremilast 30 mg BID treatment group will receive apremilast 30 mg tablets orally twice daily for the first 16 weeks

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

The study will consist of four phases:

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

  Subjects will receive treatment with one of the following:

  – apremilast 30 mg tablets orally BID or

  – placebo tablets (identical in appearance to apremilast 30 mg tablets) orally BID
- Apremilast Extension Phase – Weeks 16 to 32

  – All subjects will be switched to (or continue with) apremilast 30 mg BID at Week 16. All subjects will maintain this dosing through Week 32.
- Observational Follow-up Phase

  – Four-week Post-treatment Observational Follow-up Phase for all subjects who complete the study or discontinue from the study early.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database lock will be performed; the primary data analysis will be conducted CCI [redacted] CCI [redacted]. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data CCI [redacted]. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study. At the end of the study, ie, when all subjects have also completed (or have been discontinued) the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final analysis will be performed and a final Clinical Study Report will be generated.

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.

Study Population

Adult subjects ≥ 18 years of age with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index [PASI] ≥ 12, and Body Surface Area [BSA] ≥ 10%, and Static Physician Global Assessment [sPGA] ≥ 3 [moderate or greater]) who also have moderate to severe plaque psoriasis of the scalp (Scalp Physician Global Assessment ≥ 3 [moderate or greater], and Scalp Surface Area ≥ 20%, and having had an inadequate response or intolerance to at least one topical therapy [for example, potent or super potent topical corticosteroids, vitamin D analogs, and combination products] for plaque psoriasis of the scalp).

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

Study Treatments

All IP 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 (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 and at Week 16 for subjects initially randomized to placebo when they switch to apremilast 30 mg BID treatment.

During Week 0 (Days 1 to 7), subjects will be dispensed dose titration blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo tablets. The blister cards will contain all IP required for 4 weeks of treatment, with the first 7 days containing the titration supplies or matching placebo (see Table 4: Treatment Schema for Dose Titration at Visit 2 [Week 0]) which details the titration supplies from Day 1 to Day 7 in the Placebo-controlled Treatment Phase. 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.
- Weeks 16 to 32: Apremilast Extension Phase: Apremilast 30 mg BID.
  - Week 16 to 17: subjects will be dose titrated as described below.

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 2:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT).

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 (see Table 5 Treatment Schema for Dose Titration at Visit 7 [Week 16]) which details the titration supplies from Day 1 to Day 7 in the Apremilast Extension Phase. Dose titration blister cards will be used for subjects switching from placebo to apremilast; dummy titration blister cards (dosing at 30 mg BID directly) will be used for subjects initially randomized to receive apremilast 30 mg BID. At all other visits during the Apremilast Extension Phase, all subjects will receive apremilast 30 mg tablets which are to be taken twice daily.

Dose modifications are not permissible in this study.

Overview of Key Efficacy Assessments

Primary Efficacy Assessment

- Scalp Physician Global Assessment (ScPGA)

Additional Efficacy Assessments

- Subject's Assessment of Whole Body Itch numeric rating scale (NRS)
- Subject's Assessment of Scalp Itch NRS
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Health-Related Quality of Life (HRQoL) questionnaires
  - Dermatology Life Quality Index (DLQI)
  - CCI [redacted]

Overview of Key Safety Assessments

Safety assessments will include:

- Adverse events (AE)
- 12-lead electrocardiograms (ECG)
- Chest radiographs (CXR)
- Physical examinations
- Vital signs
- Pregnancy tests for females of childbearing potential (FCBP)
- Clinical laboratory tests

CCI [redacted]

Statistical Methods

The study will randomize approximately 300 subjects in a 2:1 ratio to apremilast 30 mg BID or placebo arms stratified by baseline ScPGA score (moderate [3], severe [4]). With this sample size, a chi-square test at the 2-sided 0.05 significance level will have 90% power to detect a minimum treatment difference of 18% (38% for apremilast 30 mg BID versus 20% for placebo) between the two arms for proportions of subjects achieving ScPGA response at Week 16 (defined as ScPGA score of clear [0] or almost clear [1] with at least a 2 point reduction from baseline at Week 16).

Analyses for efficacy endpoints will be mainly on the intent-to-treat (ITT) population, defined as all randomized subjects. Statistical comparisons will be made between the two treatment arms.

All statistical tests will be at the 2-sided 0.05 significance level and the corresponding p-values and confidence intervals will be reported. The primary and secondary efficacy endpoints will be hierarchically ranked for testing in order to control the overall type I error rate in claiming statistical significance at the 2-sided 0.05 significance level.

The primary endpoint, the proportion of subjects who achieved ScPGA response at Week 16 between apremilast 30 mg BID and placebo, will be compared using Cochran–Mantel–Haenszel (CMH) test adjusted by stratification factors in randomization. Missing values at Week 16 will be imputed using the multiple imputation (MI) method as the primary analysis. Sensitivity analyses will be performed using the last observation carried forward (LOCF) method and the non-responder imputation (NRI) method. The binary secondary efficacy endpoints will be analyzed similarly as the primary endpoint.

The analysis for the continuous secondary endpoint will be performed using the analysis of covariance (ANCOVA) model. The ANCOVA model will use the change from baseline as the dependent variable and will include treatment group and stratification factor as independent variables and the baseline value as a covariate variable.

All efficacy endpoints will be summarized by study visit for both the Placebo-controlled Phase (Weeks 0 to 16) and Apremilast Extension Phase (Weeks 16 to 32). When appropriate, exploratory endpoints at Week 16 will also be analyzed using CMH or ANCOVA methods similar to the primary and secondary endpoints.

The safety analyses will be performed using the safety population defined as all subjects who received at least one dose of IP. Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, and electrocardiogram (ECG) measurements. Data from safety assessments will be summarized descriptively for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast Exposure Period. Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. TEAEs leading to death or to IP withdrawal and serious TEAEs will also be summarized and listed separately.

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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). The scalp is the most frequent area affected by plaque psoriasis, occurring in up to 80% of patients (van de Kerkhof, 1998). These lesions can affect the hair-bearing areas of the scalp, extending past the hair line, as well as in the retroauricular area and on the neck. The lesions and associated flaking can be visible as well as highly pruritic, causing a negative impact on the patient's quality of life (Kragballe, 2013; Szepietowski, 2016).

The presence of scalp hair makes application of topical therapies or use of phototherapy difficult and inconvenient, limiting their effectiveness as well as compliance (Warren, 2008; Feldman, 2003). Currently approved topical corticosteroids and calcipotriene preparations may be limited by short treatment durations and poor treatment compliance. In addition, potent topical corticosteroid therapies can be associated with side effects such as tachyphylaxis, skin atrophy, striae, telangiectasia, and hypothalamic-pituitary-adrenal (HPA) axis suppression (van der Vleuten, 2001; Hogan, 1989). Other topical therapies, such as coal tar and anthralin preparations have cosmetically unappealing formulations, foul odor, limited efficacy, and potential carcinogenic risk (Chan, 2009). Second-line therapies such as phototherapy and systemic medications have been used, however, safety and efficacy data from controlled clinical trials for these agents is limited (Chan, 2009). Efficacy data from controlled clinical trials involving treatment with biologics, such as ixekizumab has only recently been published (Reich, 2016). Thus, there remains an unmet medical need in treating plaque psoriasis of the scalp, particularly in patients with moderate to severe plaque psoriasis of the scalp.

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

1.3. Rationale

1.3.1. Study Rationale and Purpose

Plaque psoriasis of the scalp is often challenging to treat. Scalp skin is also relatively inaccessible, making topical therapies difficult to apply and inconvenient to use (Ortonne, 2009). Given the visibility of the lesions and the scaling/flaking as well as the itch associated with the disease, patients with plaque psoriasis of the scalp often experience considerable physical, psychological and social impacts to quality of life.

There remains an unmet medical need in treating plaque psoriasis of the scalp as currently approved topical corticosteroids and calcipotriene preparations may be limited by short treatment durations, poor treatment compliance, limited efficacy, and cosmetic appeal. As well, potent topical corticosteroid therapies can be associated with side effects such as tachyphylaxis, skin atrophy, striae, telangiectasia, and hypothalamic-pituitary-adrenal (HPA) axis suppression. Other topical therapies, such as coal tar and anthralin preparations, have the additional risk of carcinogenesis. Second-line therapies for plaque psoriasis of the scalp include phototherapy and systemic medications, however safety and efficacy data from controlled clinical trials for most of these agents is limited. Efficacy data from controlled clinical trials involving treatment with biologics, such as ixekizumab has only recently been published.

Apremilast (CC-10004) is a specific phosphodiesterase type 4 (PDE4) inhibitor approved for the treatment of both psoriasis and psoriatic arthritis. In Phase 2 and Phase 3 trials, apremilast demonstrated efficacy in treating subjects with moderate to severe plaque psoriasis. Furthermore, exploratory analyses performed in these studies showed that apremilast also provided significant benefit in the treatment of moderate to severe plaque psoriasis of the scalp.

This study is intended to directly assess the safety and efficacy of apremilast 30 mg twice daily (BID) in the treatment of subjects with moderate to severe plaque psoriasis of the scalp.

1.3.2. Rationale for the Study Design

Exploratory analyses from the two pivotal Phase 3 studies of apremilast in subjects with moderate to severe plaque psoriasis (Study PSOR-008 and Study PSOR-009) demonstrated that apremilast 30 mg BID provided a treatment benefit in the subset of subjects who also presented with plaque psoriasis of the scalp of moderate or greater severity at baseline using a six-point Scalp Physician Global Assessment (ScPGA). The 6-point ScPGA scale ranged from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), to 5 (very severe).

This study will directly investigate the safety and efficacy of apremilast 30 mg BID, compared with placebo, in the treatment of subjects with moderate to severe plaque psoriasis of the scalp. The primary endpoint will be the proportion of subjects who achieved ScPGA response at Week 16 (defined as ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16), based on the intent-to-treat (ITT) population. Based on Health Authority feedback, this study will use a 5-point ScPGA scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe), instead of the 6-point scale used in prior

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

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

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

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

1.3.3. Rationale for Dose, Schedule and Regimen Selection

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

1.3.4. Rationale for Choice of Comparator

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

CCI [redacted]

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the clinical efficacy of apremilast 30 mg twice daily (BID) compared with placebo, in subjects with moderate to severe plaque psoriasis of the scalp, at Week 16.
Secondary Objective(s)
The secondary objectives are: • To evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo, in subjects with moderate to severe plaque psoriasis of the scalp. • To evaluate the effect of apremilast 30 mg BID compared with placebo on itch over the whole body caused by plaque psoriasis • To evaluate the effect of apremilast 30 mg BID compared with placebo on itch associated with plaque psoriasis of the scalp • To evaluate the onset of effect on itch over the whole body caused by plaque psoriasis with apremilast 30 mg BID compared with placebo • To evaluate the onset of effect on itch associated with plaque psoriasis of the scalp with apremilast 30 mg BID compared with placebo • To evaluate the effect of apremilast 30 mg BID compared with placebo on health-related quality of life
Exploratory Objective(s)
The exploratory objectives are: CCI [redacted] • To evaluate the effect of apremilast 30 mg BID compared to placebo on Dermatological Life Quality Index (DLQI) CCI [redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Scalp Physician Global Assessment (ScPGA)	Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16.	Week 16
Secondary	Itch Numeric Rating Scale (NRS) [whole body]	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score	Week 16
	Itch NRS (Scalp)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the scalp itch NRS score	Week 16
	Onset of effect on itch NRS (whole body)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score	By Visit in Placebo-controlled Phase (Week 12, Week 8, Week 4, Week 2)
	Onset of effect on itch NRS (Scalp)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the scalp itch NRS score	By Visit in Placebo-controlled Phase (Week 12, Week 8, Week 4, Week 2)
	Dermatological Life Quality Index (DLQI)	Change from baseline in DLQI total score	Week 16
Exploratory	CCI [redacted]	[redacted]	[redacted]
	ScPGA	Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	By Visit
	Itch NRS (whole body)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score	By Visit in Apremilast Extension Phase
	Itch NRS (Scalp)	Proportion of subjects with ≥4-point reduction (improvement) from baseline in the scalp itch NRS score	By Visit in Apremilast Extension Phase
	CCI [redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

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

3. OVERALL STUDY DESIGN

3.1. Overall Study Design

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

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

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

The study will consist of four phases:

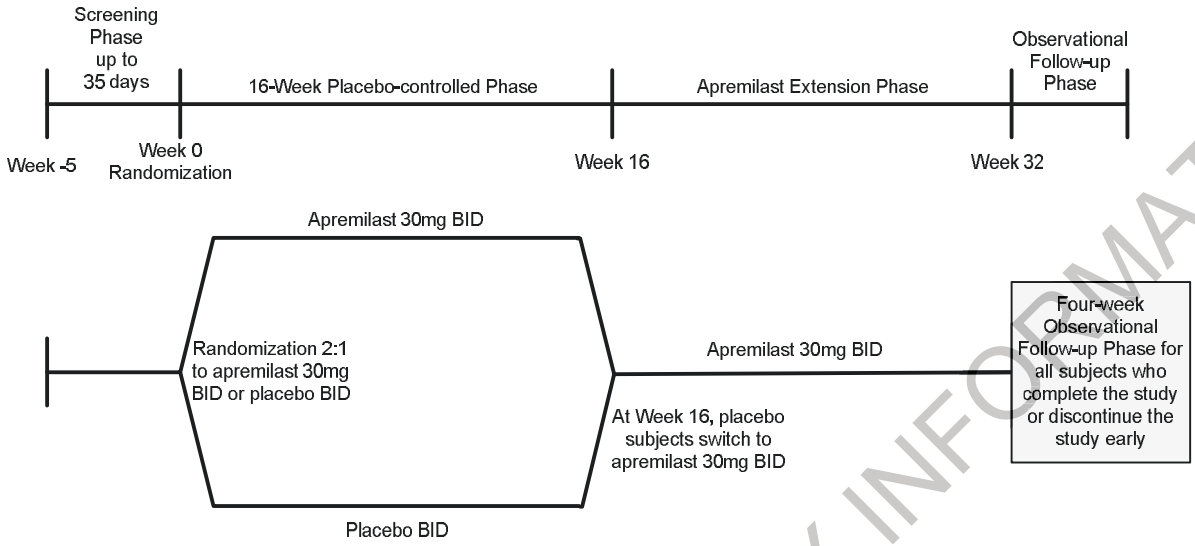
- Screening Phase – up to 35 days
- Double-blind Placebo-controlled Phase – Weeks 0 to 16

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

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database lock will be performed; the primary data analysis will be conducted CCI [redacted]. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data CCI [redacted]. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study. At the end of the study, after all subjects have completed, or have been discontinued from the Apremilast

Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final analysis will be performed and a final Clinical Study Report will be generated.

Figure 1: Study Design



Abbreviation: BID = twice daily.

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

3.2. Study Duration for Subjects

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

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

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

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

4.2. Inclusion Criteria

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

1. Males or females, ≥ 18 years of age at the time of signing the informed consent document
2. Understand and voluntarily sign an informed consent form (ICF) prior to any study-related assessments/procedures being conducted.
3. Be willing and able to adhere to the study visit schedule and other protocol requirements.
4. Have a diagnosis of moderate to severe plaque psoriasis of the scalp at screening and baseline as defined by:
    a. ScPGA (See Appendix B) score of ≥ 3 (moderate or severe) and,
    b. Scalp Surface Area (SSA) involvement of ≥ 20% and,
    c. Inadequate response or intolerance to at least one topical therapy (for example, potent or super potent topical corticosteroids, vitamin D analogs, and combination products) for plaque psoriasis of the scalp.
5. Must be a candidate for phototherapy and/or systemic therapy for either body or scalp psoriasis lesions.
6. Have moderate to severe plaque psoriasis at screening and baseline as defined by:
    a. Psoriasis Area and Severity Index (PASI) (CCI [redacted]) score ≥ 12 and,
    b. Body Surface Area (BSA) ≥ 10% and,
    c. Static Physician Global Assessment (sPGA) (CCI [redacted]) ≥ 3 (moderate)
7. Must be in good health (except for psoriasis) as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), clinical laboratories, and urinalysis
8. Must meet the following laboratory criteria
    a. White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L)
    b. Platelet count ≥ 100,000/µL (≥ 100 x 10^9/L)
    c. Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L)
    d. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤ 2 x upper limit of normal (ULN)
    e. Total bilirubin ≤ 2 mg/dL (34 µmol/L)
    f. Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)

g. Hemoglobin A1c ≤ 9.0%

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

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

   OR

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

4.3. Exclusion Criteria

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

1. Other than psoriasis, history of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease.
2. Any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study.
3. Any condition that confounds the ability to interpret data from the study.
4. Pregnant or breast feeding
5. Hepatitis B surface antigen positive at Screening
6. Anti-hepatitis C antibody positive at Screening
7. AST (SGOT) and/or ALT (SGPT) > 1.5 X ULN **and** total bilirubin > ULN and/or albumin < lower limit of normal (LLN)
8. Active tuberculosis (TB) or a history of incompletely treated TB

[†] A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

[§] The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

9. Clinically significant abnormality on 12-lead ECG at screening
10. Clinically significant abnormality based upon chest radiograph with at least a posterior to anterior (PA) view (radiograph must be taken within 12 weeks prior to screening or during the Screening Visit). An additional lateral view is strongly recommended but not required.
11. History of positive human immunodeficiency virus (HIV), or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease)
12. Active substance abuse or a history of substance abuse within 6 months prior to signing the informed consent form.
13. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of signing the informed consent form. Any treatment for such infections must have been completed at least 4 weeks prior to randomization.
14. Malignancy or history of malignancy, except for:
    a. treated (ie, cured) basal cell or squamous cell in situ skin carcinomas;
    b. treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within 5 years of signing the informed consent.
15. 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.
16. Psoriasis flare/rebound (defined as a sudden worsening of body plaque psoriasis or plaque psoriasis of the scalp which requires administration of prohibited medications) within 4 weeks of signing the informed consent form or between the Screening and Baseline Visits.
17. Current or planned concurrent use of the following therapies that may have a possible effect on psoriasis of the body and/or scalp during the course of the treatment phase of the trial:
    a. Topical therapy, including medicated shampoos, coal tar and salicylic acid preparations, within 2 weeks prior to randomization (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol).
        i. Exceptions:
            1. non-medicated shampoos for scalp lesions
            2. unmedicated emollients for body lesions
    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. Intralesional corticosteroids on the scalp within 2 weeks prior to randomization

d. Phototherapy treatment of body or scalp psoriasis lesions within 4 weeks prior to randomization (ie, ultraviolet B (UVB), psoralen and ultraviolet A radiation [PUVA])

e. Biologic therapy:

   i. TNF or IL-17 blockers such as adalimumab, brodalumab, certolizumab pegol, etanercept, infliximab, ixekizumab, secukinumab (or biosimilars for each) within 12 weeks prior to randomization

   ii. Anti-IL-12 or anti-IL-23 monoclonal antibodies such as ustekinumab, guselkumab, or tildrakizumab, within 24 weeks prior to randomization

f. Use of any investigational drug beginning 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer)

18. Evidence of scalp and/or skin conditions that would interfere with clinical assessments
19. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources
20. Prior treatment with apremilast
21. History of allergy or hypersensitivity to any components of the IP

5. TABLE OF EVENTS

Table 3: Table of Events

	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]**
Administrative/Demographics											
Informed Consent[d]	X	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion	X	X	-	-	-	-	-	-	-	-	-
Medical and Disease History	X	-	-	-	-	-	-	-	-	-	-
Prior / Concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X
Safety Assessment(s)											
Height, BMI	X	-	-	-	-	-	-	-	-	-	-
CXR[e]	X	-	-	-	-	-	-	-	-	-	-
Hepatitis B and C, TB[f]	X	-	-	-	-	-	-	-	-	-	-
Hemoglobin A1C	X	-	-	-	-	-	-	-	-	-	-
Weight	X	X	-	-	X	-	X	-	X	X	X
Complete Physical Exam	X	-	-	-	-	-		-	-	X	-
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test for FCBP and Contraception Education[g]	X	X	-	-	-	-	-	-	-	X	-
12-lead ECG	X	-	-	-	-	-	-	-	-	-	-
Clinical Laboratory Evaluations[h]	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]**
Vasculitis Assessment [i]	-	-	-	-	-	-	-	-	-	-	-
Psychiatric Evaluation [j]	-	-	-	-	-	-	-	-	-	-	-
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Psoriasis Flare Assessment [k]	-	-	-	-	-	-	-	-	-	-	-
Clinical Efficacy Assessment(s)[l]											
Whole Body Itch NRS[m]	-	X	X	X	X	X	X	X	X	X	-
Scalp Itch NRS[m]	-	X	X	X	X	X	X	X	X	X	-
ScPGA	X	X	X	X	X	X	X	X	X	X	X
CCI											
Patient Reported Outcomes											
CCI											
DLQI	-	X	-	X	X	-	X	-	-	X	-
CCI											

Table 3: Table of Events (Continued)

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

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

[a] All baseline assessments must be completed prior to randomization and dispensing of IP.
[b] Visit 10 will serve as the Early Termination Visit for any subject who prematurely discontinues from the study.
[c] All subjects who complete the study or discontinue the study early will be asked to enter the Four-week Post-treatment Observational Follow-up Phase.
[d] Written informed consent will be obtained by the Principal Investigator or designee prior to performing any study assessments.
[e] CXRs taken within 12 weeks prior to screening will be accepted. CXRs should be performed as indicated by local treatment guidelines or practice for monitoring while on immunosuppressive/immunomodulatory therapy. If such guidelines are not available/applicable, routine CXRs should be performed as per the Table of Events or when clinically indicated.
[f] The QuantiFERON® Gold test should be used for TB testing in lieu of the tuberculin skin test (TST) or purified protein derivative (PPD) test, if possible.
[g] FCBP: Serum pregnancy tests will be performed at the Screening and Early Termination/Last Treatment Visit. Urine dipstick pregnancy test(s) will be performed at baseline, prior to dosing. An unscheduled pregnancy test should be administered if the subject has missed a menstrual period. The Investigator will educate all FCBP about the options for and correct use of contraceptive methods at the Screening and Baseline Visits and at any time when a FCBP's contraceptive measures or ability to become pregnant changes.
[h] Refer to Section 6.5, Procedures, for details regarding hematology, clinical chemistries, and urinalysis parameters to be tested.
[i] At any time vasculitis is suspected. See Section 6.5, Procedures
[j] At any time when suicidal thoughts or a suicide attempt is identified. See Section 6.5, Procedures
[k] At any time, a psoriasis flare may be reported as an adverse event, provided it meets the protocol definition. See Section 6.5, Procedures
[l] Clinician assessments are to be performed after subject completes numeric rating scales and patient reported outcomes questionnaires as scheduled in the Table of Events. Clinician assessments must be done in the following order: ScPGA, CCI .
[m] Subject assessment of whole body itch must be performed prior to scalp itch assessment.
[n] Subject assessments must be completed in the following order: whole body itch NRS, scalp itch NRS, CCI DLQI, CCI as scheduled in the Table of Events.
[o] Photographs will be obtained from subjects who provide separate consent to be photographed and at select sites only.

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.

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 and the Study Manual, should be recorded, including smoking and alcohol history, as well as previous relevant surgeries (please refer to the eCRF Completion Guidelines and the Study Manual for further details). Disease history includes history of psoriasis and psoriatic arthritis.

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 tuberculosis (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 and the Study Manual 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 randomization 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) ScPGA; CCI [redacted]

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

- 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)
- Chest radiograph (historic scans within 12 weeks of screening are allowed)
- 12-lead electrocardiogram (ECG)
- Scalp Physician Global Assessment
- CCI [redacted]
- Hematology panel
- Chemistry panel (including Hemoglobin A1C)
- Urinalysis
- Hepatitis B and C screening
- TB testing
- 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)

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. For visits within the Observational Follow-up Phase, an administrative window of ± 2 weeks from the last dose of IP 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) scalp itch NRS, [redacted] 4) DLQI, [redacted]

During the treatment period, efficacy assessments may be performed by the investigator or qualified designee at any time during a study visit, but only after the subject has completed the NRS and health-related quality of life (HRQoL) assessments, when required. 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) ScPGA; [redacted].

The following evaluations/assessments will be performed at the frequency specified in the Table of Events, Table 3.

- Patient reported outcomes or health-related quality of life (HRQoL)
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Vital signs
- 12-lead electrocardiogram (ECG)
- Weight
- [redacted]
- Hematology panel
- Chemistry panel
- Urinalysis
- Adverse event evaluation (continuously)
- Efficacy assessments (see Section 6.4)
- Urine pregnancy test (prior to dosing on Day 1)
- IP dispense and return
- Photography (select sites and involving subjects signing a separate photography ICF)

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.

During the end of treatment visit, subjects must complete the itch NRS and subject questionnaires prior to any other study procedure being performed. The subject must complete the questionnaires in the following order: 1) body itch NRS, 2) scalp itch NRS, 3) DLQI, [redacted].

During the end of treatment visit, efficacy assessments may be performed by the investigator or qualified designee at any time during a study visit, but only after the subject has completed the NRS and HRQoL assessments, when required. 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) ScPGA, [redacted].

The following evaluations will be performed as specified in the Table of Events, Table 3:

- Patient reported outcomes or health-related quality of life (HRQoL)
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Complete physical exam
- Vital signs
- Weight
- Hematology panel
- Chemistry panel
- Urinalysis
- Adverse event evaluation (continuously)
- Efficacy assessments (see Section 6.4)
- Serum pregnancy test
- IP return
- Photography (select sites and involving subjects signing a separate photography ICF)

6.3. Follow-up Period

All subjects should be followed for 28 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1.

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) ScPGA, [redacted]

The following evaluations will be performed at the Observational Follow-up Visit as specified in the Table of Events,Table 3.

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Weight
- Vital signs
- Adverse event evaluation
- Efficacy assessments (ScPGA, CCI [redacted])

6.4. Efficacy Assessments

The following assessments will be conducted as outlined in the Table of Events, Table 3:

- **Numeric Rating Scale Assessments**

  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 C.

  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).

  Scalp Itch Numeric Rating Scale Assessment

  After completing the Whole Body Itch NRS, the subject will be asked to assess scalp 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 D.

  The Scalp Itch NRS was derived from the Whole Body Itch NRS. CCI [redacted]

- **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 B for grading criteria.

- CCI [redacted]

CCI [redacted]

6.5. Safety Assessments

- **Contraception Education**

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

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

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

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

  A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP subjects at screening and at the Early Termination or Last Treatment Visit. In addition, a local urine pregnancy test kit will be provided by the central laboratory and will be performed at the site on all FCBP subjects at the Baseline Visit, prior to dosing. An unscheduled pregnancy test should be performed if the FCBP subject has missed a menstrual period.

- **Chest Radiograph (CXR)**

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

- **Hepatitis B and C**

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

- **TB Testing**

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

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

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

- **Complete Physical Examination**

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

- **Vasculitis Assessment**

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

- **Psychiatric Evaluation**

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

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

- **Twelve-lead Electrocardiogram**

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

- **Clinical Laboratory Evaluations**

  Clinical laboratory evaluations will be performed by a central laboratory and as indicated in Table 3. Clinical laboratory evaluations include complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count); serum chemistries (total protein, albumin, calcium, phosphorous, glucose, total cholesterol [TC], triglycerides, high-density lipoprotein [HDL], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], adiponectin, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST; serum glutamic-oxaloacetic transaminase, SGOT], alanine aminotransferase [ALT; serum glutamic pyruvic transaminase, SGPT], sodium, potassium, chloride, bicarbonate [carbon dioxide, CO_2], blood urea nitrogen, creatinine, lactate dehydrogenase [LDH], and magnesium); as well as Hemoglobin A1C at the Screening Visit, and dipstick urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen). Dipstick urinalysis will be performed by the central laboratory; microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the dipstick urinalysis is abnormal.

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

- **Psoriasis Flare Assessments**

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

- **Adverse Events**

  Details of AE reporting may be found in Section 10.1.

CCI [redacted]

CCI [redacted]

6.7. Patient Reported Outcomes

Questionnaires should be completed by the subject after the whole body itch NRS and scalp itch NRS efficacy assessments and in the order that they are described below and as indicated in Table 3.

- CCI [redacted]

- **Dermatology Life Quality Index (DLQI)**

  During the treatment phase (see Table 3), DLQI (Finlay, 1994) will be assessed by the subject upon arrival at the site, after completing the Whole Body Itch NRS, Scalp Itch NRS, CCI [redacted] and prior to any other procedures or assessments being performed. The DLQI was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease (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 F.

CCI [redacted]

[redacted]

6.8. Photography

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

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

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

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

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

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

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

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 2:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). IP will be dispensed as indicated below.

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

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

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	10mg A 20mg P 30mg P	10mg P 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg P 20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A
Placebo	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg 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	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A
Placebo to APR 30 BID	10mg A 20mg P 30mg P	10mg P 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg P 20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg P 30mg A	20mg P 30mg A	20mg P 30mg 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 1 (Days 1-7) 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 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 M, Appendix N, and Appendix O.

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 overdose definition will apply to only apremilast (or matching placebo). Other required or optional non-IP intended for prophylaxis of certain side effects, etc, 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 2:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to enter the IRT to randomize subjects.

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 may include, but may not be limited to, 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 IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6.1. Record of Administration

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

7.7. Investigational Product Compliance

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

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

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics (PK), or excretion, please see the Investigator's Brochure and/or local package insert.

8.1. Permitted Concomitant Medications and Procedures

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

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

The following topical therapies will be permitted during the study:

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

8.2. Prohibited Concomitant Medications and Procedures

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

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

- 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 Medication

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 3, multi-center, randomized, placebo-controlled, double-blind study of the efficacy and safety of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis of the scalp. Treatment assignment will be stratified by baseline ScPGA score [moderate (3), or severe (4)].

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 moderate to severe plaque psoriasis of the scalp.

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

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 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 ScPGA evaluation, and have no 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 3b studies, including CC-10004-PSOR-008, PSOR-009 and PSOR-010 which demonstrated positive treatment effects between apremilast 30 mg BID and placebo in the proportion of subjects achieving ScPGA response at Week 16 (range 18% to 29%). Approximately 300 subjects will be randomized in a 2:1 ratio to apremilast 30 mg BID or placebo. With this sample size, a chi-square test at the 2-sided 0.05 significance level will have 90% power to detect a minimum treatment difference of 18% (38% for apremilast 30 mg BID versus 20% for placebo) between the two arms for proportions of subjects achieving ScPGA response at Week 16 (defined as ScPGA score of clear [0] or almost clear [1] with at least a 2 point reduction from baseline at Week 16).

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

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

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

9.5. Subject Disposition

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

9.6. Efficacy Analysis

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

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

9.6.1.1. Primary Efficacy Endpoint

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

The treatment difference between apremilast 30 mg BID and placebo will be compared using CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization. The 2-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided. Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc. 2008) as the primary analysis, with sensitivity analysis using the last observation carried forward (LOCF) method and the non-responder imputation (NRI) method.

The SAS procedure MI will be used to impute missing ScPGA scores at the scheduled assessments in the Placebo-controlled Phase (Weeks 0-16) to create M=25 complete data sets. The missing data patterns will be checked by treatment and stratification factor at Baseline (Week 0), and Weeks 2, 4, 8, 12 and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest ScPGA scores. The seed will be set to 804529, the imputed values will be rounded to integers and a single chain will be used to produce imputations.

In the second step, the predictive mean matching method will be used to impute the remaining missing values for the 25 data sets with monotone missing patterns. The MONOTONE REGPMM statement will be used with seed 447159. The missing values at each visit will be imputed based on treatment, stratification factor, and ScPGA scores at baseline and previous visits. The number of closest observations to be used in the selection will be K=2.

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

9.6.1.2. Secondary Efficacy Endpoints

For the binary endpoints defined as ≥4-point reduction (improvement) from the baseline visit in either the whole body pruritus NRS score or the scalp pruritus NRS score at post-baseline visits, the analyses will be based on subjects in the ITT population with baseline whole body pruritus NRS score ≥4 or baseline scalp pruritus NRS score ≥4, respectively. For the continuous secondary endpoint (ie, change from baseline in DLQI total score at Week 16), the analyses will be based on ITT population. Unadjusted 2-sided p-values and 2-sided 95% confidence intervals (CIs) will be reported.

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

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

Statistical analyses for the ten endpoints will be performed one by one downward from Week 16 to Week 2. Multiplicity adjustment is specified in Section 9.6.1.3.

The binary endpoints will be analyzed similarly as the primary endpoint. The treatment difference at each time point between apremilast 30 mg BID and placebo will be compared using CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization. The 2-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will

be provided. Missing values will be imputed using the similar MI method as the primary endpoint, with sensitivity analysis using the LOCF method and NRI method.

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

9.6.1.3. Multiplicity Adjustment

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

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

- Proportion of subjects with ≥4 point reduction (improvement) from baseline in the whole body itch NRS score at Week 2
- Proportion of subjects with ≥4 point reduction (improvement) from baseline in the scalp itch NRS score at Week 2
- Change from baseline in Dermatology Life Quality Index total score at Week 16

9.6.1.4. Exploratory Endpoints

Descriptive summary statistics or proportion of subjects achieving specified criteria will be summarized by treatment group. When appropriate, exploratory endpoints at Week 16 will also be analyzed using CMH or ANCOVA methods similar to the primary and secondary endpoints.

9.6.1.5. Subgroup Analysis

Subgroup analyses for ScPGA response at Week 16 and proportions of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS or scalp itch NRS scores at post baseline time points based upon baseline demographic (age, gender, race, etc.) or baseline disease characteristics will be provided to determine the robustness of the treatment effect.

CCI [redacted]

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

Efficacy endpoints for time points beyond Week 16 will be summarized according to the treatment assigned at randomization. For all subjects, changes in measurements will be calculated relative to measurements obtained at baseline (Week 0). Descriptive summary statistics or proportion of subjects achieving specified criteria will be summarized by treatment group. For continuous variables, descriptive statistics for baseline and changes or percent changes from baseline will be provided. Categorical variables will be summarized with frequency tabulations. 2-sided 95% confidence intervals will be provided for changes or percent changes and response rates.

9.7. Safety Analysis

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

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

events leading to death or to IP withdrawal and serious AEs will also be summarized and listed separately.

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

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

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

9.8. Interim Analysis

No interim analysis will be conducted.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database lock will be performed, the primary data analysis will be conducted CCI CCI. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data CCI All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study. At the end of the study, after all subjects have completed, or have been discontinued from the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final analysis will be performed and a final Clinical Study Report will be generated.

9.9. Other Topics

9.9.1. Investigational Product Compliance (Tablets)

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

9.9.2. Concomitant Therapy

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

9.9.3. Steering Committee

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

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

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

10. 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 case report form (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 should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

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. AEs and SAEs will be recorded on the AE page of 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 facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events 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.

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

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

10.2.2. Severity/Intensity

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

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

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

is evidence to suggest a causal relationship between the IP and the adverse event.

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 both AEs and SAEs, 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 an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, 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 both AEs and SAEs.

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 serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of 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-subunit of human chorionic gonadotropin [β-hCG] or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

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

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

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

10.5. Reporting of Serious Adverse Events

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

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

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

Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

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

10.5.1. Safety Queries

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

10.6. Expedited Reporting of Adverse Events

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

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

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

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

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

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

Celgene Drug Safety Contact Information:

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

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

- Adverse event
- Lack of efficacy
- Withdrawal by subject
- Death
- Lost to follow-up
- Non-compliance with IP
- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

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

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

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

11.2. Study Discontinuation

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

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

- 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 contact IRT for unblinded 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 adverse events 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 compact disc, read only memory device (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 standard operating procedures (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, European Medicines Agency [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.

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.

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity 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
CCI [redacted]	[redacted]
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
CD-ROM	Compact disc, read only memory device
CIOMS	Council for International Organization of Medical Sciences
CMH test	Cochran-Mantel-Haenzel test
CO_2	Carbon dioxide
CRO	Contract Research Organization
CRF	Case report form
CXR	Chest radiograph
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
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
CCI [redacted]	[redacted]

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GI	Gastrointestinal
CCI [redacted]	[redacted]
HDL	High-density lipoproteins
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LLN	Lower level of normal
LOCF	Last observation carried forward
LS	Least squares
CCI [redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NRI	Non-responder imputation
NRS	Numeric Rating Scale
PA	Posterior to anterior
CCI [redacted]	[redacted]
PDE4	Phosphodiesterase type 4
PP	Per protocol

Table 6: Abbreviations and Specialist Terms (Continued)

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

Appendix B: 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** = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) **Scalp Scaling** = ± (surface dryness with some desquamation) **Scalp Erythema** = ± (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 C: Modified Whole Body Itch Numeric Rating Scale (NRS)

Instruction: Please think about **your whole body (including your scalp)** when answering the question below.

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

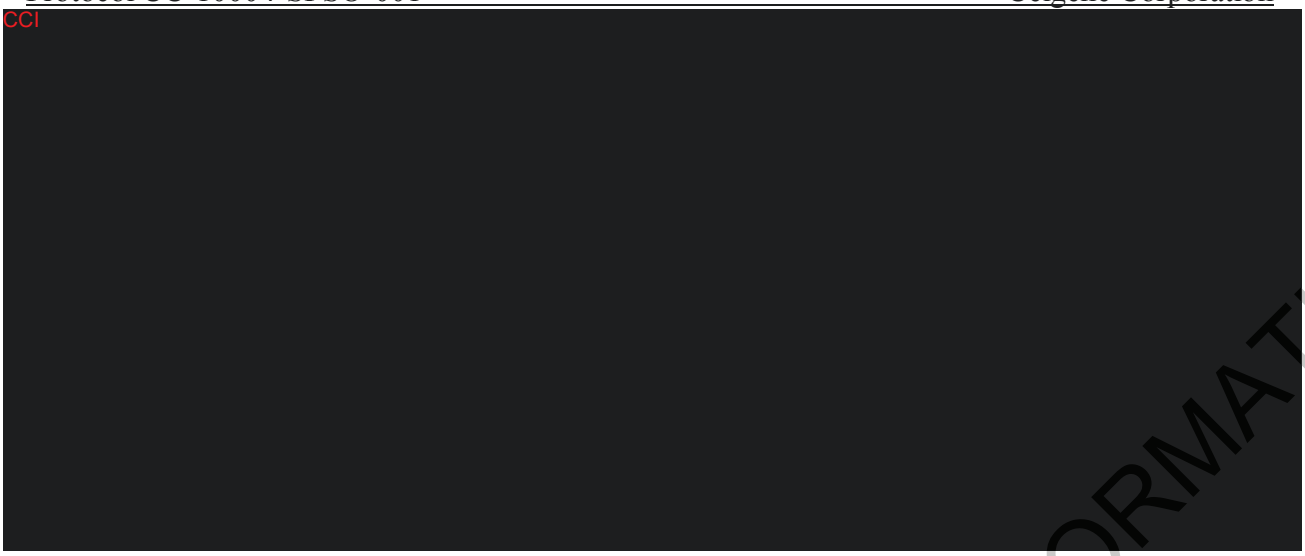
Naegeli, 2015.

Appendix D: Scalp Itch Numeric Rating Scale (NRS)

Please rate the itching severity of your **scalp** 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 scalp itch										10 = Worst scalp itch imaginable

CCI



Appendix F: 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?	_ Very much _ A lot _ A little _ Not at all	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	_ Very much _ A lot _ A little _ 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**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
7.	Over the last week, has your skin prevented you from **working** or **studying**?	_ Yes _ No	_ Not relevant
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	_ A lot _ A little _ Not at all	

Appendix F: Dermatology Life Quality Index (DLQI) (Continued)

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	_ Very much _ A lot _ A little _ Not at all	_ 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?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant

Finlay, 1994.

CCI

CCI

CCI

CCI

CCI

Appendix K: Treatment Schema for Dose Titration at Baseline

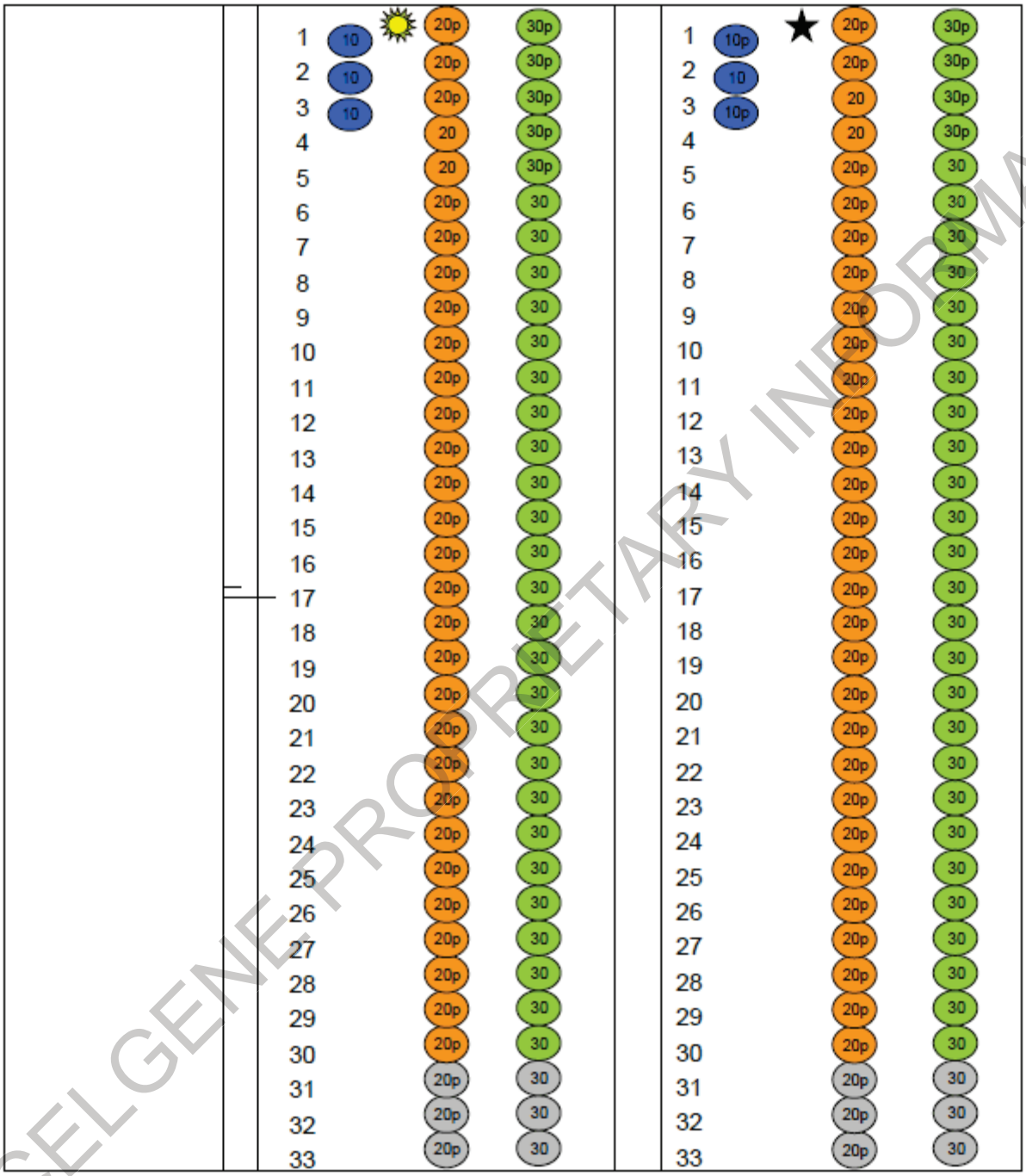
Dose	Day 1		Day 2		Day 3		Day 4		Day 5		Days 6 -7	
Group	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Placebo (dummy titration)	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	20 mg placebo + 30 mg placebo	20 mg placebo + 30 mg placebo	20 mg placebo + 30 mg placebo	20 mg placebo + 30 mg placebo	20 mg placebo + 30 mg placebo	20 mg placebo + 30 mg placebo
30 mg apremilast (titration)	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg apremilast + 30 mg placebo	20 mg apremilast + 30 mg placebo	20 mg apremilast + 30 mg placebo	20 mg apremilast + 30 mg placebo	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast

Appendix L: Treatment Schema for Dose Titration at Week 16

Dose Group	Day 112		Day 113		Day 114		Day 115		Day 116		Days 117 through 118	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Placebo to 30 mg apremilast (titration)	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg placebo + 30 mg placebo	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg apremilast + 20 mg placebo + 30 mg placebo	10 mg placebo + 20 mg apremilast + 30 mg placebo	20 mg apremilast + 30 mg placebo	20 mg apremilast + 30 mg placebo	20 mg apremilast + 30 mg placebo	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast
30 mg apremilast (dummy titration)	10 mg placebo + 20 mg placebo + 30 mg apremilast	10 mg placebo + 20 mg placebo + 30 mg apremilast	10 mg placebo + 20 mg placebo + 30 mg apremilast	10 mg placebo + 20 mg placebo + 30 mg apremilast	10 mg placebo + 20 mg placebo + 30 mg apremilast	10 mg placebo + 20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast	20 mg placebo + 30 mg apremilast

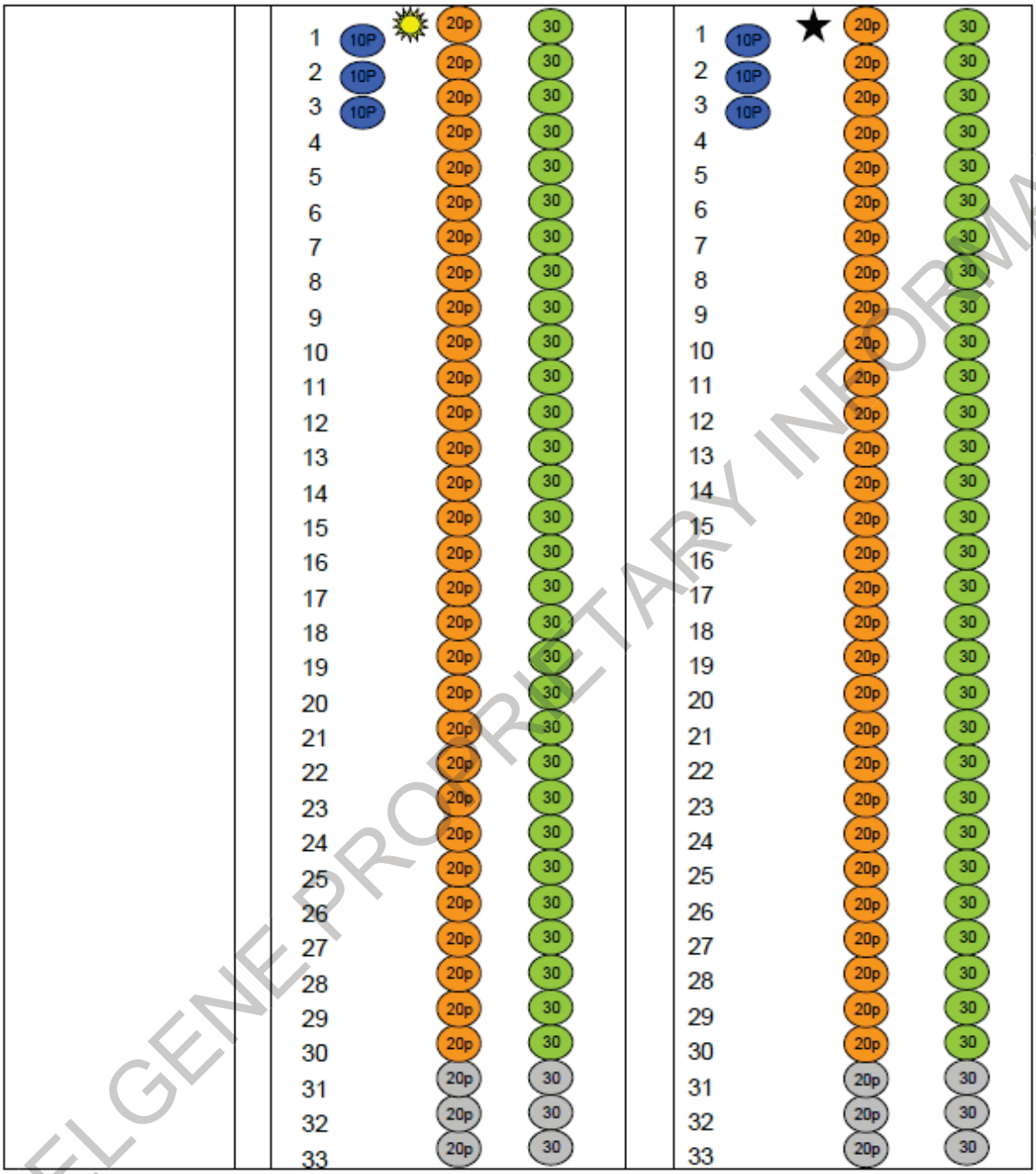
Appendix M: Titration Blister Card Configuration

CC-10004-SPSO-001 30mg Titration Card (30 day +3 Extra)



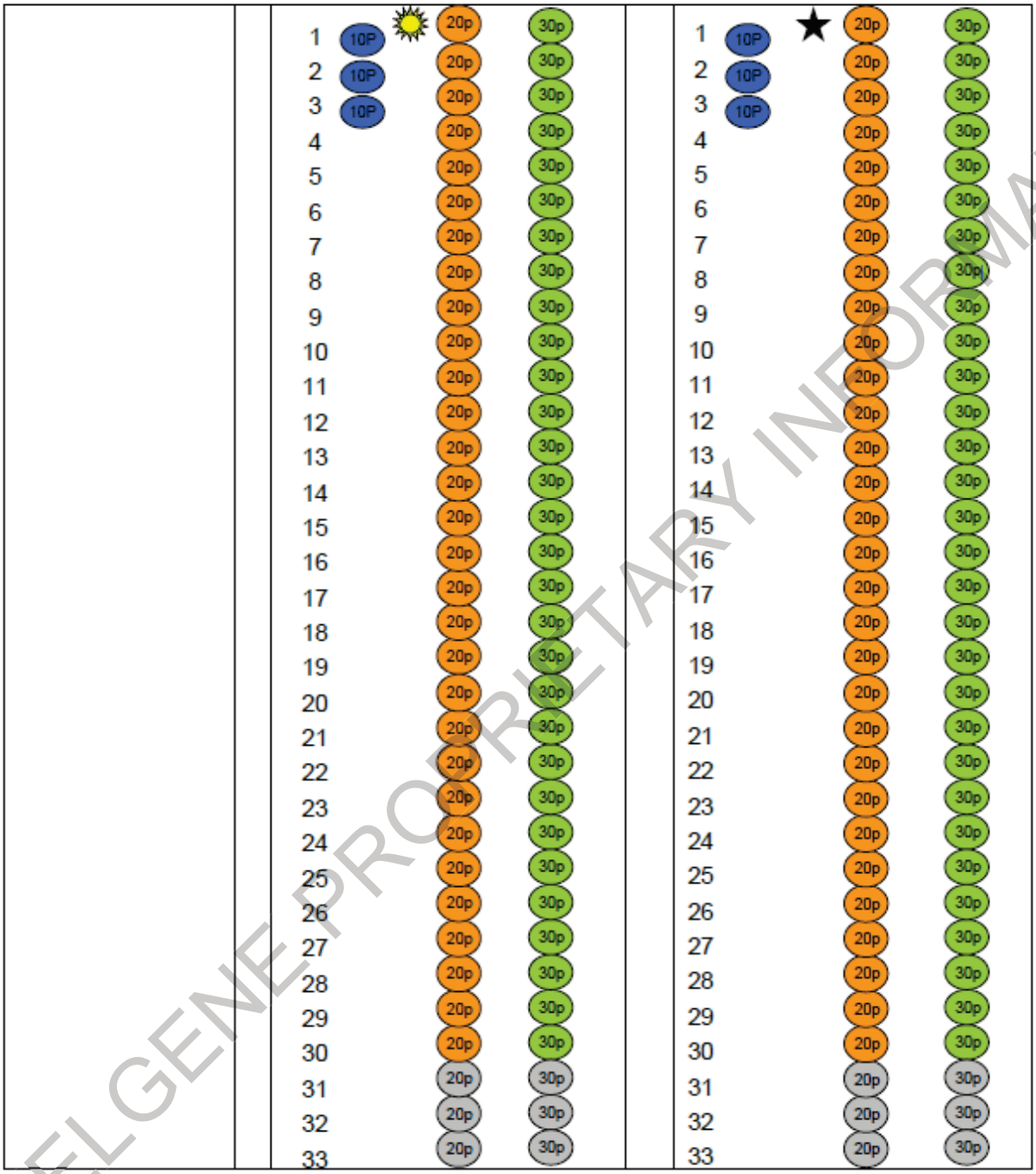
Appendix N: Active Treatment Blister Card Configuration

CC-10004-SPSO-001 30mg Treatment Card (30 day +3 Extra)



Appendix O: Placebo Treatment Blister Card Configuration

CC-10004-SPSO-001 Placebo Treatment Card (30 day +3 Extra)



Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: PPD
Title: PPD
Date: Sunday, 03 December 2017, 11:28 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Changes included in this amendment are summarized below:

- Modified Section 4.2 Inclusion Criteria 9 such that approved contraceptive options includes 2 options to reflect the standard contraception language for all Apremilast studies.
- In Section 6.4 Efficacy Assessment: added instructional text to Scalp Physician Global Assessment to guide investigators on method of assessment.
- Provided clarification to Section 6.5 Safety Assessment that subjects with positive TB testing at screening who have documentation of completed TB treatment will qualify for the study. This is in line with the Exclusion Criteria 8.
- Modified Sections 9.2, 9.5, 11.1 and 11.2 by changing protocol violations to protocol deviations to reflect current sponsor standards.
- Modified Section 8.2 Prohibited Concomitant Medications and Procedures: Topical therapy. Replaced acetylsalicylic acid with salicylic acid preparations. This is in line with Exclusion Criteria 17.
- Provided updates to the following appendices to reflect the validated and IRB approved questionnaires that were provided to the subjects since the initiation of the study:
    - Appendix C: Modified Whole Body Itch Numeric Rating Scale;
    - Appendix D: Scalp Itch Numeric Rating Scale;
    - Appendix F: The Dermatology Life Quality Index;
    - CCI [redacted]