DISCLOSURE

REDACTED PROTOCOL AMENDMENT 2

CC-10004-PPSO-001

A PHASE 2, MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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A PHASE 2, MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, Open-label Study to Assess the Safety, Tolerability and Pharmacokinetics of Apremilast (CC-10004) in Pediatric Subjects with Moderate to Severe Plaque Psoriasis

Indication

The indication is moderate to severe plaque psoriasis in adolescents (ages 12 to 17 years, inclusive) and in children (ages 6 to 11 years, inclusive).

Objectives

Primary Objective:

- To select a pediatric dose of apremilast based on the safety, tolerability, and pharmacokinetics (PK) of apremilast (APR) in adolescents and children with moderate to severe plaque psoriasis.

Secondary Objective:

- To evaluate the taste and acceptability of apremilast tablet using a faces Likert Scale.

Exploratory Objective:

- To evaluate the effect of apremilast on psoriasis in adolescents and children as measured by the Psoriasis Area and Severity Index (PASI).

Study Design

This is a Phase 2, multicenter, open-label study of apremilast in subjects aged 6 to 17 years, inclusive, with moderate to severe plaque psoriasis. The study will assess the safety, tolerability, and PK of apremilast during the first 2 weeks of treatment. At least 32 subjects will be enrolled. Subjects will be divided into 2 age groups (adolescents [ages 12 to 17 years, inclusive] and children [ages 6 to 11 years, inclusive]), with at least 16 subjects in each group. Apremilast treatment will start in older and heavier subjects. Subjects will complete the first 2 weeks of treatment with apremilast for PK analysis and then continue treatment for 48 weeks in the extension period that will explore the safety and efficacy of apremilast.

This Study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

This study will be conducted in subjects aged 6 to 17 years, inclusive, with chronic moderate to severe plaque psoriasis, defined as Psoriasis Area Severity Index (PASI) ≥ 12, Body Surface Area (BSA) ≥ 10%, and static Physician Global Assessment (sPGA) of ≥ 3 (moderate to severe) [See Appendix A], diagnosed at least 6 months prior to Screening. Subjects whose psoriasis is inadequately controlled by or inappropriate for topical psoriasis therapy will be included. Previous treatment with one systemic agent will be allowed but subjects treated with more than one systemic agent will be excluded. Subjects must be able to swallow apremilast tablets.

Length of Study

The study will last for up to a total of 107 weeks which includes screening, treatment (PK portion of the study and the extension treatment period), two short-term follow-up periods and a long-term follow-up period.

Each subject will undergo a screening period of up to 5 weeks, an initial treatment period of 2 weeks, and an extension treatment period of 48 weeks, that will allow subjects access to apremilast treatment if medically appropriate (following the completion of the 2 week PK portion). Regardless of when they stop treatment, subjects should complete the post treatment follow-up visits at 4 and at 8 weeks after the last dose. An additional long-term follow-up should be performed 52 weeks after the last dose of apremilast. All subjects should complete the final follow-up visit at Week 102 or at a timepoint 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

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

Study Treatments

Apremilast doses of 10-mg, 20-mg or 30-mg tablets have been selected to determine the dose range in adolescents and children with moderate to severe plaque psoriasis. These pediatric dosages are expected to achieve exposures similar to those achieved in adult psoriasis and psoriatic arthritis (PsA) subjects treated with apremilast 30 mg orally twice daily (BID).

A staggered, stepwise approach by age range and weight (starting with older and heavier subjects) is considered appropriate for this first-time-in-children study. Doses for younger and lower body weight subjects will be adjusted based on safety and PK data from older and heavier subjects.

Subjects will be divided into 2 age groups with at least 16 subjects in each group. Dosing within and between groups will be staggered as described below, based on PK data collected and on a minimum of 2 weeks of safety data:

Group 1 (ages 12 to 17 years, inclusive; weight ≥ 35 kg)

- At least 8 subjects will initially be enrolled into Group 1 and will weigh ≥ 35 kg.
  - Dosing for subjects with a weight ≥ 35 kg to < 70 kg will be a 20 mg BID dose regimen (10 mg BID less than the maximum adult dose).
  - Dosing for subjects with a weight ≥ 70 kg will be a 30 mg BID dose regimen (same as for adults).
- Dose regimens (dose strength and/or dose frequency) for the remaining subjects in Group 1 will be determined based on the initial 2 week PK and safety assessments from the first 8 subjects in Group 1 to complete this period. These data will be reviewed by an independent data monitoring committee (DMC) to determine if it is appropriate to proceed with dosing the balance of Group 1 subjects and to proceed with dosing in the Group 2 subjects. In the event of a dose regimen adjustment, some

or all of the first 8 subjects in Group 1, depending on weight, will return to the site for the appropriate dosing adjustment.

- For the remaining subjects in Group 1, the dose strength and/or dose frequency will be adjusted for any safety concerns or for unexpected changes in exposure.
- Group 2 will be open to enrollment once at least 8 subjects from Group 1 have completed the first 2 weeks of apremilast dosing, PK data analysis, and safety assessments and an evaluation of these data by the DMC has been completed.

Group 2 (ages 6 to 11 years, inclusive; weight ≥ 15 kg)

- At least 8 subjects will initially be enrolled into Group 2 and will weigh ≥ 15 kg. The dose regimens (dose strength and/or dose frequency) for these first 8 subjects will be based upon the PK and safety assessments from the first 8 subjects in Group 1. If PK and safety are not affected by age and body weight, 20 mg BID will be administered to Group 2 children.
- Dose regimens (dose strength and/or dose frequency) for the remaining subjects in Group 2 will be determined based on PK and safety assessments from the data collected from the first 8 subjects in each group. These data will be reviewed by an independent DMC to determine if it is appropriate to proceed with dosing the balance of Group 2 subjects. In the event of a dose regimen adjustment after the second PK and safety assessment, the first 8 subjects in Group 2 will return to the site for the appropriate dosing adjustment.
- For the remaining subjects in Group 2, the dose (dose strength and/or dose frequency) will be based upon the subject's weight as determined by the PK and safety assessments. The dose strength and/or dose frequency will be adjusted for any safety concerns or for unexpected changes in exposure.

An independent DMC will review available safety and PK data at the following timepoints:

1. After the first 8 subjects in Group 1 have completed the 2 weeks of apremilast dosing, PK, and safety assessments.
2. After the first 8 subjects in Group 2 have completed the 2 weeks of apremilast dosing, PK, and safety assessments.

Overview of Safety Assessments

Safety will be monitored throughout the study. The following will be used to assess safety:

- Adverse events (AEs)
- Physical examinations
- Vital sign measurements
- Clinical laboratory safety tests
- 12-lead electrocardiograms (ECGs)
- Concomitant medications / procedures
- Pregnancy tests

Overview of Pharmacokinetic Assessments

Blood samples, with volumes appropriate for the weight of the child, will be collected at pre-specified times to determine levels of apremilast in plasma/blood. The following PK parameters will be estimated for apremilast using a non-compartmental approach if data permit:

- Maximum observed plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the plasma concentration-time curve from time zero to 12 hours postdose (AUC_{0-12})
- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-t})
- Apparent total plasma clearance when dosed orally (CL/F)
- Apparent total volume of distribution when dosed orally, based on steady-state (Vss/F) or the terminal phase (Vz/F)
- Terminal-phase elimination half-life ($t_{1/2}$)

The following population PK parameters will be determined as appropriate:

- CL/F
- Apparent total volume of distribution when dosed orally (V/F)
- Absorption rate constant (first-order; Ka)
- Lag (if applicable)

Overview of Secondary Objective of Tablet Taste and Acceptability

- Apremilast tablet palatability will be assessed at Visit 2 (Day1) using a faces Likert Scale

Overview of Exploratory Efficacy Assessments

- Psoriasis Area Severity Index

  Percent change in the PASI score from the Baseline Visit at Weeks 2, 4, 8, 16, 24, 32, 40 and 50

Statistical Methods

No formal sample size calculation is performed. A sample size of at least 16 subjects per group has been selected to provide an adequate PK profile and safety assessment in subjects of different ages and body weight ranges. If needed, dropouts will be replaced to ensure that evaluable PK data from at least 32 subjects is collected.

Pharmacokinetic analyses will be based on the pharmacokinetic population, defined as all enrolled subjects who take at least one dose of the investigational product (ie, apremilast) and have evaluable pharmacokinetic (PK) data. Pharmacokinetic data is considered evaluable if there are measurable drug levels of apremilast in plasma from at least 3 time points which extend over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a

dose. Pharmacokinetic parameters will be calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. Pharmacokinetic parameters and plasma concentrations for apremilast will be presented using descriptive statistics. Population PK analyses will be performed using non-linear mixed effect modeling (NONMEM). Covariate analysis will be performed to identify relevant covariates.

Safety and efficacy analyses will be based on the safety population, defined as all enrolled subjects who take at least one dose of apremilast. Safety endpoints, including adverse events, laboratory data and vital sign measurements, will be summarized using descriptive statistics. Adverse events will be coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) dictionary. Exploratory efficacy endpoints will be summarized using descriptive statistics.

No formal interim analysis is planned for this study. However, an analysis of the PK and 2 weeks of safety data from the initial 8 adolescent subjects enrolled into Group 1 will be used to model the most appropriate dose for subsequently enrolled subjects. Similarly, 2 week PK and safety data from the first 8 subjects from Group 2 will be used to model the most appropriate dose for subsequently enrolled subjects.

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1. INTRODUCTION

1.1. Apremilast

Apremilast (APR) (also called CC-10004), an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro- and anti-inflammatory mediators. Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase (PDE) and the dominant PDE in inflammatory cells. Inhibition of PDE4 elevates intracellular cAMP levels, which in turn downregulates the inflammatory response by modulating the expression of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-23, and other inflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriasis and psoriatic arthritis (PsA) (Claveau, 2004; Schafer, 2010; Hamzaoui, 2011).

Apremilast is approved for the treatment of psoriasis and PsA in adults in the United States (US), Canada, European Union (EU), Switzerland, Australia and Israel. Apremilast is being developed for use in the treatment of other immune-mediated inflammatory conditions such as ulcerative colitis, Behçet's Disease, .

1.2. Psoriasis

Psoriasis is a chronic, inflammatory skin disorder estimated to affect up to 2.5% of the world's population (Christophers, 2001). Plaque-type psoriasis is the most common form of the disease in both adults and children (Fan, 2007; Mallbris, 2005; Morris, 2001). The prevalence of psoriasis in children in the United States from birth to age 18 is 1%, with an incidence of 40.8 per 100,000 (Tollefson, 2010). Psoriasis is characterized by thickened, well-demarcated erythematous plaques of skin covered with silvery scales. The nails and, less often, the mucous membranes may also be affected (Weinstein, 2003). One-third of patients present with the first signs and symptoms of psoriasis by the age of 20 years. (Tollefson, 2010; Benoit, 2007; Raychaudhuri, 2001). For mild plaque psoriasis, which comprises the majority of pediatric cases, the disease can be treated with topical therapies. Phototherapy is not recommended for fair-skinned or younger children and psoralens and long-wave ultraviolet radiation (PUVA) is not recommended for use in pediatric psoriasis patients at all, due to the increased risk of malignancies (Ståhle, 2010). Most pediatric patients present with mild, localized psoriasis that is treated primarily with topical medications. Systemic medications are typically reserved for more extensive or refractory disease. Management of psoriasis in children can be challenging owing to a paucity of data and lack of standardized guidelines specific to the pediatric population. (Vogel, 2012).

Approved therapies for moderate to severe psoriasis in children are very limited. As a consequence, some pediatric patients are treated off-label with the same systemic agents prescribed for adults. In children, these treatments are reserved for severe psoriasis due to the risks of hepatic, renal, and neurological toxicities that often require routine clinical and laboratory monitoring, as well as an increased risk of infections and malignancies. Pediatric psoriasis tends to be less severe than that seen in adults and may also be more responsive to treatment than in adults (Paller, 2008); therefore, it is important that the severity of the disease justifies the risks of treatment for the pediatric population.

1.3. Human Pharmacology

To date, no studies with apremilast have been conducted in subjects < 18 years of age.

In healthy adult subjects under fasting conditions, apremilast is rapidly absorbed following oral administration. Apremilast demonstrates linear pharmacokinetics, with area under the plasma concentration-time curve (AUC) increasing in a dose-proportional manner through 50 mg BID or 80 mg once daily. Co-administration with food does not affect the PK bioavailability of apremilast (CC-10004-CP-022). Apremilast is primarily eliminated as metabolites formed via both cytochrome P450 (CYP)-mediated oxidative metabolism (and subsequent glucuronidation) and non-CYP-mediated hydrolysis, with less than 3% excreted unchanged in urine (CC-10004-PK-002). Only 2 minor human apremilast metabolites retain pharmacologic activity, indicating that the in vivo pharmacological activity of apremilast is attributed to the parent compound. The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects (CC-10004-CP-012), with a terminal elimination half-life of approximately 6 to 9 hours. CYP3A4, CYP1A2, and CYP2A6 all participate in apremilast metabolism. Co-administration with ketoconazole increased mean apremilast area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and maximum plasma concentration of the drug (C_{max}) by approximately 36% and 5%, respectively, but did not alter the elimination half-life of apremilast (CC-10004-PK-005). Co-administration of multiple oral doses of rifampin increased apremilast apparent clearance by about 9.6 L/h to 34.5 L/h, which resulted in a decrease in apremilast mean AUC (approximately 72% lower) and C_{max} (approximately 43% lower) relative to that of apremilast given alone (CC-10004-CP-025). Methotrexate (MTX), a commonly prescribed anti-inflammatory drug, does not affect apremilast PK exposure. Apremilast does not affect the PK exposure of MTX and its metabolite, 7-OH MTX (CC-10004-PK-010). Hepatic impairment does not affect apremilast exposure (CC-10004-CP-011), and thus no dose adjustment is necessary for subjects with hepatic impairment. In the subjects with mild renal impairment, there were no clinically meaningful differences in the PK of apremilast relative to the matched healthy group. There were an ~22% higher $AUC_{0-\infty}$ and ~13% lower C_{max} of apremilast noted in the moderate renal impairment group relative to the matched healthy subject group, however, the differences noted were not statistically significant. Moreover, when compared to the healthy subjects matched to the mild renal impairment group, the mean AUC from moderate renal impaired subjects were comparable and the mean C_{max} was 18% lower. Thus, the numerical differences noted in the moderate renal impairment group are likely within the between-subject variability of apremilast exposure and are not clinically meaningful (CC-10004-CP-029). In subjects with severe renal impairment, a single oral dose administration of a 30-mg apremilast tablet resulted in an increase in overall mean exposure ($AUC_{0-\infty}$) by approximately 88% (CC-10004-CP-019). Apremilast PK and exposure are comparable across ethnic groups of Caucasian, Japanese and Chinese subjects (CC-10004-CP-018). Analyses showed apremilast exposure is also similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans. Apremilast exposure (AUC) in elderly healthy subjects (70.5 ± 4.15 years of age [mean ± standard deviation (SD)]) was approximately 13% higher than that in young healthy subjects (34.3 ± 7.17 years of age [mean ± SD]; CC-10004-CP-024) although not statistically different. Young and elderly combined, apremilast AUC exposure was approximately 30% higher in females than in males.

The metabolic profile of a single 20-mg oral dose of [^{14}C]-apremilast was characterized in a healthy volunteer absorption/distribution/metabolism/excretion (ADME) study. The mean total urinary and fecal radioactive recovery of apremilast (and its metabolites) was 97.1%, with mean contributions of 57.9% and 39.2% from urine and feces, respectively (CC-10004-PK-002).

Detailed information regarding the available pharmacology, toxicology, drug metabolism, clinical studies, and safety profile of apremilast are available in the Investigator's Brochure.

[redacted]

However, when apremilast is given to subjects whose body weights range from 15 kg to < 70 kg, initial dosing regimens should be adjusted based on body weight. As a result, the proposed dosing regimen in this study will be weight-based and a staggered, stepwise study design (starting enrollment with older and heavier adolescents) will guide dosing of subsequently enrolled subjects (younger and lower body weight children).

The PK and pharmacodynamics (PD) of apremilast in pediatric subjects have not been investigated. Considering the similarity of the disease process between adult and pediatric patients, it is appropriate to choose the dose for the pediatric population that will provide overall drug exposure similar to that of the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency (EMA) approved adult dose in psoriasis, assuming a similar exposure and response relationship in adult and pediatric patients.

1.4. Clinical Efficacy and Safety Data

At the time of protocol finalization, apremilast had been administered to adult subjects (≥ 18 years of age) at daily doses ranging from 10 to 100 mg/day in completed Phase 1 and Phase 2 clinical studies, and doses of 20 mg BID (APR 20 BID) to 30 mg BID (APR 30 BID) in ongoing Phase 2 and 3 clinical studies.

A dose ranging study in adult subjects with psoriasis has been performed to determine the optimal adult dose of apremilast (Study CC-10004-PSOR-005). Apremilast dose regimens of 10 mg, 20 mg and 30 mg BID were tested versus placebo. Both the 20 mg and 30 mg BID doses were significantly better than placebo, with a 29% response in PASI-75 at 20 mg BID, and a 41% response in PASI-75 for the 30 mg BID dose. Furthermore, the safety profiles of the 20 mg and 30 mg BID regimens were acceptable and similar. Based on these findings, apremilast 30

mg BID was determined to be the optimal dose for treatment of psoriasis for the Phase 3 registration trials.

The efficacy, safety, and tolerability of APR 30 BID were assessed in a total of approximately 1250 adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy in 2 pivotal Phase 3 studies (Study CC-10004-PSOR-008 and Study CC-10004-PSOR-009). The baseline demographic characteristics of subjects were similar across both studies, generally well balanced across the treatment groups, and representative of the typical subject population in psoriasis clinical studies in adults. Approximately 55% of the subjects had been treated previously with systemic therapy (ie, conventional systemic and/or biologics). Approximately 40% of subjects were previously treated with conventional systemic therapies, approximately 30% had prior exposure to biologics, and 17% to 29% had prior exposure to TNF blockers.

Apremilast demonstrated a treatment benefit in adult subjects with moderate and severe psoriasis, as both studies achieved the primary endpoint by demonstrating that a significantly greater proportion of subjects randomized to APR 30 BID achieved a PASI-75 response at Week 16 compared with placebo. In Study PSOR-008, 33.1% of subjects receiving APR 30 BID achieved a PASI-75 response at Week 16 compared with 5.3% of subjects receiving placebo ($p < 0.0001$). In Study PSOR-009, 28.8% of subjects achieved a PASI-75 response at Week 16 compared with 5.8% of subjects receiving placebo ($p < 0.0001$).

Clinically meaningful and statistically significant improvements were also observed with APR 30 BID for many other efficacy endpoints in both studies, including the major secondary endpoint, sPGA clear (0) or almost clear (1), PASI-50 response, mean change in PASI, BSA, pruritus and skin discomfort/pain compared with placebo. Clinical response to apremilast treatment was rapid, with significant improvement compared to placebo as early as Week 2. Maximal responses were generally achieved by Week 16, and sustained during ongoing treatment.

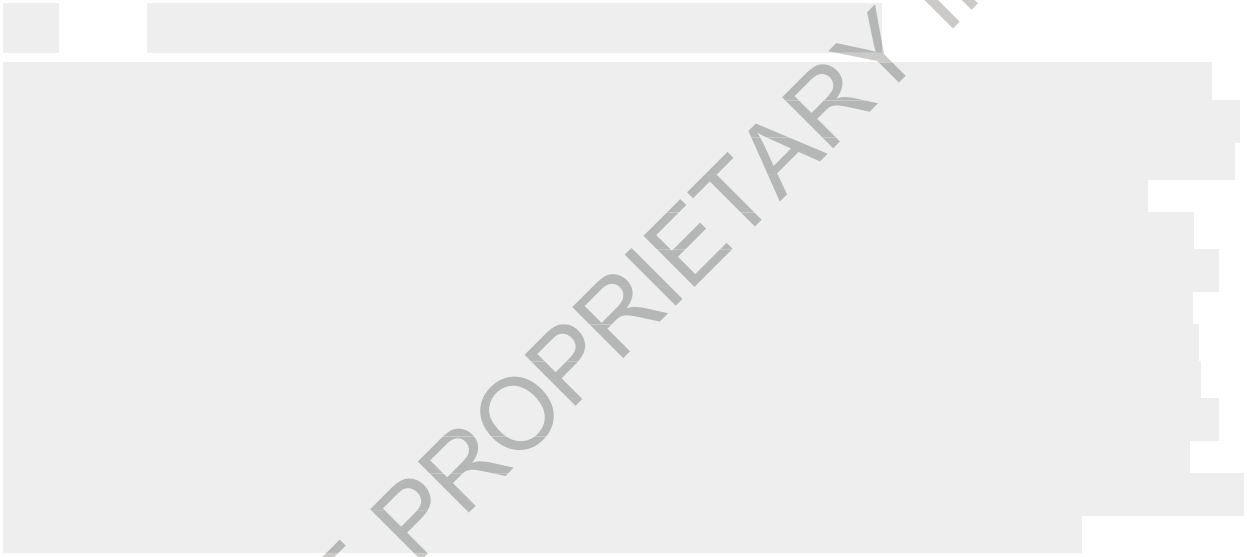
The overall safety and tolerability profile of APR 30 BID is acceptable for the treatment of moderate to severe plaque psoriasis. The most commonly reported adverse events in the psoriasis Phase 3 program were diarrhea, nausea and upper respiratory tract infection. The most common adverse reactions leading to discontinuation for subjects taking apremilast were nausea, diarrhea, and headache. The vast majority of subjects in the APR 30 BID group reported these events as mild or moderate in severity. None of the most common events were reported as serious adverse events (SAEs).

In 3 Phase 3 pivotal studies in adult subjects with active psoriatic arthritis despite prior treatment with small molecules or disease modifying anti-rheumatic drugs (DMARDs), evaluating apremilast 20 mg BID and 30 mg BID in a total of 1493 subjects (Studies CC-10004-PSA-002, CC-10004-PSA-003, and CC-10004-PSA-004), apremilast demonstrated a statistically significant response, as measured by American College of Rheumatology (ACR) 20 at Week 16, the primary endpoint, for both of the apremilast treatment groups, compared with placebo. The studies were sized to demonstrate an approximate 20% treatment difference when comparisons are made between any active treatment group and placebo. The ACR20 responses ranged from 18.3% to 19.0% in the placebo group, 28.4% to 37.4% in the apremilast 20 mg BID treatment group ($p \leq 0.0295$ versus placebo), and 32.1% to 40.7% in the apremilast 30 mg BID treatment group ($p \leq 0.0060$ versus placebo). In subjects who were DMARD-naïve (Study CC-10004-PSA

005), the primary endpoint was met for both the APR 20 BID and APR 30 BID treatment groups, compared with placebo (28.0% and 30.7% versus 15.9%, respectively [p = 0.0062 and 0.0010, respectively]). Among subjects who were initially randomized to apremilast, ACR20/50/70 response rates were maintained through Week 52 across all the studies. At Week 16 improvements in the skin manifestations of psoriasis were seen in the apremilast-treated subjects. Among subjects who remained on the apremilast treatment to which they were randomized at study start, these improvements were maintained through Week 52.

Overall Safety Profile of Apremilast

The safety profile of apremilast has been well characterized on the basis of data from 4089 subjects exposed to apremilast for a total of 3541 subject-years, including 1631 subjects exposed for 1 year or more. Apremilast was generally well tolerated, demonstrating an acceptable safety profile with long-term exposure (1 year or more). The most frequently observed adverse reactions were gastrointestinal (GI) disturbances, most commonly diarrhea and nausea. The vast majority of these events were reported as mild or moderate in severity, and led to discontinuation in a small proportion of subjects. In general, these events were self-limiting, did not require intervention, and resolved with uninterrupted apremilast treatment.



1.6. Risks/Benefits of Investigational Product and Safety Population

The safety and tolerability profiles of the apremilast 20 mg BID and 30 mg BID dose groups are both acceptable based on results from the clinical development program for apremilast. Treatment-emergent adverse events (TEAEs) associated with apremilast treatment were diarrhea, nausea, headache (including tension headache), and upper respiratory tract infection, which were usually mild or moderate in severity and often resolved while subjects continued to take apremilast. Diarrhea, nausea and headache tended to occur early in treatment. The overall discontinuation rate due to AEs was low and was most frequently due to nausea, diarrhea, or headache. Treatment with apremilast was associated with observed weight loss without overt clinical consequences. The results of pivotal Phase 3 clinical trials in psoriasis and PsA demonstrate that the 30 mg BID dose presents a favorable benefit/risk profile in adult subjects

with moderate to severe psoriasis and PsA. All apremilast approvals to date for both PsA and psoriasis have been for the 30 mg BID dose regimen.

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and the safety profile of apremilast.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to select a pediatric dose of apremilast based on the safety, tolerability, and PK of apremilast in adolescents and children with moderate to severe plaque psoriasis.

2.2. Secondary Objectives

The secondary objective is to evaluate the taste and acceptability of apremilast tablet using a faces Likert Scale.

2.3. Exploratory Objectives

The exploratory objective of the study is to evaluate the effect of apremilast on psoriasis in adolescents and children as measured by PASI.

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

Safety

The safety (reported AEs) and laboratory findings of subjects in each age group will be described and evaluated in relation to the extent of exposure to apremilast.

The following will be monitored, evaluated, recorded, and reported:

- Adverse events (AEs)
- Physical examinations
- Vital sign measurements
- Clinical laboratory safety tests
- 12-lead electrocardiograms (ECGs)
- Concomitant medications / procedures
- Pregnancy tests

Pharmacokinetics

The following PK parameters will be estimated for apremilast using a non-compartmental approach if data permit:

- Maximum observed plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the plasma concentration-time curve from time zero to 12 hours postdose (AUC_{0-12})
- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-t})
- Apparent total plasma clearance when dosed orally (CL/F)
- Apparent total volume of distribution when dosed orally, based on steady-state (Vss/F) or the terminal phase (Vz/F)
- Terminal-phase elimination half-life ($t_{1/2}$)

The following population PK parameters will be determined as appropriate:

- CL/F
- Apparent total volume of distribution when dosed orally (V/F)
- Absorption rate constant (first-order; Ka)
- Lag (if applicable)

3.2. Secondary Endpoint(s)

The taste and acceptability of apremilast tablet will be assessed using a faces Likert Scale on Day 1, initial dosing.

3.3. Exploratory Endpoint(s)

The exploratory endpoint is the percent change in PASI scores from Baseline.

Measurements of PASI will be performed at Screening, Baseline, Weeks 2, 4, 8, 16, 24, 32, 40, 50,54, 58, Unscheduled visits, and Early Termination visits as indicated in the Table of Events (Section 5).

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, multicenter, open-label study in subjects with moderate to severe plaque psoriasis aged 6 to 17 years, inclusive, intended to assess the safety, tolerability, and PK of apremilast with 2 weeks of oral apremilast treatment followed by a 48-week extension of apremilast treatment. Moderate to severe plaque psoriasis is defined as Psoriasis Area Severity Index (PASI) ≥ 12, Body Surface Area (BSA) ≥ 10%, and static Physician Global Assessment (sPGA) of ≥ 3 (moderate to severe) [See Appendix A]. The total study duration for each subject will last for up to a total of 107 weeks which includes screening, treatment (including the PK portion of the study and the extension treatment period), two short-term follow-up periods and a long-term follow-up period (Figure 1).

Each subject will undergo a screening period of up to 5 weeks, a treatment period of 2 weeks with PK sample collection, and an extension treatment period of 48 weeks, to allow subjects access to apremilast treatment if medically appropriate (following the completion of the 2 week PK portion). Regardless of when they stop treatment, subjects should complete two post treatment follow-up visits at approximately 4 and 8 weeks after the last dose.

All subjects should complete the final follow-up visit at Week 102 or at a timepoint 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

At least 32 subjects will be enrolled into this study to provide an adequate PK profile and safety assessment in subjects of different ages and body weight ranges. Subjects will be divided into 2 age groups (adolescents [ages 12 to 17 years, inclusive] and children [ages 6 to 11 years, inclusive]), with at least 16 subjects in each group. Apremilast treatment will start in older and heavier subjects.

A staggered, stepwise approach by age range and weight (starting with older and heavier subjects) is considered appropriate for this first-time-in-children study. Doses for younger and lower body weight subjects will be adjusted based on safety and PK data from older and heavier subjects. Dosing within and between groups will be staggered as described below, and in Figure 2, based on PK data collected and a minimum of 2 weeks of safety data.

Group 1 (ages 12 to 17 years, inclusive; weight ≥ 35 kg)

- At least 8 subjects will initially be enrolled into Group 1 and will weigh ≥ 35 kg.
  - Dosing for subjects with a weight ≥ 35 kg to < 70 kg will be administered as a 20 mg BID dose regimen (10 mg BID less than the adult dose).
  - Dosing for subjects with a weight ≥ 70 kg will be administered as a 30 mg BID dose regimen (same as for adults).
- Dose regimens (dose strength and/or dose frequency) for the remaining subjects in Group 1 will be determined based on PK and safety assessments from the first 8 subjects in Group 1 to complete this period. These data will be reviewed by an independent data monitoring committee (DMC) to determine if it is appropriate to

proceed with dosing the balance of Group 1 subjects and to proceed with dosing in the Group 2 subjects.

- For the remaining subjects in Group 1, the dose strength and/or dose frequency will be adjusted for any safety concerns or for unexpected changes in exposure. In the event of a dose regimen adjustment, some or all of the first 8 subjects in Group 1, depending on weight, will return to the site for the appropriate dosing adjustment. Group 2 will open to enrollment once at least 8 subjects from Group 1 have completed the 2 weeks of apremilast dosing, PK data analysis, and safety assessments and an evaluation of these data by the DMC has been completed.

Group 2 (ages 6 to 11 years, inclusive; weight ≥ 15 kg)

- At least 8 subjects will initially be enrolled into Group 2 and will weigh ≥ 15 kg. The dose regimens (dose strength and/or dose frequency) for these first 8 subjects will be based upon the PK and safety assessments from the first 8 subjects in Group 1. If PK and safety are not affected by age and body weight, 20 mg BID will be administered to Group 2 children.
- Dose regimens (dose strength and/or dose frequency) for the remaining subjects in Group 2 will be determined based on PK and safety assessments from the data collected from the first 8 subjects in each group. These data will be reviewed by an independent DMC to determine if it is appropriate to proceed with dosing the balance of Group 2 subjects.
- For the remaining subjects in Group 2, the dose (dose strength and/or dose frequency) will be based upon the subject weight as determined by the PK and safety assessments. The dose strength and/or dose frequency will be adjusted for any safety concerns or for unexpected changes in exposure. In the event of a dose regimen adjustment after the second PK and safety assessment, the first 8 subjects in Group 2 will return to the site for the appropriate dosing adjustment.

An independent DMC will review available safety and PK data at the following timepoints:

1. After the first 8 subjects in Group 1 have completed the first 2 weeks of apremilast dosing, PK, and safety assessments.
2. After the first 8 subjects in Group 2 have completed the first 2 weeks of apremilast dosing, PK, and safety assessments.

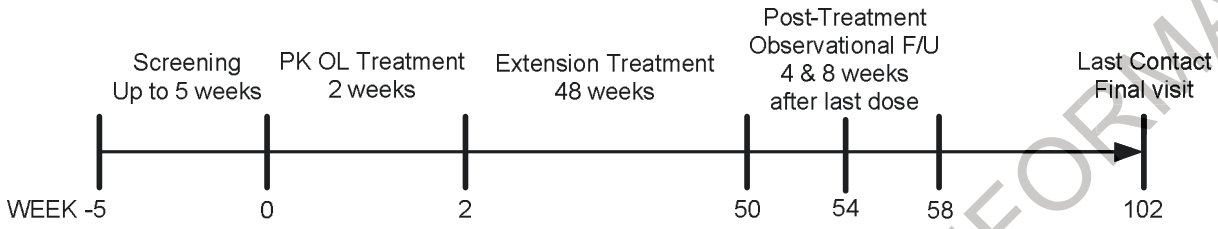
Treatment administration and schedule are discussed in Section 8.2.

At this time, there are no consistent AEs or laboratory findings that would generally constitute a reliable stopping rule for this study. Subjects will be monitored for AEs, vital signs, and laboratory assessments at each study visit. All AEs, clinically significant changes in laboratory measures and clinically meaningful changes in vital signs will be recorded. Clinically meaningful changes that increase the risk to the subject, as assessed by the Investigator or Sponsor, may result in discontinuation of the subject from the study. Subjects who have psoriasis disease flare at anytime during the treatment (PK, or extension treatment period) of the study and require additional psoriasis medication including conventional systemic therapies such

as methotrexate, systemic corticosteroids, or biologics, will be discontinued from the study and treated according to local treatment guidelines.

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

Figure 1: Overall Study Design



PK= Pharmacokinetics; OL= Open Label (Apremilast); F/U= Follow Up

Figure 2: Subject Treatment Groups

Group 1:

N=16

Ages: 12 to 17 years, inclusive

Weight: ≥ 35 kg

Group 1:

Initial Dose:

20 mg BID for subjects weighing ≥ 35 kg to < 70 kg

30 mg BID for subjects weighing ≥ 70 kg

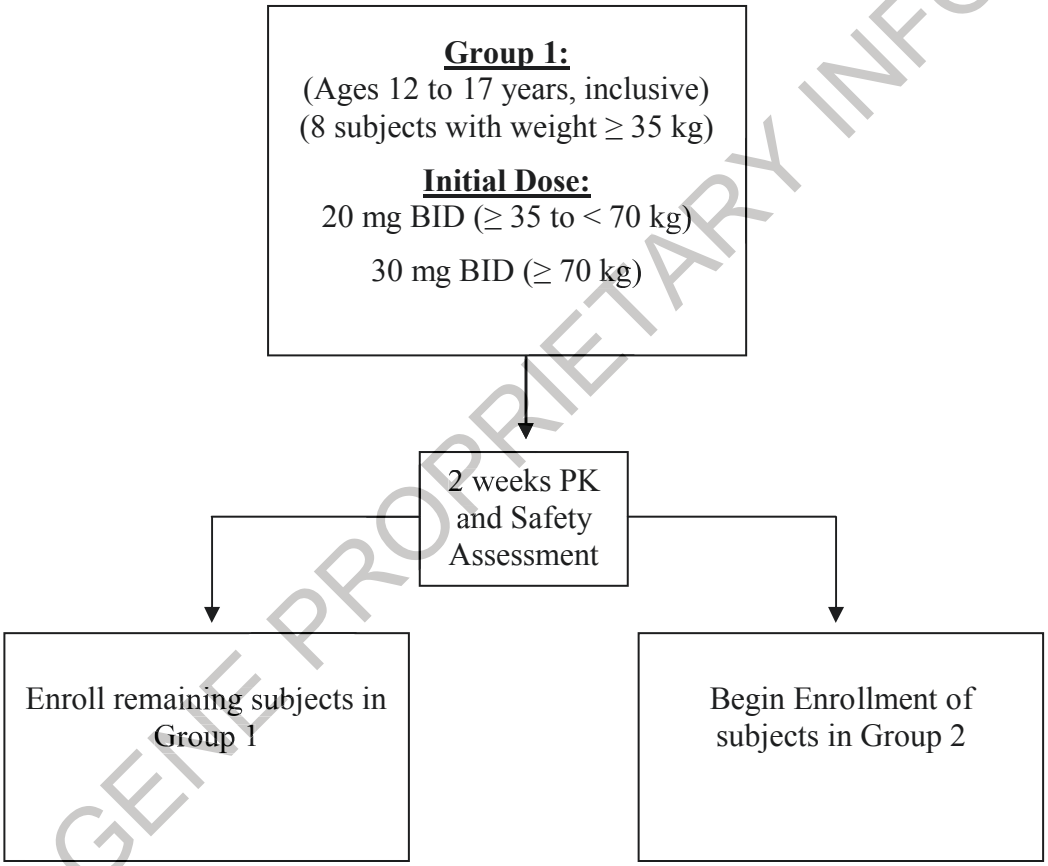


Figure 2: Subject Treatment Groups (Continued)

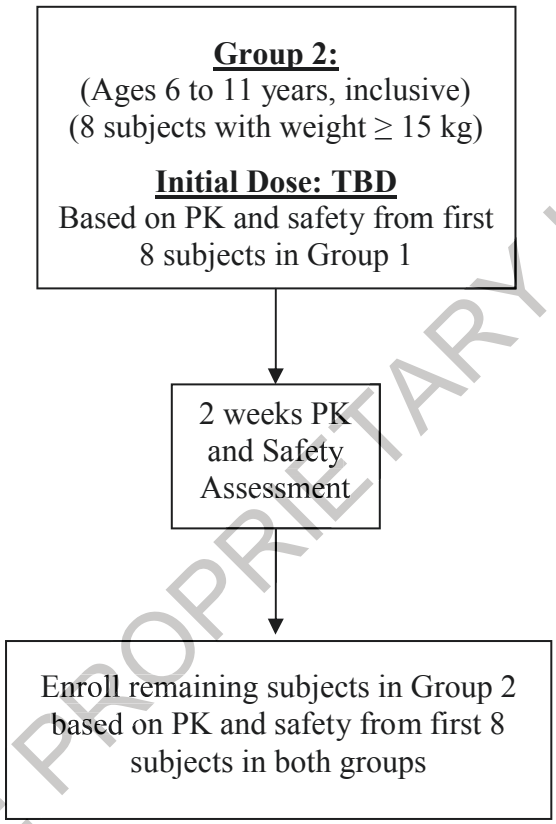
Group 2:

N=16

Ages: 6 to 11 years, inclusive

Weight: ≥ 15 kg

Dose: Based upon completion of PK and safety data analysis from at least 8 subjects from Group 1.



BID = twice daily; N = number of subjects; PK = pharmacokinetic; TBD = to be determined.

4.2. Study Design Rationale

There is a paucity of treatments available for pediatric patients with moderate to severe psoriasis. Consequently, these subjects are treated off-label with the same systemic agents prescribed for adults. The currently available systemic therapies for psoriasis are associated with significant cumulative toxicities and are associated with risks of hepatic, renal and neurological toxicities that often require routine clinical and laboratory monitoring, as well as an increased risk of infections and malignancies. Given the chronic nature of psoriasis, there is a need for medication that can be dosed chronically with less risk. It is, therefore, important for new medications to demonstrate both efficacy and safety with continuous use. Apremilast provides a favorable

benefit/risk profile supporting the use of APR 30 BID in the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic and phototherapy.

Adolescents and children may differ from adults in their ADME of apremilast, hence evaluation of the safety and PK properties of apremilast in adolescents and children prior to initiation of an efficacy study in this subject population is warranted. Although apremilast has only been investigated in adult subjects, it is known that there is a general similarity of disease process, as reflected in PD parameters, between adult and pediatric populations. Assuming a similar exposure-response relationship in adults compared to adolescents and children, it is appropriate to initiate dosing in the pediatric population at a dose of 20 or 30 mg BID, depending on weight, that will provide overall drug exposure similar to that associated with the selected optimal adult dose.

In CC-10004-PSOR-008-PK, the concentration versus time profile of apremilast was well described by a population PK model.

A comparable exposure in pediatric subjects is expected to achieve a similar clinical response seen in psoriasis adult patients following 30 mg BID.

This Phase 2 study will evaluate the clinical safety and PK of apremilast. The proposed dosing regimen in this study will be weight-based and a staggered, stepwise study design (starting enrollment with older and heavier adolescents) will guide dosing of subsequently enrolled subjects (younger and lighter weight children) (Figure 2). Efficacy of apremilast in the treatment of pediatric subjects with moderate to severe psoriasis will also be explored in this study.

4.3. Study Duration

The study will last for up to a total of 107 weeks which includes screening, treatment, including the PK portion of the study and the extension treatment period, short-term follow-up and a long-term follow-up.

Each subject will undergo a screening period of up to 5 weeks, a treatment period of 2 weeks, and an extension treatment period of 48 weeks, to allow subjects access to apremilast treatment if medically appropriate (following the completion of the 2 week PK portion).

Regardless of when they stop treatment, subjects should complete two post treatment follow-up visits at approximately 4 and 8 weeks after the last dose.

All subjects should complete the final follow-up visit at Week 102 or at a timepoint 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

4.4. End of Trial

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

An abbreviated clinical study report will be written following analysis of the PK results. The results of the extension treatment period will be added once this portion of the study has been completed.

5. TABLE OF EVENTS

Table 1: Table of Events

Procedure	Visit 1 Screening Week -5 Days -35 to -1	Visit 2 Baseline Week 0 Day 1	Visit 3 Final PK Week 2 Day 14 (+/-1)	Visit 4-10 Extension Treatment Weeks 4, 8, 16, 24, 32, 40, 50 Days 28, 56, 112, 168, 224, 280, 350 (+/-4)	Visits 11 & 12 Follow-up[a] Weeks 54 & 58 Days 378 & 406 (+/-7)	Visit 13 Final Follow-up[b] Week 102 Day 714 (+/-7)	UNS[c]	ET
Study Entry								
Informed Consent / Assent	X	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-
Demographic Data	X	-	-	-	-	-	-	-
Complete Medical History	X	-	-	-	-	-	-	-
Prior and Concurrent Therapies and Procedures	X	X	X	X	X	-	X	X
Stool Diary Collection[d]	-	-	X	X	X	-	X	X
Tanner Staging Assessment	-	X	-	-	X[e]	-	-	-
Columbia-Suicide Severity Rating Scale (C-SSRS) Screening	X[f]	-	-	-	-	-	-	-
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit	-	X[g]	X[g]	X[g]	X[g]	-	X[g]	X[g]
Safety Assessments								
Adverse Events	After signing ICF and until 28 days after the last dose							
Pregnancy Test (FCBP only)[h]	X	X	-	X	X	-	-	X
Physical Examination	X	-	-	-	-	X[i]	-	-
Abbreviated Physical Examination	-	X[j]	X[j]	X[j]	X[j]	-	X[j]	X[j]
Hepatitis B and C Testing	X	-	-	-	-	-	-	-

Table 1: Table of Events (Continued)

Procedure	Visit 1 Screening Week -5 Days -35 to -1	Visit 2 Baseline Week 0 Day 1	Visit 3 Final PK Week 2 Day 14 (+/-1)	Visit 4-10 Extension Treatment Weeks 4, 8, 16, 24, 32, 40, 50 Days 28, 56, 112, 168, 224, 280, 350 (+/-4)	Visits 11 & 12 Follow-up[a] Weeks 54 & 58 Days 378 & 406 (+/-7)	Visit 13 Final Follow-up[b] Week 102 Day 714 (+/-7)	UNS[c]	ET
Vital Signs[k]	X	X	X	X	X	-	X	X
Height	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Body Mass Index (BMI)	X	X	X	X	X	X	X	X
Hematology Laboratory Tests	X	X	-	X	X	-	X[l]	X
Serum Chemistry Laboratory Tests	X	X	-	X	X	-	X[l]	X
Urinalysis	X	X	-	X	X	-	X[l]	X
12-lead ECG	X	-	X[m]	X[m]	-	-	-	X[m]
Apremilast								
Tablet Taste and Acceptability Testing (via Likert Scale)	-	X	-	-	-	-	-	-
Oral Dose Apremilast[n]	-	X	X	X	-	-	-	-
Apremilast Drug Accountability	-	X	X	X	-	-	X	X
Drug Dispensation	-	X	X	X[o]	-	-	-	-
Pharmacokinetic Assessments								
Blood Collection for PK[p]	-	X	X	-	-	-	-	X[q]
Exploratory Assessments								
Psoriasis Area Severity Index (PASI)	X	X	X	X	X	-	X	X

ET = early termination; ECG = electrocardiogram; FCBP = females of childbearing potential; ICF = informed consent form; PK = pharmacokinetics; UNS = unscheduled visit.

[a] All subjects should complete the initial follow-up visits 4 and 8 weeks after taking their last dose of apremilast regardless of when they stop taking apremilast.

[b] All subjects should complete the final follow-up visit at Week 102 or at a timepoint 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

[c] Refer to 6.14.1 for details.

[d] Subjects and their parent/guardian will complete the Stool Diary every day, beginning after the first dose of apremilast, up to the 4-week post last dose follow-up visit (Visit 11).

[e] Tanner Staging assessment will be performed at Baseline and the 8 week post last dose of apremilast follow-up visit (Visit 12).

[f] Any subject, during screening or at baseline, that answers 'Yes' to any question on the Columbia-Suicide Severity Rating Scale, will be ineligible for study participation and should be referred immediately for a psychiatric evaluation.

[g] Any subject that answers 'Yes' to any question on the Columbia-Suicide Severity Rating Scale, at anytime during the study (post baseline) will be immediately withdrawn from study treatment and must be referred immediately for a psychiatric evaluation.

[h] Serum and urine pregnancy testing will be required for FCBP at Baseline. Urine pregnancy testing will be performed at Screening and at each visit during the extension period, the Week 54 and 58 Follow-up Visits, and the ET visit (if applicable). If a urine test is positive, a serum test will be done for confirmation.

[i] Laboratory tests may be performed as clinically indicated based on the investigator's medical judgment. The subject will be asked if he/she has used any investigational drug within the 52 weeks prior to the Week 102 visit.

[j] An abbreviated physical examination may be performed at the discretion of the Investigator, if clinically needed.

[k] Vital signs will be obtained after the subject has been in the supine position for at least 5 minutes.

[l] Urinalysis, hematology, and serum chemistry laboratory tests may be performed at the discretion of the Investigator, if clinically needed.

[m] Electrocardiogram (ECG) will be completed at Screening and after the last dose of investigational product (Week 50/ET). If a subject withdraws from the study prior to entering the extension treatment period, an ECG should be completed at the Week 2 (Final PK) visit.

[n] Apremilast will be administered orally twice daily from Day 1 through the morning of Day 14. Evening doses should be administered approximately 12 hours after the morning dose. The evening dose taken on Day 14 must not be taken until AFTER the last PK blood sample is drawn. On PK days (Day 1 and Day 14), all subjects will be administered the morning dose of apremilast by mouth in the fasted state. Food and beverages (except water) will be withheld from subjects for at least 8 hours prior to the morning dose until at least 2 hours after the morning dose on PK days (Day 1 and Day 14). For all evening doses and all morning doses administered on non-PK days, apremilast tablets should be taken approximately 12 hours apart and without any food restrictions. NOTE: Dosing regimens may vary depending on dose strength/dose frequency determined from the Group 1 PK and safety data.

[o] No drug will be dispensed at Week 50.

[p] Group 1 (ages 12 to 17 years, inclusive, at the time of Screening): Day 1: 2 hours after the morning dose. Day 14 (last dose of PK treatment period): Predose (prior to morning dose) and 1, 2, 3, 5, 8, and 12 hours post morning dose.
Group 2 (ages 6 to 11 years, inclusive, at the time of Screening): Day 1: 2 hours after the morning dose. Day 14 (last dose of PK treatment period): Predose (prior to morning dose) and 2, 5, and 12 hours after the morning dose.

[q] Do not collect PK after Day 14.

6. PROCEDURES

The following procedures will be conducted as outlined in the Table of Events, Section 5.

6.1. Informed Consent and Subject Assent

Both an age-specific assent (by the study subject) and an informed consent form [(ICF) by subject's legal guardian] must be signed before any study-related assessments are performed. This process must be repeated again with new signatures if a subject fails screening for any reason and chooses to return and rescreen for a second attempt to meet study entrance criteria.

6.2. Inclusion/Exclusion Criteria

Subjects must meet all eligibility criteria (Section 7.2 and Section 7.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study. Inclusion and exclusion criteria will be assessed at Screening and reviewed again prior to first dose.

6.3. Demographic Data

The demographic data will include (but not be limited to) the subject's date of birth, age, gender, and race/ethnic origin. The demographic profile will be recorded in the source documents and electronic case report form (eCRF).

6.4. Complete Medical History

Relevant medical history should be recorded, including previous relevant surgeries. Disease history should include history of plaque psoriasis.

6.5. Prior and Concurrent Therapies and Procedures

All medications and therapies (including prescription and non-prescription systemic and topical medications, as well as herbal supplements) taken by the subject up to 30 days prior to Visit 1 should be recorded, including the stop dates for medications prohibited in the study, at the time of consent. All medications and therapies being taken by the subject at any time during the study must also be recorded. The stop dates and the reasons for discontinuation of any medication or therapy discontinued at any time during the study should be recorded.

All procedures performed up to 30 days prior to Visit 1 should be recorded.

Additional instructions can be found in the electronic case report form (eCRF) Completion Guidelines.

Subjects are eligible for study participation if not previously exposed to more than one systemic agent for psoriasis.

Refer to Section 9 for further details regarding permitted and prohibited concomitant medications and procedures.

6.6. Safety Assessments

6.6.1. Adverse Events

Safety assessments will be performed as outlined in the Table of Events, Section 5.

Details of AE reporting can be found in Section 11. All AEs, whether reported by subjects spontaneously or when elicited by direct questioning, will be monitored and recorded from the time the subject signs the ICF until 28 days after the last dose of apremilast. Serious adverse events (SAEs) suspected of being related to apremilast and made known to the Investigator at any time will be monitored and recorded.

6.6.2. Contraception Education

There are no adequate and well controlled studies of apremilast in pregnant women.

All females of childbearing potential (FCBP) must practice abstinence or use one of the approved contraceptive options as described in Section 7.2 while on investigational product and for at least 28 days after administration of the last dose of the investigational product.

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

More information regarding the effects of apremilast on reproduction in animal and in vitro studies can be found in the Investigator's Brochure.

6.6.3. Serum and Urine Pregnancy Tests for Females of Childbearing Potential

A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for all FCBP at Baseline and as confirmation of any positive urine test. Urine pregnancy testing will be performed on all FCBP at Screening, Baseline and at the extension treatment period visits and the 4 and 8 week post last dose follow-up visits (Early Termination Visit as well if applicable). A urine pregnancy test kit will be provided by the central laboratory. Pregnancy testing should be performed if the FCBP has missed a menstrual period or the contraception method has changed.

For the purposes of this study, a female subject is considered of childbearing potential if she is ≥ 12 years old or has reached menarche, whichever occurred first.

6.6.4. Complete Physical Examinations

A complete physical examination includes evaluations of general appearance, skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, GI, neurological, and musculoskeletal systems will be performed at Screening.

6.6.5. Abbreviated Physical Examination

An abbreviated physical examination includes evaluation of the general appearance, respiratory, cardiovascular and GI systems may be performed at any visit after screening at the discretion of the investigator, if clinically needed.

6.6.6. Hepatitis B and C Testing

Hepatitis testing will be performed at Screening and will include hepatitis B surface antigen and hepatitis C antibody.

6.6.7. Vital Signs, Height, Weight and Body Mass Index

Vital signs, including temperature, respiratory rate, pulse, and seated blood pressure, will be taken during the visits indicated in the Table of Events, (Section 5). Height, weight and body mass index will be measured and recorded at Screening and then as indicated in the Table of Events, Section 5.

Vital signs will be obtained after the subject has been in the supine position for at least 5 minutes. Since drinking hot or cold beverages (including water) has a significant impact on recorded oral body temperature, no beverages should be ingested within 15 minutes when using an oral thermometer.

Investigators are to report any clinically significant abnormal findings as AEs.

6.6.8. Clinical Laboratory Evaluations

A central laboratory will be used for this study. Clinical laboratory evaluations will be performed as indicated in the Table of Events, Section 5. The Principal Investigator (PI) or medically-qualified designee will review and assess all clinical laboratory data. The laboratory reports should be initialed and dated by the PI or medically-qualified designee, and the clinical or nonclinical significance of any abnormal laboratory results should be indicated. Abnormal laboratory results may be repeated to rule out laboratory errors. Any clinically significant abnormal laboratory result should be reported as an AE and should be followed to resolution (ie, stabilizes, returns to baseline or becomes clinically insignificant).

Additional clinical safety laboratory evaluations should be performed if judged clinically appropriate by the Investigator or by a medically qualified designee, or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is warranted.

6.6.8.1. Hematology

Hematology laboratory evaluations will include red blood cells (RBCs), hemoglobin, hematocrit, white blood cells (WBCs), absolute and differential and platelet count.

6.6.8.2. Serum Chemistry

Serum chemistry laboratory evaluations will include sodium, potassium, chloride, carbon dioxide, calcium, blood urea nitrogen, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamate pyruvic transaminase (ALT/SGPT), gamma-glutamyl transpeptidase, lactate dehydrogenase, phosphate, and magnesium.

6.6.8.3. Urinalysis

Urinalysis will include specific gravity, pH, glucose, protein, ketones, and hemoglobin/blood. A microscopic examination (eg, casts, RBCs, and WBCs) will be performed in the event of a positive result.

6.6.8.4. Vaccinations

Apremilast's effect on vaccinations has not been studied, therefore, a conservative approach will be taken and vaccinations will be withheld during the first 14 days of dosing. Inactivated vaccines will be allowed during the extension treatment period, however, live vaccines are not allowed during active treatment with apremilast.

6.6.9. Twelve-lead Electrocardiogram

The timeframes for all 12-lead electrocardiograms (ECGs) are indicated in the Table of Events, Section 5.

An ECG will be performed after the subject has been supine for approximately 3 minutes. Sites are to utilize their own, local ECG machines for the study and the ECG readings will be further interpreted by the Investigator by clinically correlating with the subject's condition. The Investigator's clinical interpretation will be recorded in the electronic Case Report Form (eCRF) as: normal; abnormal, not clinically significant; abnormal, clinically significant; indeterminate; or not evaluable. Any abnormal findings in the ECG reading should be recorded in the ECG eCRF. "Abnormal, clinically significant" results should be recorded in the Medical History eCRF if found predose or in the AE eCRF if found postdose of the investigational product. If a subject has an "abnormal, clinically significant" result at Screening, then he/she should be excluded.

An ECG may be performed outside of the timeframes indicated in the Table of Events if the investigator feels that this is warranted based on medical evidence.

6.7. Tablet Taste and Acceptability Testing

The taste and acceptability of apremilast tablet will be assessed using a faces Likert Scale on Day 1, initial dosing. An example of a faces Likert Scale is illustrated in Section 19, Appendix C.

6.8. Oral Dose of Apremilast

Apremilast will be administered orally twice daily from Day 1 through the morning of Day 14 for pharmacokinetics assessment. Evening doses should be administered approximately 12 hours after the morning dose. The evening dose taken on Day 14 must not be taken until AFTER the last PK blood sample is drawn.

Dosing regimens may vary depending on dose strength/dose frequency determined from the PK and safety data collected from the initial 8 subjects in Groups 1 and 2. See Section 8.2 for additional details concerning treatment administration.

During the extension phase, apremilast will be administered orally twice daily. Evening doses will be administered approximately 12 hours after the morning dose.

6.9. Apremilast Drug Accountability

The Investigator(s) or designee(s) will account for all apremilast that is issued to and returned by the subject throughout the study.

6.10. Stool Diary

Diarrhea is the passage of three or more watery/liquid stools per day (WHO, 2015).

Subjects and their parent/guardian will be supplied with paper diaries that will be filled out daily to record and describe any diarrhea, including duration, frequency, treatment, and associated symptoms (Appendix B). Subjects and their parent/guardian will complete the Stool Diary every day beginning after the first dose of apremilast, up to the 4-week post last dose follow-up visit (Visit 11).

6.11. Tanner Staging

Assessments of sexual maturity (Tanner Staging) will be performed at baseline and the 8 week post last dose follow-up visit (Visit 12). A description of each Tanner stage is provided in Appendix D (WHO, 2015).

6.12. Worsening Psoriasis and Rebound Assessments

A worsening of plaque psoriasis, including flare, during treatment will not be collected as an adverse event unless it is considered a serious adverse event (SAE). Disease activity (worsening or improvement in severity) will be collected using PASI.

Rebound is defined as a severe and sudden worsening of disease that occurs between the time of study treatment discontinuation and the 4 and 8 week Follow-up Visits. This exacerbation is characterized by a PASI ≥ 125% of baseline or a new generalized pustular, erythrodermic or more inflammatory psoriasis after stopping therapy (Gordon, 2005).

6.13. Psychiatric Evaluation

Psoriasis has been associated with an increased risk of developing psychiatric disorders, including depression and anxiety in pediatric patients (Kimball, 2012). Depression has been reported in the apremilast clinical trials. The investigators should advise subjects, their caregivers, and families of the need to be alert for the emergence or worsening of depression or other mood changes, and if such changes occur, to contact the investigator (Apremilast Investigator's Brochure).

All subjects will complete the Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix E) assessment. This questionnaire is suitable for assessment of suicidal ideation and behavior in clinical and research settings (Posner, 2011). Any subject, during screening or at baseline, that answers 'Yes' to any question on the C-SSRS, will be ineligible for study participation and should be referred immediately for a psychiatric evaluation.

During the study (post baseline), each subject will complete an additional C-SSRS questionnaire at each study visit. Any subject that answers 'Yes' to any question on the C-SSRS at anytime during the study will be immediately withdrawn from study treatment and must be referred immediately for a psychiatric evaluation. The subject should return for the Observational

Follow-up Visits four and eight weeks after Early Termination and the long-term follow-up visit 52 weeks after the last dose.

A copy of the psychiatric evaluation report, if available, should be in the subject's source document.

6.14. Clinic Visits

Subjects will be expected to visit the clinic for Screening, at Baseline (which includes Day 1 dosing and PK), at Day 14 (for AM dosing and PK), and 7 additional visits at Weeks 4, 8, 16, 24, 32, 40, and 50, during the extension period and for the Follow-up Visits 4 and 8 weeks after the last dose of apremilast is taken (eg, at Weeks 54 & 58). The visit window for the Day 14 Visit is ± 1 day. The visit window for the Week 4, 8, 16, 24, 32, 40, and 50 visits is ± 4 days and for the follow-up visits is ± 7 days.

All subjects should complete the two initial follow-up visits 4 and 8 weeks after taking their last dose of apremilast regardless of when they stop taking apremilast.

All subjects should complete the final follow-up visit at Week 102 or at a timepoint 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

6.14.1. Unscheduled Visits

Unscheduled visits may be necessary during the course of the study to capture a subject's status between regularly scheduled visits. Examples include, but are not limited to, a worsening of psoriasis symptoms, occurrence of an AE, or follow-up to a previously reported AE.

The following assessments will be performed at these visits:

- Assess vital signs (temperature, respiratory rate, pulse, and seated blood pressure) and weight
- Record concomitant medications and AEs
- Drug accountability
- PASI

The following assessments may also be performed at the discretion of the Investigator, if clinically needed:

- Obtain blood sample and/or urine sample for any necessary laboratory test indicated in the Table of Events, Section 5
- Perform abbreviated physical examination

6.15. Blood Collection for Pharmacokinetic Analysis

Blood samples will be collected through an indwelling venous cannula, by direct venipuncture or by finger sticks at pre-specified time points for measurement of apremilast in plasma and/or blood. Concentrations of apremilast in plasma or blood will be measured using a validated liquid chromatography tandem mass spectrometry assay and dried blood spot (DBS) assay,

respectively. Specific details regarding the collection, processing, storage, and shipment of all PK samples are provided in Section 19, Appendix F.

Pharmacokinetic blood draws will be performed at the following nominal time(s):

Group 1 (ages 12 to 17 years, inclusive):

Day 1: 2 hours post morning dose.

Day 14 (last dose of PK treatment period): Predose (prior to morning dose), 1, 2, 3, 5, 8, and 12 hours after the morning dose.

Group 1 Notes:

- For Group 1 subjects, a DBS will be collected by fingerstick in parallel (each time point) to the standard plasma PK sample collection. Detailed instructions for the collection and processing are provided in Section 19, Appendix F. Plasma sampling may be discontinued from the protocol procedure at anytime, per the direct instruction of the Sponsor, in the situation that the DBS sample collection method is comparable to the plasma sample collection method.

Group 2 (ages 6 to 11 years, inclusive):

Day 1: 2 hours post morning dose.

Day 14 (last dose of PK treatment period): Predose (prior to morning dose), and 2, 5, and 12 hours post morning dose.

Group 2 Notes:

- If the DBS assay using minimal blood volume is verified during Group 1 study conduct, the DBS assay may be used in place of the plasma PK sampling for the balance of Group 1 and any subject in Group 2. If the DBS assay is not acceptable, DBS will be discontinued from the protocol procedure per the direct instruction of the Sponsor, and thus only the standard plasma PK sampling will be used for the duration of the study.

Actual PK blood sample collection times will be recorded in the source documents and eCRF. Explanations should be provided in the source documents and eCRF for missed or mishandled samples and for samples collected outside the acceptable time window as described in Table 2.

All enrolled subjects who take at least one dose of apremilast and have evaluable PK data will be included in the PK analysis. Pharmacokinetic data is considered evaluable if there are measurable drug levels of apremilast in plasma from at least 3 time points which extend over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

Table 2: Acceptable Time Windows for Pharmacokinetic Blood Sampling

Scheduled PK Blood Draw Time	Acceptable Time Window
Predose	Within 60 minutes prior to dosing
0 to 3 hours postdose (inclusive)	± 5 minutes
4 to 12 hours postdose (inclusive)	± 10 minutes

PK = pharmacokinetic.

6.16. Exploratory Assessments

6.16.1. Psoriasis Area Severity Index (PASI)

Psoriasis Area Severity Index scores will be determined for all subjects throughout the study. The PASI calculation is described in Appendix G.

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

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

Measurements of PASI will be performed at Screening, Baseline and all following visits as indicated in the Table of Events (Section 5).

7. STUDY POPULATION

7.1. Number of Subjects and Sites

At least 32 subjects (16 subjects in Group 1 and 16 subjects in Group 2) with moderate to severe plaque psoriasis will be enrolled at approximately 20 sites in the United States, Canada and Europe.

7.2. Inclusion Criteria

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

1. Male or female subjects 6 to 17 years of age, inclusive, at the time the informed consent document is signed by the legal guardian
2. **Group 1 Only:** ages 12 to 17 years, inclusive, and weighs ≥ 35 kg
3. **Group 2 Only:** ages 6 to 11 years, inclusive, and weighs ≥ 15 kg
4. Subject is able to swallow the apremilast tablet
5. Able to sign an assent with a legal guardian who can understand and voluntarily sign an informed consent
6. Able to adhere to the study visit schedule and other protocol requirements
7. Must agree to withhold vaccinations during the first 2 weeks of dosing. Inactivated vaccines will be allowed during the extension treatment period
8. Diagnosis of chronic plaque psoriasis for at least 6 months prior to Screening
9. Have moderate to severe plaque psoriasis at Screening and Baseline as defined by:
    - PASI score ≥ 12; and
    - Body surface area (BSA) ≥ 10%; and
    - sPGA ≥ 3 (moderate to severe)
10. Disease inadequately controlled by or inappropriate for topical therapy for psoriasis
11. Candidate for systemic or phototherapy
12. Have not been exposed to any or have been exposed to no more than one systemic agent for psoriasis
13. At Screening, laboratory values must be within the following ranges:

- White blood cell (WBC) count

Age (yrs)	Males (x 10^3 /µL)	Females (x 10^3 /µL)
6-11	3.5 – 13.65	3.5 – 13.65
12-18	3.5 – 13.15	3.5 – 13.15

- Platelet count

Age (yrs)	Males (x 10^3 /µL)	Females (x 10^3 /µL)
6-11	117 – 394	117 - 394
12-18	126 – 400	126 - 400

- Serum creatinine ≤ 1.2 X upper limit of normal (ULN) for age and gender. Please see reference ranges of the central laboratory.
- AST (SGOT) and ALT (SGPT) ≤ 1.5 X ULN for age and gender. If initial test of ALT or AST is > 1.5 X ULN, one repeat test is allowed during screening. Please see reference ranges of the central laboratory.
- Total bilirubin ≤ 2 mg/dL (≤ 34 µmol/L). If initial test result is > 2 mg/dL, one repeat test is allowed during the screening period.
- Hemoglobin (Hb)

Age (yrs)	Males (g/dL)	Females (g/dL)
6-11	10.0 – 15.5	10.0 – 15.5
12-18	11.0 – 18.1	10.0 – 16.4

14. Male subjects who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on apremilast and for at least 28 days after the last dose of apremilast
15. All females of childbearing potential (FCBP) must either practice abstinence* from heterosexual contact or use one of the approved contraceptive options as described below while on apremilast and for at least 28 days after administration of the last dose of apremilast. For the purposes of this study, a female subject is considered of childbearing potential if she is ≥ 12 years old or has reached menarche, whichever occurred first

    At the time of study entry, 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 abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy

    Females of childbearing potential must have a negative pregnancy test at Screening and Baseline. All 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 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

* Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7.3. Exclusion Criteria

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

1. History of or currently active inflammatory bowel disease
2. Major concurrent medical conditions, pregnancy or lactation
3. Any condition that confounds the ability to interpret data from the study
4. Guttate, erythrodermic, or pustular psoriasis
5. Psoriasis flare or rebound within 4 weeks prior to Screening
6. Evidence of skin conditions that would interfere with clinical assessments
7. History of human immunodeficiency virus infection, or positive result to hepatitis B surface antigen or hepatitis C antibodies at Screening
8. Clinically significant abnormality on 12-Lead ECG at Screening
9. History of active mycobacterial infection with any species (including Mycobacterium tuberculosis) within 3 years of the Screening Visit and without documentation of successful treatment
10. Congenital and acquired immunodeficiencies (eg, Common Variable Immunodeficiency), immunoglobulin A deficiency
11. History of recurrent significant infections
12. Active infection or infection treated with antibiotic treatment within 2 weeks of first dose
13. Any history of or active malignancy
14. History of allergy/intolerance to any component of the investigational product, ie, apremilast, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose 15 cP, titanium dioxide, polydextrose FCC, talc, maltodextrin, medium chain triglycerides, iron oxide red, iron oxide yellow, and iron oxide black.
15. Deficiencies in lactose metabolism, ie, galactose-1-phosphate uridylyltransferase, UDP-glactose 4-epimerase, galactokinase or Fanconi Bickel syndrome, including congenital lactase deficiencies, and glucose-galactose malabsorption.
16. Any other significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study or which places the subject at unacceptable risk if he/she were to participate in the study
17. Prior history of suicide attempt at any time in the subject's lifetime prior to screening or enrollment in the study or major psychiatric illness requiring hospitalization within 3 years

18. Answering "Yes" to any question on the Columbia-Suicide Severity Rating Scale during screening or at baseline
19. Having received biologic therapy within 5 terminal half-lives, including but not limited to the following time periods:
    - Four weeks prior to baseline for etanercept
    - Ten weeks prior to baseline for adalimumab
    - Twenty-four weeks prior to baseline for ustekinumab
20. Topical therapy within 2 weeks of baseline (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol)
    - Exceptions: low-potency corticosteroids (please refer to the Investigators' Manual) will be allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study
    - Subjects with scalp psoriasis will be permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions
    - An unmedicated skin moisturizer (eg, Eucerin®) will be also permitted for body lesions only. Subjects should not use these topical treatments within 24 hours prior to the clinic visit
21. Systemic therapy for psoriasis within 4 weeks prior to baseline (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters)
22. Use of phototherapy (ie, UVB, PUVA)within 4 weeks prior to baseline
23. Use of any investigational drug within 4 weeks prior to baseline, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer)
24. Children in Care: a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation
25. Prior treatment with apremilast

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Sufficient quantities of apremilast will be supplied by Celgene and should be stored as directed on the label. Apremilast will be supplied in tablets with the following strengths: 10 mg, 20 mg and 30 mg for oral administration only. All dose strengths will be supplied to the sites in bottles or equivalent. The excipients contained in the apremilast tablets used in this study are listed in Section 7.3 (exclusion criterion #14). Refer to the Investigator's Brochure for additional detailed information regarding apremilast.

8.2. Treatment Administration and Schedule

On PK days (Day 1 and Day 14), all subjects will be administered the morning dose of apremilast by mouth in the fasted state. Food and beverages (except water) will be withheld from subjects for at least 8 hours prior to the morning dose until at least 2 hours after the morning dose. All apremilast administered while the subject is in the clinic will be administered by trained staff with approximately 240 mL of noncarbonated, room temperature water or as much as needed to ensure apremilast is swallowed. The person responsible for dosing will check the subject's mouth to ensure that the formulation has been swallowed intact.

For all evening doses and all morning doses administered on non-PK days, apremilast tablets will be taken approximately 12 hours apart and without any food restrictions. Apremilast tablets should always be taken with water as described in the previous paragraph. Dosing regimens may vary depending on dose strength/dose frequency determined from the Group 1 and Group 2 PK and safety data. See Section 6.8 for additional details concerning oral dosing of apremilast.

The sponsor may provide financial assistance for overnight accommodations near the study site before and/or on PK blood draw visit days for the sake of subject convenience.

8.2.1. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of apremilast. Overdose for this protocol, on a per dose basis, is defined as ingestion of greater than 100 mg of apremilast tablets in any specific dosing period (ie, 24 hours) whether by accident or intentionally. Adverse events associated with an overdose must be collected on the Adverse Events page of the eCRF (see Section 11.1) for all overdosed subjects, but the overdose itself is not considered an AE. Other required or optional nonstudy drugs intended for prophylaxis of certain side effects, etc, are excluded from this definition.

Detailed information about any Celgene drug overdose in this study, regardless of whether the overdose was accidental or intentional, should be reported on the drug exposure eCRF page.

8.3. Method of Treatment Assignment

Prior to dosing, subjects will be identified by their unique screening number assigned by the clinical site. On the morning of Day 1 and prior to receiving any apremilast, subjects who continue to be qualified for participation in the study will be enrolled and assigned a unique study number. All subjects enrolled in this protocol will receive apremilast.

8.4. Packaging and Labeling

The label(s) for apremilast will include Sponsor name, address and telephone number, the protocol number, apremilast name, dosage form and strength (where applicable), amount of apremilast 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.

8.5. Investigational Product Accountability and Disposal

The Investigator(s) or a qualified designee(s) is/are responsible for taking an inventory of each shipment of apremilast received, and comparing it with the accompanying apremilast accountability form. The Investigator(s) or qualified designee(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, where it will be maintained in the trial master file.

At the study site, all apremilast will be stored in a secure, locked area to prevent unauthorized access. Investigational product must be stored as directed on the bottle label(s).

The Investigator(s) or qualified designee(s) is responsible for the accountability of all apremilast issued to the site during the course of the study.

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

8.6. Investigational Product Compliance

All doses administered in the clinic will be administered under direct supervision of trained staff. The individual(s) responsible for dosing will check the subject's mouth to ensure that the tablet has been swallowed whole (ie, not chewed or crushed).

The study staff will maintain an ongoing record of the dispensing and administration of apremilast for each subject via an accountability record or equivalent document that will be verified by Celgene's study monitor.

For apremilast dispensed to the subject/guardian for outpatient administration, study personnel will review the instructions printed on the package with the study subject and/or legal guardian prior to dispensing apremilast in tablet form. Investigational product will be dispensed as noted in the Table of Events, Section 5. The subjects will be instructed to return the apremilast 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 apremilast as instructed at each study visit. Any problems with apremilast 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.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) should be discussed with Celgene.

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

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Topical anesthetics will be permitted to prevent and control pain and discomfort associated with finger sticks during the DBS sample collection. Topical anesthetics (such as Eutectic Mixture of Local Anesthetics) should be administered as directed per the package insert. Prior to the blood collection procedure, fingers should be thoroughly wiped clean of the topical medication to avoid contamination of the PK blood sample.

Only inactivated vaccines will be allowed during the extension treatment phase.

Furthermore, subjects may take any medication that is not restricted by the protocol, is not expected to interfere with the conduct of the study and will not affect study assessments. Chronic medication should be dosed on a stable regimen and continued through the 2-week treatment phase.

All medications (prescription and non-prescription), treatments and therapies taken by the subject from Screening throughout the 50 weeks of treatment and the 4 and 8 week follow-up periods, including those initiated within 30 days 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 name of the medication/treatment, 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.

The following topical therapy will be permitted:

- Low-potency or weak corticosteroids (such as hydrocortisone, desonide, alclometasone dipropionate) will be allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study.
- Subjects with scalp psoriasis will be permitted to use coal tar shampoo and/or salicylic acid soap preparations on scalp lesions
- An unmedicated skin moisturizer (eg, Eucerin®) will also be permitted for body lesions only

Subjects should not use these topical treatments within 24 hours to the clinic visit.

9.2. Prohibited Concomitant Medications and Procedures

The following psoriasis medications cannot be administered while subjects are receiving study medication.

- Topical therapy unless otherwise specified (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol: see Section 9.1)

- Systemic therapy including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters
- Phototherapy including UVB and PUVA
- Biologic agents such as etanercept, infliximab, adalimumab, certolizumab pegol, or ustekinumab
- Prolonged sun exposure or use of tanning booths or other ultraviolet light sources
- Use of an investigational drug

All vaccines will be withheld during the first 2 weeks of dosing. Live vaccines are not allowed at any time during active treatment with apremilast.

Subjects who need to be treated with protocol-prohibited medication will be withdrawn from the study.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

Descriptive statistics (mean, standard deviation [SD], median, minimum and maximum, and sample size) will be provided for quantitative data. Frequency tabulations will be compiled for classification of qualitative data. Graphical displays will be provided where useful to assist in the interpretation of results.

10.2. Study Population Definitions

Two study populations will be analyzed:

- Safety population: all enrolled subjects who take at least one dose of apremilast will be included in the safety population. Safety and efficacy analyses will be based on this population.
- Pharmacokinetic population: all enrolled subjects who take at least one dose of apremilast and have evaluable pharmacokinetic (PK) data will be included in the PK analysis. Pharmacokinetic data is considered evaluable if there are measurable drug levels of apremilast in plasma from at least 3 time points which extend over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

10.3. Sample Size and Power Considerations

No formal sample size calculation is performed. A sample size of at least 16 subjects per group has been selected to provide an adequate PK profile and safety assessment in subjects of different ages and body weight ranges. If needed, dropouts will be replaced to ensure that evaluable PK data from at least 32 subjects is collected.

10.4. Background and Demographic Characteristics

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

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Exploratory Efficacy Analysis

Exploratory efficacy endpoint(s) will be summarized using descriptive statistics.

10.7. Safety Analysis

Safety analyses will be performed for all subjects who received at least one dose of apremilast. Adverse events will be classified using MedDRA. Treatment-emergent AEs will be summarized by system organ class, preferred term, severity, and relationship to apremilast. Adverse events leading to death or to discontinuation from treatment and SAEs will be listed. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity. Laboratory data will be summarized descriptively by visit (n, mean, median, SD, minimum, and maximum). Vital sign measurements, by visit, including weight, and concomitant medications and procedures, will be summarized descriptively. Data from the C-SSRS assessments and the stool diary will be summarized, respectively.

An independent DMC will review available safety and PK data at the following timepoints:

1. After the first 8 subjects in Group 1 have completed the 2 weeks of apremilast dosing, PK, and safety assessments.
2. After the first 8 subjects in Group 2 have completed the 2 weeks of apremilast dosing, PK, and safety assessments.

10.7.1. 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 AEs, serious adverse events (SAEs), discontinuations and laboratory findings will be reviewed internally by a Safety Management Team (SMT) at Celgene. The review follows the Council for International Organizations for Medical Sciences, Working Group 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 an SMT charter.

10.7.2. External Safety Monitoring During Apremilast Program: Role of the Independent Data Monitoring Committee

Monitoring will also be performed by an independent, external Data Monitoring Committee (DMC) that will assess safety as outlined in the DMC charter (available upon request). The DMC is comprised of three independent external trialists and an independent external statistician for whom there is no identified conflict of interest. The DMC will meet as outlined in Section 10.7 or ad hoc at the request of the SMT. The DMC scope, conduct, processes, and accountabilities are prespecified in its charter. Recommendations of the DMC based on the overall benefit/risk evaluation may include proceeding with the study per protocol, proceeding with the study with modification, or study suspension.

10.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. Pharmacokinetic parameters and plasma concentrations for apremilast will be presented as descriptive statistics. The descriptive statistics will include but will not be limited to the following: sample size [N], mean, SD, coefficient of variation [CV%] geometric mean, and

geometric CV%. Results will be presented in tabular and graphic formats as appropriate. Population PK analyses will be performed using non-linear mixed effect modeling (NONMEM). Covariate analysis will be performed to identify relevant covariates. For all PK parameters, the population geometric mean will be estimated and provided. The between-subject variability will be reported as an apparent coefficient of variation (ie, square root of the estimated variance) if data permits. The following PK parameters will be determined:

- C_{max}
- t_{max}
- AUC_{0-12}
- AUC_{0-t}
- CL/F
- Vss/F or Vz/F
- $t_{1/2}$

The following population PK parameters will be determined as appropriate:

- CL/F
- V/F
- Ka
- Lag (if applicable)

10.9. Interim Analysis

No formal interim analysis is planned for this study. However, an extract of the PK and 2 weeks of safety data from the initial 8 adolescent subjects enrolled into Group 1 will be used to model the most appropriate dose for subsequently enrolled subjects (such that the exposure will be similar to the exposures in adult subjects administered apremilast 30 mg BID).

Pharmacokinetic data and 2-week safety data from at least 8 Group 1 subjects will be utilized to determine the appropriate dosage (dose strength/dose frequency) for subjects enrolled into Group 2.

10.10. Other Topics

10.10.1. 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.

10.10.2. 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. Separate data summaries of background medications will be provided.

10.10.3. Taste and Acceptability

The taste and acceptability of apremilast tablet will be summarized.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (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 11.3), 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

For this study, reports of overdose of apremilast that do not have an associated AE(s) should not be reported as an AE(s). These reports should be discussed in the study compliance section of clinical study reports. See Section 8.2.1 for the definition and collection of overdose.

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 apremilast as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to apremilast. Adverse events and SAEs will be recorded on the AE page of the eCRF 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.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. 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)
- Results in 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.
- 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 starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.
- An elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.

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

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

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily living (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 activities of daily living (ADLs), but able to carry out daily social and functional activities
- Drug therapy may be required

Severe (nonserious 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.

11.2.3. Causality

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

Not Suspected:	Means a causal relationship of the AE to apremilast administration is **unlikely or remote,** or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility t**hat the administration of apremilast caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between apremilast and the AE.

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

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

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

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

11.2.6. Outcome

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

11.3. 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 apremilast dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. 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).

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

For the purposes of this study, a female subject is considered of childbearing potential if she is ≥ 12 years old or has reached menarche, whichever occurred first.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on apremilast, or within 28 days of the subject's last dose of apremilast, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by 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 or designee will monitor the progress of the pregnancy of a female subject until completion of the pregnancy, and must notify Celgene Drug Safety, or designee, 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 or therapeutic 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 (ie, 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 apremilast 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.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking apremilast should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. 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 eCRF. 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. 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 apremilast) that occur during the study (from the time the subject signs informed consent to 28 days after the last dose of apremilast), or any SAE made known to the Investigator at anytime thereafter that are suspected of being related to apremilast. 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 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.

11.5.1. 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 telephone.

11.6. 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's 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.

For countries within the European Economic Area, Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

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

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

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

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

12. DISCONTINUATIONS

Subjects who have psoriasis disease flare during the apremilast treatment periods and require systemic conventional therapies, biologics, phototherapy, or prohibited topical therapies (defined in Section 9.1 Permitted Concomitant Medications and Procedures) will be discontinued from the study and properly treated according to local treatment guidelines. In the case of psoriasis disease flare during the apremilast treatment periods, the reason for discontinuation will be disease progression / disease flare. Subjects will not be withdrawn from the study if the disease flare and the need for treatment occur during the follow-up periods. Every attempt will be made to collect all or specific final data on a discontinued subject.

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

- Adverse Event(s)
- Lack of efficacy
- Non-compliance with study drug
- Study terminated by sponsor
- Withdrawal of consent
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation

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

13. EMERGENCY PROCEDURES

13.1. 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 (CRO) 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.

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, apremilast will be identified on the package labeling.

14. REGULATORY CONSIDERATIONS

14.1. 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 Conference on 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.

14.2. 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 eCRFs 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.

14.3. Informed Consent and Subject Assent

Both an age-specific assent (by the study subject) and an informed consent form (ICF; by subject's legal guardian) must be signed before any study-related assessments are performed.

Documentation that the subject assent and legal guardian informed consent occurred prior to the study subject's entry into the study and of the assent/informed consent process should be recorded in the study subject's source documents including the date. The original assent and informed consent documents signed and dated by the study subject, subject's legal guardian, and by the person facilitating the process, 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's legal guardian. In addition, if a protocol is amended and it impacts on the content of the assent and informed consent, the two documents must be revised. Study subjects participating in the study, and their legal guardians, must repeat the assenting/consenting process with the revised assent/consent documents when the amended protocol is implemented. The revised documents signed and dated by the study subject, subject's legal guardian, and by the person facilitating the process, must be maintained in the Investigator's study files and a copy given to the study subject's legal guardian.

14.4. 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 informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. 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.

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

Before the start of the study, the study protocol, informed consent document, 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.

Apremilast 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 informed consent document 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.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

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

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

14.8. Termination of the Study

Celgene reserves the right to terminate this study 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.

15. DATA HANDLING AND RECORDKEEPING

15.1. 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 eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (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.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of apremilast. 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 informed consent documents 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
- Apremilast 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/Institution should take measures to prevent accidental or premature destruction of these documents.

16. 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 standard operating procedures.

16.1. 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 Investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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.

16.2. Audits and Inspections

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

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, Food and Drug Administration [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.

17. PUBLICATIONS

As described in Section 14.2, 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.

18. REFERENCES

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19. APPENDICES

Appendix A: Static Physician Global Assessment (sPGA)

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

Appendix B: Stool Diary

DAILY STOOL DIARY

1. Did you have 3 or more liquid or watery stools today?
   - ☐ No
   - ☐ Yes

2. If yes, did you take any medications for your liquid or watery stools?
   - ☐ No
   - ☐ Yes

3. If yes, type the medication name(s) below:

   ---

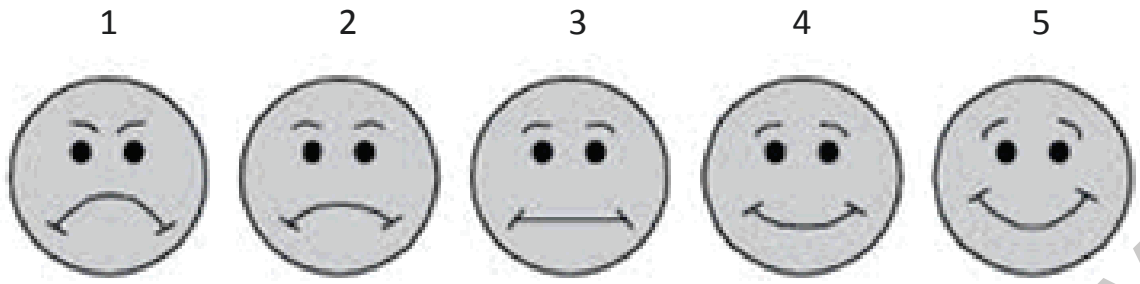
4. Please indicate if you experienced any of these symptoms with your liquid or watery stools today
   - ☐ Nausea
   - ☐ Vomiting
   - ☐ Abdominal cramps
   - ☐ Abdominal pain
   - ☐ Fever
   - ☐ Bloating
   - ☐ Other: _____

Date: _____

Signature of person completing form

Subject or parent/guardian: _____

Appendix C: Example of a Faces Likert Scale



Dislike very much | Dislike a little | Not sure | Like a little | Like very much

Appendix D: Tanner Stages

Female

Stage	Breast growth	Pubic hair growth	Other changes
I	Pre-adolescent	None	Pre-adolescent
II	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II
III	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III
IV	Separation of contours; areola and nipple form secondary mound above breasts tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1–3 years after thelarche
V	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.

Male

Stage	Testes growth	Penis growth	Pubic hair growth	Other changes
I	Pre-adolescent testes (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable
IV	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair
V	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

Appendix E1: Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Baseline/Screening:

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

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

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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

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

SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**		**Past 6 Months**	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
INTENSITY OF IDEATION				
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	**Most Severe**		**Most Severe**	
Frequency ***How many times have you had these thoughts?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____		____	

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gun shot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	Yes ☐ No ☐ Total # of Attempts: ____ Yes ☐ No ☐ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted: ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted: ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

Appendix E2: Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Since Last Visit:

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

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

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale

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

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

 C-SSRS—Children's Since Last Visit (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Children's Since Last Visit (Version 6/23/10) Page 2 of 2

Appendix F: Apremilast Plasma and Dried Blood Spot for Pharmacokinetic Sample Handling Instructions

Labels must contain the following information:

- Protocol No.: **CC-10004-PPSO-001**
- Subject ID number
- Group: (1 or 2)
- Nominal Time: eg, 0.5 hours after dosing
- Sample Type: **Plasma (primary)**, **or Plasma (back-up)**

All blood and plasma collection tubes and storage vials should be labeled and chilled on wet ice **prior to** sample collection and processing.

1. **Blood Sample Collection for Plasma PK samples**
   - Fill an ice bucket with a sufficient amount of wet ice and place blood collection tubes into the ice bath to pre-chill all collection tubes before blood draw
   - Collect approximately 1 mL of whole blood into a pre-chilled **lithium heparin** tube
   - Accurately record the time of blood collection
   - Gently invert the tube 3 to 5 times and immediately immerse it into the ice bath to prevent possible compound degradation at room temperature.
2. **Blood Sample Processing to Obtain Plasma**
   - **Within 30 minutes of collection**, the blood sample must be centrifuged at 1,500 g (about 3,000 rpm) for 10 min at 4°C to obtain plasma
   - Transfer approximately 0.5 mL of plasma into the pre-labeled, pre-chilled, **citric acid-containing** polypropylene storage tube (to be provided by Celgene) as primary sample
   - Gently invert the tube 3 to 5 times
   - Transfer approximately 0.2 mL of plasma from the primary sample into the pre-labeled, polypropylene storage tube as backup sample
   - Keep both the primary and backup sample tubes on ice before they are ready to be transferred into a freezer
   - **Within 60 minutes of blood collection**, transfer plasma samples in storage vials into a –20°C freezer, where they will remain stored until shipping
   - Immediately record the time of sample entry into the freezer.

NOTE: All secondary (backup) samples will be maintained at the Investigator site until they are requested by the Celgene representative to be shipped to the central laboratory (or another facility) or be destroyed at the Investigator site.

3. **Blood Collection for DBS PK Samples**
    - Load a fresh capillary onto the DBS pipette and collect approximately 50 µL of whole blood into the **lithium heparin** capillary tube
    - Accurately record the time of blood collection
    - Immediately spot one drop of blood (approximately 15 µL) onto the DBS card target area. Do not allow the capillary to touch the DBS target. Repeat for 2 more spots (there will be 4 targets on the card but only 3 targets will be used)
    - Eject the used capillary into the supplied container and reload a fresh capillary for the next sample collection
    - Dry the DBS card for 2 to 4 hours at room temperature. Place the DBS card in a plastic zip top bag along with a desiccant pouch. All DBS cards from a subject should be placed in a single zip top bag for storage at room temperature.
4. **PK Sample Shipment**
    - All PK sample label information on the storage tubes/DBS cards must be checked against the requisition form. The samples collected in storage tubes must be shipped frozen and on dry ice to the central laboratory. The DBS cards are to be shipped at room temperature.
    - The central lab must be contacted via email PRIOR TO shipping, and confirmation of receipt from the central laboratory must be documented at the site.
5. **Sample Collection Documents to Accompany Shipment(s)**

A copy of the completed specimen inventory log(s) must accompany the shipment, and must list the following information **at a minimum**:

- Sponsor name: **Celgene Corp**
- Celgene Study Number: **CC-10004-PPSO-001**
- Subject ID Numbers
- Group (1 or 2)
- Collection Date (ie, 29 May 2013)
- Nominal collection time point for plasma/DBS samples
- Sample type (**eg, *Plasma or DBS***)

Appendix G: Psoriasis Area Severity Index

PSORIASIS AREA AND SEVERITY INDEX (PASI)

Please write in the appropriate number for rows 1 - 3 using the scale below:
0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe

	Head	Trunk	Upper Limbs	Lower Limbs
1. Erythema				
2. Thickness				
3. Scaling				
4. Total Each Column				
AREA OF PSORIATIC INVOLVEMENT				
5. Degree of Involvement	0 = No involvement 1 = < 10% 2 = 10 < 30% 3 = 30 < 50% 4 = 50 < 70% 5 = 70 < 90% 6 = 90 - 100%			
6. Insert Degree of Involvement from Row 5				
7. Multiply Row 4 by Row 6				
8.	x .10	x .30	x .20	x .40
9. Multiply Row 7 by Row 8				

10. Total PASI SCORE (Add together each column in Row 9)	

NOTE: Shaded areas are not to be completed.

Fredriksson, 1978.

Appendix H: List of Abbreviations and Definition of Terms

Abbreviation or Term	Explanation
AE(s)	Adverse Event(s)
ACR	American College of Rheumatology
ACR20	ACR criteria for 20% improvement
ACR50	ACR criteria for 50% improvement
ACR70	ACR criteria for 70% improvement
ADLs	Activities of daily living
ADME	absorption/distribution/metabolism/excretion
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
APR	Apremilast
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{0-12}	Area under the plasma concentration-time curve from time zero to 12 hours postdose
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-\tau,ss}$	The area under the plasma drug concentration–time curve over the dosing interval τ at steady state
BID	Twice daily
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CFR	Code of federal regulations
CL/F	Apparent total plasma clearance when dosed orally
C_{max}	Peak (maximum) observed plasma concentration of drug
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation
CYP	Cytochrome p-450
DBS	Dried blood spot

Abbreviation or Term	Explanation
DMARD(s)	Disease modifying anti-rheumatic drug(s)
DMC	Data Monitoring Committee
ECG(s)	Electrocardiogram(s)
eCRF	Electronic case report form
EMA	European Medicines Agency
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP(s)	Good Clinical Practice(s)
GI	Gastrointestinal
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NOAEL	No observed adverse effect level
NONMEM	Non-linear mixed effect modeling
PASI	Psoriasis Area and Severity Index
PASI-50	At least a 50% reduction in PASI
PASI-75	At least a 75% reduction in PASI
PDE4	Phosphodiesterase four
PD	Pharmacodynamic
PK	Pharmacokinetics
PI	Principal investigator
PsA	Psoriatic arthritis
PUVA	Psoralens and long-wave ultraviolet radiation

Abbreviation or Term	Explanation
RBC(s)	Red blood cell(s)
SAE(s)	Serious adverse event(s)
SD	Standard deviation
SMT	Safety management team
sPGA	Static Physician Global Assessment
SOP(s)	Standard operating procedure(s)
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal-phase elimination half-life
TEAE(s)	Treatment-emergent adverse event(s)
t_{max}	Time to maximum plasma concentration
TNF-α	Tumor necrosis factor alpha
ULN	Upper limit of normal
US	United States
V/F	Apparent total volume of distribution when dosed orally
Vss/F	Apparent total volume of distribution when dosed orally, based on steady-state
Vz/F	Apparent total volume of distribution when dosed orally, based on the terminal phase
UVB	Ultraviolet light B
WBC(s)	White blood cell(s)

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:
Title:
Date: Tuesday, 10 May 2016, 02:11 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

1. **Revised white blood cell (WBC) levels, platelet count, and hemoglobin for subject eligibility (Section 7.2, Inclusion Criterion #13)**

The amendment provides allowance for laboratory values that are lower than the lower limit of normal (LLN) reference ranges used by the Central Laboratory for the PPSO-001 study. The revised eligibility criteria are gender- and age-specific and would allow for up to 10% lower than the LLN for hemoglobin and platelet count levels, and for up to 20% lower for the WBC count, to adjust for the effects in blood cells of inflammatory conditions such as psoriasis and for certain medications used to treat it, without compromising the safety of subjects participating in the study.

2. **Added the excipients of apremilast to screen for potential sensitivity (Section 7.3, Exclusion Criterion #14)**

The excipients of apremilast are specified and listed in the exclusion criteria to inform subjects of all ingredients/contents of the investigational product to properly identify or rule out during screening a potential allergy or intolerance that may arise from any of the ingredients.

3. **Added an exclusion criterion for deficiencies in lactose metabolism (Section 7.3, Exclusion Criterion #15)**

Because the investigational product formulation contains lactose, an exclusion was added for subjects who may have an allergy to lactose.

Minor changes, in this amendment include:

- Modified "highly effective" to "effective" in the Option 1 description of contraception methods for females (Section 7.2, Inclusion Criterion #15), which is consistent with the type of contraceptive described.
- Added a reference to Section 7.3 for the list of excipients of apremilast formulation (Section 8.1).

Other significant changes in this amendment include:

1. **Extended eligibility to patients previously exposed to biologic therapy (Protocol Summary, Section 6.5, Section 7.2. Inclusion Criteria #12 and #13, Section 7.3, Exclusion Criteria #19, Section 9.2)**

The amendment will allow inclusion of potential subjects who have been previously exposed to a systemic biologic therapy for psoriasis or other indication provided that the last dose was given at least 5 terminal half-lives prior to randomization. The greater availability of biologic therapies globally and the practice of prescribing them for a number of diseases including plaque psoriasis

in children have become more common. Excluding patients who have had treatment with biologics has become unrealistic in terms of recruiting patients for the PPSO-001 study. The amendment will help improve recruitment while retaining the intent of enrolling a pediatric population with active moderate-to-severe plaque psoriasis. Systemic therapy with biologics will be counted in the maximum total number (1) of systemic therapies for eligibility purposes. Inclusion #12 is modified for this reason. Exclusion #19 was added to specify required washout periods for previous biologic therapies.

2. **Removal of the 24-hour post-Day 14 dosing pharmacokinetics (PK) blood draw time point (Section 5, Table 1 footnotes, Section 6.15, Table 2)**

The amendment will remove the last blood draw (24 hours after the Day 14 dose) that was included in the intensive PK assessments for Group 1 subjects. Inclusion of this last time point for the adolescent subjects was deemed, via study site feedback, to be a major factor in dissuading prospective subjects from participating in the study because of time away from school and activities, as well as parents' time away from work. Analysis of the intensive PK results can be performed without the 24-hour post-dose blood sample.

Other minor changes in this amendment include:

- The PK endpoint for area under the concentration-time curve from last dose to infinity ($AUC_{0-\infty}$) was removed from the Protocol Summary, Section 3.1, and Section 10.8 because removal of the 24-hour post-dose blood draw requirement eliminates the data to accurately determine terminal elimination phase or lambda, which is used to calculate $AUC_{0-\infty}$.
- A statement was added in Section 1.4 to show the percentage of subjects in studies PSOR-008 and 009, that had prior exposure to biologic therapy to illustrate that previous exposure to biologics was common and was allowed in adult psoriasis studies.
- A bullet point for "Pregnancy test" was added to the Section 3.1 list of primary endpoints. Although it already appeared in the Protocol Summary Section, this addressed the omission.
- A reminder to take the Day 14 dose only after the 12-hour post-dose blood draw was added for clarification to Section 5, Table 1 footnotes and Section 6.8.
- Since the 24-hour post-last dose blood draw was removed, text indicating that there would be no Day 14 evening dose was removed as well from Section 5, Table 1, Section 6.8, and Section 6.15.
- Additional text was included in Section 6.1 to clarify that the consenting/assenting process must be repeated for any subject who fails screening and returns to be rescreened.
- Text was added to Section 6.15, Group 2 Notes, to clarify that not all 16 subjects in Group 1 will need to have both the dried blood spot (DBS) assay and a venous blood draw if the DBS method of blood sample analysis is validated before all Group 1 subjects have blood taken using both methods.
- More sites will be added to the study so an update of the approximate number of sites was entered in Section 7.1.

- Text describing the shipping of PK samples was clarified in Appendix F.

1. JUSTIFICATION FOR AMENDMENT

Primary Objective: (Protocol Summary, Section 2)

The exact description of the primary objective was clarified to reflect that the study is being conducted to select a pediatric dose of apremilast.

Age ranges of two subject groups: (Protocol Summary, Section 4.1, Figure 2, Sections 6.15 and 7.2, Table 1 footnotes)

an adjustment of age groups from Group 1- ages 13 to 17 years; and Group 2 – ages 6 to 12 years to: Group 1- ages 12 to 17 years; and Group 2 – ages 6 to 11 years.

Added questionnaire: (Table 1 and footnotes, Sections 10.7, 6.13, 7.3, Appendix E1, E2 and H)

The Columbia-Suicide Severity Rating Scale (C-SSRS) was added at screening and baseline as well as all visits (except Week 102 final follow up). An exclusion criterion was added which mandates ineligibility if any question is answered YES at screening. A YES answer to any question during the study is cause for immediate withdrawal from study medication.

Psychiatric Evaluation Section: (Sections 6.13, 7.3, 10.7, and 18, Appendices E1 and E2)

This section was updated to explain the use of the C-SSRS.

Tanner Staging Assessment: Table 1and footnotes, Sections 6.11and 18, Appendix D

Added in Tanner Staging section (6.11) along with a description of the stages (Appendix D) and when to perform the assessments in Table 1.

Extension Treatment Period: (Protocol Summary, Figure 1, Table 1and footnotes, Sections 4.1 and 4.3, 4.4, 6.14, 6.6.3, 6.6.8.4, 7.2)

Optional open label was deleted from participation in the extension treatment period and the 50 week treatment extension period was changed to a 48 week treatment extension period. Sections 3.3, 4.1, 4.3, Table 1 and footnotes, Sections 6.14, and 9.1 were updated to show 50 weeks of treatment instead of 52 weeks. The total length of the study (in weeks) was also shortening to 107 weeks from 109 weeks.

Number of Visits: (Protocol Summary, Section 3.3, Table 1, and Section 6.14)

Two additional visits, at Week 24 and Week 40, were added to comply with the request for more frequent safety assessments. Language was updated in Section 6.14 from "5 additional visits" to "7 additional visits". The study days were updated in Table 1 to reflect the addition of the two visits.

Follow-up Visits: (Protocol Summary, Section 4.1, Figure 1, Section 4.3, Table 1, Table 1 and footnotes, Sections 6.6.3, 6.12, 6.14, 9.1,)

Short-term follow-up was adjusted to 4 weeks and 8 weeks after the last dose of apremilast. The original Week 56 short-term follow-up visit is now Weeks 54 and 58.

Number of Study Subjects: (Protocol Summary and Sections 4.1, 7.1, 10.3)

A change from "approximately 32 subjects" to "at least 32 subjects" and "at least 16 subjects in each group" instead of "approximately" was made. Text of "minimum of 24 evaluable subjects" was deleted.

Daily Stool Diary: (Sections 6.10, 10.7, 18, Table 1 and footnotes, Appendix B)

This was added in a protocol section as well as to the appendix to monitor any diarrhea symptoms and treatment.

Frequency of Height Measurement: (Table 1)

Height is now measured at each visit.

Study Timeline Schematic: (Figure 1)

This was updated to reflect changes which included length of extension treatment period, addition of a post 8 week follow-up, and adjustment to length of study.

The amendment also includes several other minor clarifications and corrections:

- Two additional possible ECG interpretations were added to be in alignment with the new CRF structure (Section 6.6.9)
- Psoriasis flare and rebound are now under Section 6 (Procedures) as they are no longer to be considered as adverse events (Section 6.12)
- Canada was added as a participating country (Section 7.1)
- Prior treatment with apremilast was added as an exclusion criterion (Section 7.3)
- Preganacy was added as a possible reason for withdrawal (Section 12)
- Added "Moderate to Severe" to the protocol title (title page, Protocol Summary)
- Updated EudraCT Number and IND Number (title page).
- Removed text that described use of a subject pill diary since daily pill monitoring will not be done in this study (Section 8.6,
- Added "using a faces Likert Scale" to Secondary Objective (Protocol Summary)
- Updated Exploratory Objective in Protocol Summary to match Section 2.3 (Protocol Summary)
- The word "Screening" was added to the last sentence in Section 6.16.1 to match the information in Table 1 (Section 5)
- Added abbreviation "C-SSRS" for the Columbia-Suicide Severity Rating Scale was added to Appendix H
- "Psoriasis Flare and Rebound" section title was changed to "Worsening Psoriasis and Rebound Assessments" since flare and rebound are not considered as AEs in Celgene studies. (Section 6.12)

- Changed, "….two short-term follow-ups and a long-term follow-up" to "….two short-term follow-up periods and a long-term follow-up period." for clarity and readability (Protocol Summary and Section 4.1)
- Added three references: Posner 2011. WHO 2010 and WHO 2015. Deleted one reference: Carey 2006. (Section 18)
- Deleted letter "A" from "Group 1A" in Figure 2 for clarity (Figure 2)
- Deleted the sentence, "The actual dosing time will be recorded on each dosing day (via subject diary or equivalent)" since we will not be using a pill diary in the study. (Section 6.8, 8.6)
- Deleted the sentence, "Accountability will include a review of the subject diary (or equivalent)" since we will not be using a pill diary in the study (Section 6.9).
- Collection of initials was removed from the protocol (Section 6.3, 8.3)
- Added "pregnancy tests" to Overview of Safety Assessments in the Protocol Summary. This was an oversight in the original protocol. (Protocol Summary)
- Two clarifying sentences were added to the dosing scenario. For Group 1, "In the event of a dose regimen adjustment, some or all of the first 8 subjects in Group 1, depending on weight, will return to the site for the appropriate dosing adjustment". For Group 2, "In the event of a dose regimen adjustment after the second PK and safety assessment, the first 8 subjects in Group 2 will return to the site for the appropriate dosing adjustment." (Protocol Summary and Section 4.1)
- An additional sentence was added to Section 12 (Discontinuations) in compliance with the Celgene protocol template. (Section 12)

Administrative Changes and Corrections

- Table of Contents was expanded to include sections, "Stool Diary" and "Worsening Psoriasis and Rebound Assessments
- The letter designations for the appendices were updated since two appendices were added
- A number of "X" indicators were added in Table 1 for Height, Weight, and BMI . One "X" was added to the PASI row as well to align with text in the protocol
- Table 1 footnote letter designations were updated due to the addition of 3 new footnotes
- The numbering of sections in Section 6 was updated due to the addition of a new section and movement of others
- In Section 6.14, text was added for clarity: "….the two initial…"
- Added Switzerland, Australia and Israel as countries where apremilast is approved for PsA and Psoriasis. Made clear that apremilast is approved for both PsA and psoriasis. (Section 1.1)