A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE- BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Amgen representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name: _____** By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A Phase 3, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Apremilast (CC-10004) in Pediatric Subjects from 6 Through 17 Years of Age with Moderate to Severe Plaque Psoriasis

Indication

Psoriasis is a chronic, inflammatory skin disorder that is estimated to affect up to 2.5% of the world's population (Christophers, 2001). The worldwide prevalence of psoriasis in children ranges from 0% to 1.37%. European populations have a higher prevalence than African and Asian populations (Michalek, 2017). The prevalence of psoriasis in children in the United States (US) from birth to age 18 years is 1%, with an incidence of 40.8 per 100,000 (Tollefson, 2010). The most common form of the disease in both adults and children is plaque-type psoriasis that is characterized by erythematous plaques with silvery-white scales (Fan, 2007; Mallbris, 2005; Morris, 2001; Lebwohl, 2003). The nails and scalp, less often, the mucous membranes may also be affected (Weinstein, 2003).

Most pediatric patients present with mild, localized psoriasis that can be treated primarily with topical medications. Phototherapy is not recommended for fair-skinned or younger children, and psoralens with long-wave ultraviolet radiation (PUVA) is not recommended for use in pediatric psoriasis patients, due to the increased risk of malignancies (Ståhle, 2010). Due to this risk, phototherapy is usually reserved for older children and adolescents with extensive areas of involvement or refractory plaque disease (Shah, 2013; Marqueling, 2013). Systemic medications are utilized for more extensive or refractory disease; however, approved therapies for moderate to severe psoriasis in children are limited. As of 2017, the only approved systemic medications in the US for pediatric patients with this indication are the injection-delivered anti-tumor necrosis factor (anti-TNF) biologic agents, etanercept (Enbrel) and the anti-p40 inhibitor ustekinumab (Stelara). In the EU, etanercept (Enbrel), adalimumab (Humira), and ustekinumab (Stelara) are approved for pediatric use. Fear of needles is common in both children and adults and can contribute to negative experiences with needle procedures and health care for patients, caregivers, and health professionals (McMurtry, 2016). Thus, there remains an unmet need for effective systemic therapies that offer oral convenient dosing and a favorable benefit/risk profile for the treatment of pediatric patients with moderate to severe plaque psoriasis.

Apremilast is an oral selective phosphodiesterase type 4 (PDE4) inhibitor marketed worldwide under the trade name Otezla. Apremilast 30 mg twice per day (BID) received its first global marketing approval for the treatment of adult patients with moderate to severe plaque psoriasis in 2014. Clinical data from multiple Phase 2 and Phase 3 trials have consistently demonstrated that apremilast is an effective oral therapy with an acceptable safety profile for psoriasis. The safety profile of apremilast in the post-marketing setting has remained consistent with that seen in the clinical development program. Thus, the benefit/risk profile of apremilast continues to be favorable in adult psoriasis patients.

Moderate to severe plaque psoriasis also occurs in children and adolescents. Exploratory analyses from a recent Phase 2 study (CC-10004-PPSO-001) indicate that apremilast may be effective for the treatment of moderate to severe plaque psoriasis in the pediatric population as in adults. This Phase 3 study is being conducted to evaluate the safety and efficacy of apremilast

in the treatment of pediatric subjects, ages 6 through 17 years, with moderate to severe plaque psoriasis.

Objectives

Primary Objective

- The primary objective of the study is to evaluate the clinical efficacy of apremilast compared with placebo in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis.

Secondary Objectives

- To evaluate the safety and tolerability of apremilast compared with placebo, in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis
- To evaluate the effect of apremilast compared with placebo on health-related quality of life (HRQoL).

Study Design

This is a multicenter, randomized, double-blind, placebo-controlled efficacy and safety study.

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

At least **230** pediatric subjects (ages from 6 through 17 years) will be randomized 2:1 to receive either apremilast or placebo for the first 16 weeks. Randomization to the apremilast arm or the placebo arm will be stratified by baseline age group (6 to 11 years or 12 to 17 years). A minimum of 75 subjects will be randomized in each age group. The sponsor may halt enrollment of one age group if that age group reaches **155** randomized subjects to allow the other group to randomize at least 75 subjects. Treatment will be assigned by weight with subjects 20 kg to < 50 kg receiving apremilast 20 mg BID or placebo BID and subjects ≥ 50 kg receiving apremilast 30 mg BID or placebo BID. After all subjects have completed Week 16 (Visit 7), or discontinued from the study, a Week 16 database lock will be performed; the primary data analysis will be conducted and a Week 16 clinical study report will be generated. Study investigators and subjects will remain blinded to initial treatment assignments until the final database lock at the conclusion of the study. The blind also should be maintained for persons responsible for the ongoing conduct of the study. Blinded persons may include but are not limited to: clinical research physician, clinical research scientist, clinical trial manager, study statistician, data manager, programmer, and clinical research associate. At the end of the study, after all subjects have either completed Week 52 (Visit 16) and entered the Long-term Study, or completed the Observational Follow-up Phase, or been discontinued from the Apremilast Extension Phase (Weeks 16 to 52) or the Observational Follow-up Phase, a final analysis will be performed and a final clinical study report will be generated.

The study will consist of four phases:

- Screening Phase – up to 35 days
- Placebo-controlled Treatment Phase – Weeks 0 to 16
  - Subjects will be randomly assigned in a 2:1 ratio to weight-based apremilast or placebo. Subjects 20 kg to < 50 kg will receive apremilast 20 mg BID or placebo

BID and subjects ≥ 50 kg will receive apremilast 30 mg BID or placebo BID. The primary endpoint will be the proportion of subjects with a Static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16.

- From Week 8 through Week 16, any subject with a Psoriasis Area Severity Index (PASI) increase ≥ 50% from baseline will be eligible to commence treatment with moderate-to-high potency topical steroid preparations (early escape) and continue with randomized investigational product (IP).

- Apremilast Extension Phase – Weeks 16 to 52

  Placebo subjects will be switched at Week 16 to receive apremilast 20 mg BID or 30 mg BID, according to baseline weight. All other subjects will continue to receive either apremilast 20 mg BID or apremilast 30 mg BID based on their original dosing assignment.

- Observational Follow-up Phase – 14 weeks

  All eligible subjects who complete the Apremilast Extension Phase may opt to enroll in a separate Long-term Study (for up to 4 years or until approval, whichever comes first). Subjects who choose not to participate in the Long-term Study, or discontinue the study early, should return for observational follow-up visits four, eight and fourteen weeks after the last dose of IP.

Study Population

Pediatric subjects, ages 6 through 17 years, weighing at least 20 kg, with moderate to severe plaque psoriasis defined by:

- PASI score ≥ 12; and
- Body surface area ≥ 10%; and
- sPGA ≥ 3 (moderate to severe)

Subjects must have diagnosis of chronic plaque psoriasis for at least 6 months prior to Screening.

Length of Study

The study will have a total duration of up to 71 weeks and will consist of four phases.

- Screening Phase – up to 35 days (5 weeks)
- Placebo-controlled Treatment Phase – Weeks 0 to 16
- Apremilast Extension Phase – Weeks 16 to 52
- Observational Follow-up Phase – 14 weeks (subjects continuing in the Long-term Study will not complete this phase)

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

Investigational product (IP) will be provided in blister cards throughout the Placebo-controlled Treatment Phase as well as the first month of the Apremilast Extension Phase. Apremilast blister cards provided by the sponsor, Amgen Inc., will contain 10, 20, and 30 mg tablets, depending on baseline weight. Placebo will be provided as identically appearing 10, 20, and 30 mg tablets. After completion of the Apremilast Extension Phase titration period, IP will be distributed in bottles containing 20 or 30 mg tablets for the remainder of the study. All IP will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To reduce potential gastrointestinal (GI) side effects, dose titration will be implemented during Week 0 of this study and at Week 16.

During Week 0 (Days 1 to 7), subjects will be dispensed dose titration blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo tablets. The blister cards will contain all IP required for 4 weeks of treatment. Titration supplies or matching placebo will be dispensed over the first 3 days for the 20 mg BID treatment group, and over the first 5 days for the 30 mg BID treatment group (see Table 5: Treatment Schema for Dose Titration at Visit 2 [Week 0]) which details the titration supplies from Day 1 to Day 3 or Day 1 to Day 5 in the Placebo-controlled Treatment Phase. IP will be dispensed as indicated below:

- Weeks 0 to 16 (Placebo-controlled Treatment Phase): Apremilast 20 mg BID or apremilast 30 mg BID or placebo BID.
  - Week 0: subjects will be dose titrated as described above and in Table 5.
- Weeks 16 to 52 (Apremilast Extension Phase): Apremilast 20 mg BID or 30 mg BID
  - Week 16: subjects will be dose titrated as described in Table 6.

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block, randomization in parallel 2:1 to receive either apremilast or placebo treatment, using a centralized Interactive Response Technology (IRT). Randomization to the apremilast arm or the placebo arm will be stratified by baseline age group (6 to 11 years or 12 to 17 years). Subjects with baseline weight between 20 kg to < 50 kg will receive apremilast 20 mg BID or placebo BID and subjects with baseline weight ≥ 50 kg will receive apremilast 30 mg BID or placebo BID.

At Week 16, subjects who were originally randomized to placebo at Week 0 will be switched to receive apremilast treatment, where dose levels (either 20 mg BID or 30 mg BID) would have been determined at Week 0 using their baseline weight categories (20 kg to < 50 kg, or ≥ 50 kg). Subjects randomized to the apremilast arm at Week 0 will remain on their assigned dose levels (either 20 mg BID or 30 mg BID).

During Weeks 16 to 52, study investigators and study subjects will remain blinded to the initial IP assignments. To maintain the blind, all subjects will receive dose titration cards at the Week 16 visit. Although only subjects initially randomized to placebo will be dose titrated during their first week of the Apremilast Extension Phase, all subjects entering the Apremilast Extension Phase will receive identically-appearing titration/treatment cards (see Table 6).

Overview of Key Efficacy Assessments

Primary Efficacy Assessment

- Static Physician Global Assessment (sPGA)

Additional Efficacy Assessments

- Psoriasis Area Severity Index (PASI)
- Body Surface Area (BSA)
- Scalp Physician Global Assessment (ScPGA)
- Modified Static Physician Global Assessment – Genital (sPGA-G)

Overview of Key Safety Assessments

Safety Assessments will include:

- Adverse events (AE)
- Physical examinations
- Vital signs
- Pregnancy test for females of childbearing potential (FCBP)
- Clinical laboratory tests
- Stool Diary
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Weight and height
- Tanner staging
- Psoriasis flare and rebound

Overview of Quality of Life Assessments

- Children's Dermatology Life Quality Index (CDLQI)
- Family Dermatology Life Quality Index (FDLQI)

Patient Reported Outcome Assessment

- Modified Whole Body Itch Numeric Rating Scale (NRS)

Statistical Methods

At least **230** pediatric subjects (ages from 6 through 17) will be randomized to receive either apremilast or placebo (2:1) at Week 0. The sample size estimation is based on the results of the adult Phase 3 and 3b studies with apremilast (CC-10004-PSOR-008, PSOR-009 and PSOR-010) which demonstrated positive treatment effects between apremilast and placebo in the proportion of subjects achieving sPGA response and PASI-75 response at Week 16.

With a total of **230** patients and a randomization ratio of 2:1, the study will have **90**% power to detect a 15% difference (20% versus 5%) between the apremilast arm and the placebo arm for the proportion of subjects achieving sPGA response at Week 16, based on a Chi-square test at a two-sided significance level of 0.05. The study will **also** have **more than 95**% power to detect a 20% difference (30% versus 10%) between apremilast and placebo for the proportion of subjects achieving PASI-75 response at Week 16.

Analysis for efficacy endpoints will be mainly using the intent-to-treat (ITT) population, defined as all randomized subjects. Statistical comparisons will be made between the apremilast arm and the placebo arm. All statistical tests will be at the two-sided 0.05 significance level and the corresponding p-values and two-sided 95% confidence intervals (CIs) will be reported.

To maintain an overall family-wise Type I error rate at the two-sided 0.05 significance level, a fixed-sequence testing procedure will be used to test the primary and the major secondary endpoints in a predefined order. The primary endpoint (sPGA response at Week 16) will be tested first at the two-sided 0.05 significance level. The comparison with respect to the major secondary endpoint (PASI-75 response at Week 16) will be conducted conditional on the test result of the primary endpoint, where statistical significance will be claimed only if the two-sided p-values for both endpoints are below 0.05.

The primary endpoint, the proportion of subjects who achieve sPGA response at Week 16 for apremilast versus placebo will be compared using Cochran–Mantel–Haenszel (CMH) test adjusted by stratification factor at randomization. Subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 will be assigned as non-responders. Missing values will be imputed using the multiple imputation (MI) method as the primary analysis. Sensitivity analyses will be performed using the last observation carried forward (LOCF) method, the non-responder imputation (NRI) method and the tipping point analyses. A sensitivity analysis using the PP population will also be performed. The major secondary endpoint and other binary secondary efficacy endpoints will be analyzed similarly as the primary endpoint.

Subgroup analyses for the primary and the major secondary endpoints based upon demographics (age, gender, race, weight category, etc.) and baseline characteristics will be provided to determine the robustness of the treatment effect.

The analysis for the continuous secondary endpoints will be performed using the analysis of covariance (ANCOVA) model. The ANCOVA model will use the change or percent change from baseline as the dependent variable and will include treatment group and stratification factors as independent variables and the baseline value as a covariate variable. The treatment comparison between apremilast and placebo will be conducted. Missing values will be imputed using the (MI) method.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Disease Background

Psoriasis is a chronic, inflammatory skin disorder that is estimated to affect up to 2.5% of the world's population (Christophers, 2001). The worldwide prevalence of psoriasis in children ranges from 0% to 1.37%. European populations have a higher prevalence than African and Asian populations (Michalek, 2017). The prevalence of psoriasis in children in the United States (US) from birth to age 18 years is 1%, with an incidence of 40.8 per 100,000 (Tollefson, 2010).

The first manifestation of psoriasis may occur at any age, with approximately one-third of cases reporting onset during childhood (Ståhle, 2010; Silverberg, 2010). Regardless of the timing of disease onset, the most common form of the disease in both adults and children is plaque-type psoriasis, characterized by erythematous plaques with silvery-white scales (Bronckers, 2015; Silverberg, 2010; Fan, 2007; Mallbris, 2005; Morris, 2001; Lebwohl, 2003). 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).

1.2. Compound Background

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

In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies, apremilast (OTEZLA®) is approved in multiple countries worldwide for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and the treatment of adult patients with active psoriatic arthritis.

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

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

1.3. Rationale

1.3.1. Study Rationale and Purpose

The treatment options for pediatric patients with plaque psoriasis remain limited. While most pediatric patients present with mild, localized psoriasis that can be treated primarily with topical medications, these therapies may be limited by their short treatment durations, poor treatment compliance and significant adverse effects (Chan, 2009; Kragballe, 2013). Phototherapy is not

recommended for fair-skinned or younger children, and psoralens with long-wave ultraviolet radiation (PUVA) is not recommended for use in pediatric psoriasis patients, due to the increased risk of malignancies (Ståhle, 2010). Due to this risk, phototherapy is usually reserved for older children and adolescents with extensive areas of involvement or refractory plaque disease (Shah, 2013; Marqueling, 2013).

Systemic medications are utilized for more extensive or refractory disease; however, approved therapies for moderate to severe psoriasis in children is limited. Management of psoriasis in children can be challenging owing to a paucity of data and lack of standardized guidelines to the pediatric population (Vogel, 2012). As of 2017, the only approved systemic medications in the US for pediatric patients with this indication are the anti-TNF biologic agent etanercept (Enbrel), and the anti-p40 inhibitor ustekinumab (Stelara). In the European Union (EU), etanercept (Enbrel), adalimumab (Humira) and ustekinumab (Stelara) are approved for pediatric use. Fear of needles is common in both children and adults and can contribute to negative experiences with needle procedures and health care for patients, caregivers, and health professionals (McMurtry, 2016). Thus, there remains an unmet need for effective systemic therapies that offer oral convenient dosing and a favorable benefit/risk profile for the treatment of pediatric patients with moderate to severe plaque psoriasis.

The systemic therapies used in pediatric psoriasis are essentially the same as those used in adulthood, with dosage and strength reductions calculated based on age, weight, and available formulations (Silverberg, 2010). However, most of these therapies are used off-label as they are not approved for pediatric use (Ståhle, 2010). In clinical trials, biologic therapies, etanercept (Enbrel), adalimumab (Humira), and ustekinumab (Stelara) demonstrated similar efficacy in pediatric patients with psoriasis as with the adult patients (Dogra, 2018).

Apremilast is an oral selective PDE4 inhibitor marketed worldwide under the trade name OTEZLA®. Apremilast 30 mg twice per day (BID) received its first global marketing approval for the treatment of adult patients with moderate to severe plaque psoriasis in 2014. Clinical data from multiple Phase 2 and Phase 3 trials and in the post-marketing setting have consistently demonstrated that apremilast is an effective oral therapy with an acceptable safety profile in adults. Thus, the benefit/risk profile of apremilast continues to be favorable in adult psoriasis patients.

Moderate to severe plaque psoriasis also occurs in pediatric patients. Exploratory analyses from a recent Phase 2 study (CC-10004-PPSO-001) indicate that apremilast may be effective for the treatment of moderate to severe plaque psoriasis in the pediatric population as in adults. This Phase 3 study (CC-10004-PPSO-003) is being conducted to evaluate the safety and efficacy of apremilast in the treatment of pediatric subjects, ages 6 through 17, with moderate to severe plaque psoriasis.

1.3.2. Rationale for the Study Design

This Phase 3, multi-center, randomized, double-blind, placebo-controlled study is designed to assess the efficacy and safety of apremilast in pediatric subjects aged 6 through 17 years of age with moderate to severe psoriasis.

Study CC-10004-PPSO-003 will investigate the safety and efficacy of apremilast 20 mg BID and apremilast 30 mg BID, compared to placebo, in the treatment of subjects with moderate to severe

plaque psoriasis. The primary endpoint will be the proportion of subjects who achieve a static Physician Global Assessment (sPGA) of clear (0) or almost clear (1), with at least a 2-point reduction from baseline at Week 16, in the intent-to-treat population. The first secondary endpoint will be the proportion of subjects achieving a 75% improvement in the Psoriasis Area Severity Index (PASI-75) response from baseline at Week 16. Both sPGA and PASI-75 have been required key endpoints for efficacy in psoriasis trials in both adults and children with moderate to severe plaque psoriasis.

The use of placebo for 16 weeks has been acceptable in clinical trials of pediatric subjects with moderate to severe plaque psoriasis (Paller, 2008). To retain subjects in the study until the primary endpoint at Week 16 is reached, an early escape option for subjects demonstrating a worsening of their psoriasis, measured as a ≥ 50% increase in PASI score from baseline will be permitted. These early escape subjects will be allowed to use moderate to high potency topical steroids but will be considered non-responders for the purposes of statistical analysis. The total treatment duration of the trial will be 52 weeks to assess the long-term effects of apremilast on safety and maintenance of efficacy.

Eligible subjects will be randomized 2:1 to receive either apremilast (20 mg BID for subjects weighing 20 to 50 kg, and 30 mg BID for subjects weighing ≥ 50 kg) or placebo, to reduce exposure to placebo without greatly increasing the number of subjects exposed to investigational product, while maintaining the statistical power of the study. Randomization will be stratified by baseline age group to ensure balance between treatment arms with respect to baseline age.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

Two Phase 2 dose finding studies have been conducted in adult subjects with moderate to severe plaque psoriasis. In study CC-10004-PSOR-005, a clear dose response was demonstrated with statistically significant improvement in the apremilast 20 mg BID and 30 mg BID, but not the apremilast 10 mg BID treatment groups, compared with placebo. Similar findings were observed in Study CC-10004-PSOR-011 which enrolled adult Japanese subjects with lower body weight and Body Mass Index (BMI) than the subjects enrolled in study CC-10004-PSOR-005. The safety and tolerability profiles of the apremilast 20 mg BID and 30 mg BID treatment groups were acceptable with no clinically significant safety signals observed in either dose group. In both of these studies, the apremilast 30 mg BID treatment group provided a superior benefit/risk profile compared to apremilast 20 mg BID. The apremilast 30 mg BID dose was evaluated in two large pivotal Phase 3 studies (studies CC-10004-PSOR-008 and CC-10004-PSOR-009), and was subsequently approved for use in adult patients with moderate to severe plaque psoriasis.

Moderate to severe plaque psoriasis also occurs in children and adolescents ages 6 through 17 years. The pharmacokinetic (PK) profiles of two effective adult dosages, apremilast 20 mg BID and apremilast 30 mg BID, are being evaluated in the ongoing pediatric Phase 2 study CC-10004-PPSO-001. The PK results from this study show that the apremilast exposure area under the plasma concentration-time curve (AUCtau) and peak observed plasma concentration of drug (C_{max}) on Day 14 in adolescents (12 to 17 years) treated with 30 mg BID, and children (6 to 11 years) treated with 20 mg BID appear to be comparable to the exposure observed in adult patients treated with 30 mg BID (Study CC-10004 PSOR-011). A population PK model was subsequently developed based on the data pooled from the pediatric study CC-10004-PPSO-001, and the adult studies CC-10004-PSOR-005 and CC-10004-PSOR-011. The model-based

simulations were conducted to determine the range of body weight in pediatric subjects taking apremilast 20 mg BID that could achieve similar exposure (AUCtau) to that in adult subjects taking the approved apremilast dose (30 mg BID). Two hundred clinical trials were simulated with each trial having pediatric subjects weighing between ≥ 20 kg and < 70 kg and adult reference population. The ratio of geometric mean (GM) of AUCtau for a given pediatric body weight group (body weight grouped by 5 kg increments) relative to the GM of AUCtau in adults was computed and the median of ratio and its 90% predictive interval were summarized. Based on modeling and simulation, the exposure of apremilast 20 mg BID in pediatric subjects weighing between ≥ 20 kg and < 50 kg is predicted to be similar to the exposure of apremilast 30 mg BID in adults (median of ratio within 0.8 and 1.25). The pediatric subjects weighing ≥ 50 kg are recommended to take the adult dose of 30 mg BID.

Exploratory efficacy analysis indicates that both apremilast doses (20 mg BID and 30 mg BID) may be efficacious in the treatment of moderate to severe plaque psoriasis in pediatric subjects. The safety analyses showed a similar safety profile to that of adults but with higher incidence rates of adverse events, particularly of diarrhea, nausea and vomiting. These adverse events (AEs) were mostly mild to moderate, and of short duration with the majority of these AEs lasting < 3 days. It should be noted that dose titration, which has been shown to ameliorate gastrointestinal-related adverse events in the adult studies, was not implemented in CC-10004-PPSO-001.

Based on these Phase 2 results, the Phase 3 study will evaluate the efficacy and safety of apremilast 20 mg BID for subjects < 50 kg and 30 mg BID for subjects ≥ 50 kg, compared to placebo, in the treatment of children and adolescent subjects with moderate to severe plaque psoriasis. As in the adult Phase 3 studies, dose titration will be implemented in order to mitigate potential gastrointestinal-related adverse events.

1.3.4. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

Phosphodiesterase 4 (PDE4) is the predominant cyclic adenosine monophosphate (cAMP)-selective phosphodiesterase that regulates intracellular cAMP levels and gene expression in cells of the immune system. PDE4 is highly overexpressed in the peripheral blood of a subset of psoriasis patients (Schafer, 2016). Apremilast has been found to reduce Th17 and Th22 cytokine expression in the lesional skin and peripheral blood of psoriasis patients (Gottlieb, 2013; Krueger, 2016). In adult patients with moderate to severe psoriasis, treatment with apremilast is associated with significant reductions in plasma levels of interleukin (IL)-17F, IL-17A, IL-22, and tumor necrosis factor-α (TNF-α) compared with placebo as early as Week 4; decreases in cytokine levels were sustained with continued treatment. Multivariate analyses demonstrated that while changes in IL-17F are the most important predictor of improvement in Psoriasis Area and Severity Index scores, apremilast exerts synergistic attenuating effects among a key group of cytokines involved in the pathology of psoriasis, and these effects correlate with improved skin symptoms. These in vitro and clinical data demonstrate that the beneficial effects of apremilast on known inflammatory mediators are associated with its clinical efficacy. Peripheral blood will be drawn to measure RNA expression at baseline and during the treatment period. Whole blood will be used for the analysis. The expression of specific RNAs, such as but not limited to PDE4A, PDE4B, PDE4C, PDE4D, IL17A, IL17F, IL22, and TNF-α, will be analyzed at baseline and during the placebo-controlled treatment period. These data will further define the mechanism

of action of apremilast in this patient population, and may inform on the subset of patients who are responding well to apremilast treatment.

Psoriasis is driven in part by genetic factors, including HLA-Cw6, TNF-α, LCE3B/3C, IL12B, IL23A, IL23R, LCE, TNIP1, IFHIH1, and NFKBIA. Apremilast has been shown to inhibit the expression of some of these genes, including TNF-α, IL12B, and IL23A (Gottlieb, 2013). Therefore, clinical response to apremilast may be dependent upon the underlying genetic drivers in some psoriasis patients. Pharmacogenetic testing will be conducted using deoxyribonucleic acid (DNA) isolated from a buccal swab at Visit 2 (Baseline Visit; day of randomization). DNA will be examined for the presence of polymorphisms in the genes encoding the targets of apremilast (PDE4A, PDE4B, PDE4C, and PDE4D), and in genes associated with psoriasis, including but not limited to HLA-Cw6, TNF-α, LCE3B/3C, IL12B, IL23A, IL23R, LCE, TNIP1, IFHIH1, and NFKBIA.

The microbial species present on the skin of psoriasis patients may play a role in the transition from healthy skin to psoriatic plaques (Langan 2017). The microbial composition of the patients' skin will be examined to identify the predominant bacterial and fungal species present before and after apremilast treatment, to determine if the microbiome either predicts response to apremilast or changes upon apremilast therapy.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the clinical efficacy of apremilast compared with placebo in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis.
Secondary Objectives
The secondary objectives are: • To evaluate the safety and tolerability of apremilast compared with placebo, in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis • To evaluate the effect of apremilast compared with placebo on health-related quality of life (HRQoL)
Exploratory Objectives
The exploratory objectives are: • To evaluate the effect of apremilast on plaque psoriasis • To evaluate the effect of apremilast on plaque psoriasis of the scalp • To evaluate the effect of apremilast on genital psoriasis • To evaluate the effect of apremilast on itch over the whole body caused by plaque psoriasis • To evaluate the effect of apremilast on HRQoL of family members [redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Static PGA (sPGA) 0/1	Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	Week 16
Major Secondary Endpoints	PASI-75	Proportion of subjects who achieve at least a 75% reduction in PASI (PASI-75) from baseline	Week 16
Other Secondary Endpoints	PASI-50	Proportion of subjects who achieve at least a 50% reduction in PASI (PASI-50) from baseline	Week 16
	PASI	Percent change from baseline in total PASI score	Week 16
	BSA	Percent change from baseline in affected BSA	Week 16
	CDLQI (0/1)	Proportion of subjects who achieve CDLQI (0/1)	Week 16
	CDLQI	Change from baseline in CDLQI score	Week 16
Exploratory	PASI-50	Proportion of subjects who achieve PASI-50	All visits
	PASI-75	Proportion of subjects who achieve PASI-75	All visits
	PASI-90	Proportion of subjects who achieve PASI-90	All visits
	PASI	Percent change from baseline in total PASI score	All visits
	sPGA (0/1)	Proportion of subjects with sPGA of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	All visits
	BSA	Percent change from baseline in affected BSA	Select visits
	ScPGA	Proportion of subjects with scalp psoriasis with improvement of ScPGA of clear (0) or almost clear (1)	Select visits
	sPGA-G	Proportion of subjects with genital psoriasis with improvement of sPGA-G of clear (0) or minimal (1)	Select visits
	Modified Whole Body Itch NRS	Proportion of subjects with ≥ 4-point reduction (improvement) from baseline in the whole body itch NRS score	Select visits

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Modified Whole Body Itch NRS	Change from baseline in the whole body itch NRS score	Select visits
	CDLQI (0/1)	Proportion of subjects who achieve CDLQI (0/1)	Select visits
	CDLQI	Change from baseline in CDLQI scores	Select visits
	FDLQI (0/1)	Proportion of subjects achieving FDLQI (0/1)	Select visits
	FDLQI	Change from baseline in FDLQI scores	Select visits
	[redacted]		
Safety			
Adverse events	Type, frequency, severity, and relationship of AEs to IP	Day 0 through end of Observational Follow Up	Study duration (up through 14-week follow-up)
Diarrhea	Stool Diary (frequency, duration and associated symptoms)	Completed daily by subject/parent(s)/guardian(s) and reviewed at each visit by study investigator	Study duration (up through 4-week follow-up)
Depression, suicidal thoughts and behavior	Columbia-Suicide Severity Rating Scale (C-SSRS)	Questionnaire completed at Screening, Baseline, and visits thereafter as indicated in Table 3	Study duration (up through Week 52)
Growth and Development	Tanner Staging of sexual development	Assessment of sexual maturity	Performed at beginning and end of study (Week 52 or ET)
	Body weight, height and BMI	Height and body weight are measured and recorded at each visit	Study duration

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Psoriasis Flare	Psoriasis disease flare as defined in Section 6.5.15	Proportion of subjects with sudden intensification of psoriasis (new generalized erythrodermic, inflammatory or pustular psoriasis) requiring medical intervention beyond allowable medications	Study duration (while taking study medication)
Psoriasis Rebound	Rebound as defined in Section 6.5.15	Severe and sudden worsening of disease (PASI ≥ 125% of baseline or new generalized, pustular, erythrodermic psoriasis) after treatment has been discontinued	14-week follow-up period

sPGA = static Physician Global Assessment; PASI = Psoriasis Area Severity Index; BSA = Body Surface Area; CDLQI = Children's Dermatological Life Quality Index; ScPGA = Scalp Physician Global Assessment; sPGA-G = Scalp Physician Global Assessment-Genital; FDLQI = Family Dermatological Life Quality Index; NRS = Numeric Rating Scale; [redacted].

3. OVERALL STUDY DESIGN

3.1. Study Design

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

At least **230** pediatric subjects (ages 6 through 17 years) will be randomized 2:1 to receive either apremilast or placebo for the first 16 weeks. Randomization to apremilast arm or placebo arm will be stratified by age group (6 to 11 years or 12 to 17 years). A minimum of 75 subjects will be randomized in each age group. The sponsor may halt enrollment of one age group if that age group reaches **155** randomized subjects to allow the other group to randomize at least 75 subjects. The integrated response technology (IRT) system will monitor total enrollment of each age group so enrollment can be halted once a group reaches **155** randomized subjects. Treatment will be assigned by weight with subjects 20 kg to < 50 kg receiving apremilast 20 mg BID or placebo BID and subjects ≥ 50 kg receiving apremilast 30 mg BID or placebo BID. After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database lock will be performed; the primary data analysis will be conducted and a Week 16 clinical study report will be generated. Study investigators and subjects will remain blinded to initial treatment assignments until the final database lock at the conclusion of the study. The blind also should be maintained for persons responsible for the ongoing conduct of the study. Blinded persons may include but are not limited to: clinical research physician, clinical research scientist, clinical trial manager, study statistician, data manager, programmer, clinical research associate. At the end of the study, after all subjects have either completed Visit 16 and entered the Long-term Study, or completed the Observational Follow-up Phase, or been discontinued from the Apremilast Extension Phase (Weeks 16 to 52) or the Observational Follow-up Phase, a final analysis will be performed and a final clinical study report will be generated.

The study will consist of four phases:

- Screening Phase – up to 35 days
- Placebo-controlled Treatment Phase – Weeks 0 to 16
    - Subjects will be randomly assigned in a 2:1 ratio to apremilast or placebo. Subjects 20 kg to < 50 kg will receive apremilast 20 mg BID or placebo BID and subjects ≥ 50 kg will receive apremilast 30 mg BID or placebo BID. The primary endpoint will be the proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16.
    - From Week 8 through Week 16, any subject with a PASI increase ≥ 50% from baseline will be eligible to commence treatment with moderate-to-high potency topical steroid preparations (early escape) and continue with randomized IP.
- Apremilast Extension Phase – Weeks 16 to 52
    - Placebo subjects will be switched at Week 16 to receive apremilast 20 mg BID or 30 mg BID, according to baseline weight. All other subjects will continue to receive either apremilast 20 mg BID or apremilast 30 mg BID based on their original dosing assignment.

- Observational Follow-up Phase – 14 weeks
    - All eligible subjects who complete the apremilast Extension Phase may opt to enroll in a separate Long-term Study (for up to 4 years or until approval, whichever comes first). Subjects who choose not to participate in the Long-term Study, or discontinue the study early, should return for observational follow-up visits four, eight, and fourteen weeks after the last dose of IP.

An external, independent data monitoring committee (DMC) will review available safety and efficacy data approximately semi-annually or on an ad-hoc basis throughout the study. The DMC consists of 4 external independent members (3 independent clinical trialists and 1 independent biostatistician) with voting privileges. All members are selected by Amgen with consideration for their respective expertise in the subject matter and/or in their experience in convening or participating in a DMC.

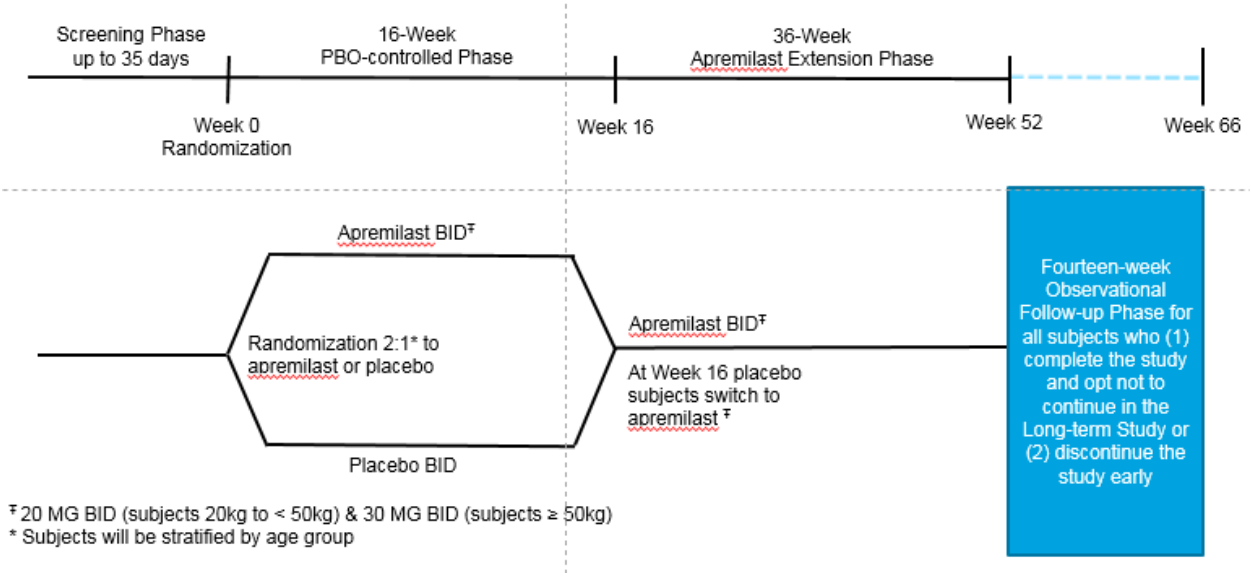
A Scientific Steering Committee (SSC) has also been formed in support of this study. The SSC provides input into the study protocol and is responsible for supporting the conduct of the trial, promoting effective enrollment and reviewing study data. The SSC is comprised of 5 clinicians that may or may not be participating in the study. The SSC will interact with Amgen and other parties on a periodic basis throughout the conduct of the trial with meetings based upon patient recruitment throughout the entire conduct of the trial.

Treatment administration and schedule are discussed in Section 7.2.

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 any time during the period of the study and require additional psoriasis medication including 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 the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Overall Study Design



3.2. Study Duration for Subjects

The study will last for up to a total of 71 weeks which includes screening, treatment, and observational follow-up.

Each subject will undergo a Screening period of up to 5 weeks, a 16-week Placebo-controlled Treatment Phase, and a 36-week Apremilast Extension Phase. All eligible subjects who complete the Apremilast Extension Phase may opt to enroll in a separate, up to 4-year Long-term Study. Subjects who choose not to participate in the Long-term Study, or discontinue the study early, should return for the three observational follow-up visits at four, eight, and fourteen weeks after the last dose of IP.

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

At least **230** pediatric subjects with moderate to severe plaque psoriasis will be randomized from investigator sites in North America, the EU, and rest of world.

4.2. Inclusion Criteria

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

1. Males or female subjects 6 to 17 years of age, inclusive, at the time the informed consent form is signed by the legal guardian
2. Subjects must have a weight of ≥ 20 kg
3. Subjects must have an age and sex specific BMI value no lower in range than the 5th percentile on the Centers for Disease Control (CDC) growth chart for children and adolescents (CDC, 2000).
4. Subject is able to swallow the study medication tablet
5. Able to sign an age-appropriate assent with a legal guardian(s) who understand(s) and voluntarily sign(s) an informed consent prior to any study-related assessments/procedures being conducted.
6. Be willing and able to adhere to the study visit schedule and other protocol requirements.
7. Diagnosis of chronic plaque psoriasis for at least 6 months prior to Screening.
8. Has 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)
9. Disease inadequately controlled by or inappropriate for topical therapy for psoriasis
10. Candidate for systemic therapy or phototherapy
11. At Screening, laboratory values must be within the following ranges:
    - White blood cell (WBC) count

Age (years)	Males (x 10^3 /µL)	Females (x 10^3 /µL)
6-11	3.5 – 13.5	3.5 – 13.5
12-18	3.5 – 13.5	3.5 – 13.5

    - Platelet count

Age (years)	Males (x 10^3 /µL)	Females (x 10^3 /µL)
6-11	125 – 500	125 – 500
12-18	125 – 500	125 – 500

- Serum creatinine ≤ 1.2 x upper-limit of normal (ULN) for age and gender. Please see reference ranges of the central laboratory
- Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [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 the 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 (years)	Males (g/dL)	Females (g/dL)
6-11	10.0 – 15.0	10.0 – 15.0
12-18	11.0 – 16.5	10.5 – 15.5

12. 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 during any dose interruption, and for at least 28 days after administration of the last dose of apremilast. For the purpose 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 highly effective methods: hormonal contraception (for example, birth control pills, intravaginal ring, transdermal patch, injection, implant); intrauterine device (IUD); tubal ligation; or partner's vasectomy.

    OR

    Option 2: Male or female 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

    NOTE: Option 2 may not be acceptable as a highly effective contraception option in all countries per local guidelines/regulations.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

[+] If a female subject is a FCBP when entering the study, the chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

4.3. Exclusion Criteria

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

1. Other than psoriasis, history of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease.
2. Any condition, including the presence of laboratory abnormalities, or psychiatric illness, that would place the subject at unacceptable risk if he/she were to participate in the study
3. Any condition that confounds the ability to interpret data from the study.
4. Evidence of skin conditions, other than psoriasis, that would interfere with clinical assessments
5. Pregnant or breastfeeding
6. Guttate, erythrodermic, or pustular psoriasis at Screening and Baseline
7. Psoriasis flare or rebound within 4 weeks prior to Screening
8. Positive Hepatitis B surface antigen, or anti-hepatitis C antibody, at Screening
9. History of positive human immunodeficiency virus infection (HIV), congenital and acquired immunodeficiencies (eg, common variable immunodeficiency, immunoglobulin A deficiency)
10. Active tuberculosis (TB) or a history of incompletely treated TB
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 15cP, titanium dioxide, polydextrose food chemical color, 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-galactose 4-epimerase, galactokinase or Fanconi Bickel syndrome, including congenital lactase deficiencies, and glucose-galactose malabsorption.
16. Prior history of suicide attempt at any time in the subject's lifetime prior to Screening or randomization in the study, or major psychiatric illness requiring hospitalization within 3 years prior to signing the assent and informed consent
17. Answer "Yes" to any question on the Columbia-Suicide Severity Rating Scale during Screening or at Baseline
18. Current or planned concurrent use of the following therapies that may have a possible effect on psoriasis

a. Topical therapy within 2 weeks prior to randomization (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol)

   Exceptions*:

   i. Low potency or weak corticosteroids (please refer to the Investigators' Manual) will be allowed as background therapy for treatment of the face, axillae and groin in accordance with manufacturer's suggested usage

   ii. Unmedicated skin moisturizer (eg, Eucerin®) will also be permitted for body lesions

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

b. Conventional systemic therapy for psoriasis within 4 weeks prior to randomization (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters)
c. Phototherapy treatment (ie, ultraviolet B [UVB], PUVA) within 4 weeks prior to randomization
d. Biologic therapy:
   i. Etanercept (or biosimilar) treatment four weeks prior to randomization
   ii. Adalimumab (or biosimilar) treatment ten weeks prior to randomization
   iii. Other TNF or IL-17 blockers (such as infliximab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, or their biosimilars) within 12 weeks prior to randomization
   iv. Anti-IL-12 or anti-IL-23 treatment (such as ustekinumab, guselkumab, or tildrakizumab) within 24 weeks prior to randomization
e. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer)

19. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources
20. 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
21. Prior treatment with apremilast

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening	Baseline[a]	Placebo-controlled Treatment Phase					Apremilast Extension Phase									Observational Follow-up[b]			UNS[c]	ET
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		
Week	**-35 to 0 (Days)**	**0 (Day 1)**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**66**		
Administrative/Demographics																					
Informed consent/Assent[d]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographic data	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior / concomitant medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior psoriasis meds/therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Safety Assessments																					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) Screening[e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit[f]	-	X	X	X	X	X	X	-	X	-	X	-	X	-	X	X	-	-	-	X	X
Complete physical examination	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	X
Abbreviated physical examination[g]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	-
Clinical laboratory evaluations	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	X	X
Psoriasis flare/rebound	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Table of Events (Continued)

	Screening	Baseline[a]	Placebo-controlled Treatment Phase					Apremilast Extension Phase									Observational Follow-up[b]			UNS[c]	ET
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		
Week	**-35 to 0 (Days)**	**0 (Day 1)**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**66**		
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Mass Index (BMI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Hepatitis B and C tests	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy test and contraception education (FCBP only)[i]	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
Stool Diary Collection[j]	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	X
Tanner Staging Assessment[k]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	X
Clinical Efficacy Assessments																					
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ScPGA	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X
sPGA-G	-	X	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-	-	X
[redacted]																					

Table 3: Table of Events (Continued)

	Screening	Baseline[a]	Placebo-controlled Treatment Phase					Apremilast Extension Phase									Observational Follow-up[b]			UNS[c]	ET
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		
Week	**-35 to 0 (Days)**	**0 (Day 1)**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**66**		
Patient Reported Outcome																					
Modified Whole Body Itch NRS	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	-	X
Quality of Life Assessments																					
CDLQI	-	X	-	X	X	-	X	-	X	-	X	-	X	-	-	X	-	-	-	-	X
FDLQI	-	X	-	X	X	-	X	-	X	-	X	-	X	-	-	X	-	-	-	-	X
Dosing																					
IP Dispensation		X	-	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	-	X	-
Oral Dose Apremilast/placebo[l]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	X	-
IP Drug Accountability	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	X	X

Abbreviations: ET = early termination; FCBP = females of childbearing potential; BMI = body mass index; BSA = body surface area; FCBP = females of childbearing potential; [redacted] UNS = unscheduled visit; sPGA = Static Physician Global Assessment; CDLQI = Children's Dermatology Life Quality Index; FDLQI = Family Dermatology Life Quality Index; ScPGA = Scalp Physician Global Assessment; PASI = psoriasis area severity index; sPGA-G = Static Physician Global Assessment – Genital; NRS = Numeric Rating Scale; [redacted]; IP = investigational product; ET = early termination.

[a] All baseline assessments must be completed prior to randomization and dispensing of IP. Week 0 is the beginning of the Placebo-controlled Treatment Phase

[b] Subjects who choose not to participate in the Long-term Study, or discontinue the study early, should return for observational follow-up visits four, eight and fourteen weeks after the last dose of IP. Subjects who discontinue early should be encouraged to come back for an Early Termination Visit within 4 days of last intake of IP.

[c] Refer to Section 6.5.16 for details.

[d] Written informed consent from subject's legal guardian and subject assent will be obtained by the Principal Investigator or designee prior to performing any study assessments.

[e] Any subject, during Screening, 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

[f] Any subject that answers 'Yes' to any question on the Columbia-Suicide Severity Rating Scale, at any time during the study (Baseline to completion or early withdrawal) will be immediately withdrawn from study treatment and must be referred immediately for a psychiatric evaluation.

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

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

[i] Serum and urine pregnancy testing will be required for FCBP at Screening. Urine pregnancy testing will be performed at Baseline and at each visit during the Placebo-controlled Treatment (except Visit 3) and Apremilast Extension Phases, the Week 56, 60, and 66 Follow-up Visits (if applicable), and the early termination (ET) visit (if applicable). If a urine test is positive, a serum test will be done for confirmation.

[j] 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 17). Subjects continuing into the Long-term Study will submit their last entries at Visit 16.

[k] Tanner Staging assessment will be performed at Baseline and Visit 16 (Week 52) or the Early Termination visit for subjects that do not complete the study.

[l] IP will be administered orally twice daily from Visit 2 to Visit 16 (Week 52). IP morning dose to be taken at the study site for Visits 4, 7, and 9.

6. PROCEDURES

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

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 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.

Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study. Inclusion and exclusion criteria will be assessed at Screening and Baseline.

Demographic Data

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

Medical and Disease History

Relevant medical history, as defined in the eCRF Completion Guidelines, should be recorded. Disease history should include history of plaque psoriasis.

Prior/Concomitant Medications 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 procedures being taken by or performed on the subject at any time during the study must be recorded. The stop dates and 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 eCRF Completion Guidelines.

Refer to Section 8 for further details regarding permitted and prohibited concomitant medications and procedures.

Oral Dose of Apremilast and Placebo

Apremilast or placebo will be administered orally twice daily. Evening doses will be administered approximately 12 hours after the morning dose.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 35 days prior randomization.

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

The Columbia-Suicide Severity Rating Scale questionnaire will be administered at this visit by the investigator or authorized site staff.

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

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

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

The following assessments will be performed at Screening as specified in the Table of Events, Section 5, after informed consent has been obtained:

- Demographics (initials, month and year of birth (or as allowed by local regulations), age, sex, race, and ethnicity-if allowed by local regulations)
- Review of inclusion/exclusion criteria to confirm subject eligibility
- Prior psoriasis therapies: includes topical, systemic, and phototherapies
- Prior and current Concomitant medications and procedures evaluation
- Medical history (all relevant medical conditions diagnosed/ occurring prior to Screening should be included)
- Complete physical exam
- Vital signs (including blood pressure, temperature, respiratory rate and pulse)
- Columbia-Suicide Severity Rating Scale Screening questionnaire
- Body weight, height and BMI
- Efficacy assessments (sPGA, BSA, and PASI)
- Hematology and chemistry panels as well as urinalysis
- Hepatitis B and C screening
- Serum and urine pregnancy tests are required for all female subjects of childbearing potential, as defined in Section 6.5.3. Counselling about pregnancy precautions and the potential risks of fetal exposure
- Adverse event assessment (begins when the subject signs the informed consent form)

6.2. Treatment Period

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

During the treatment period (Placebo-controlled Treatment and Apremilast Extension Phases), subjects must complete the whole body itch NRS and subject questionnaires prior to any other study procedure being performed and in the following order when applicable: 1) whole body itch NRS; 2) children's dermatological life quality index (CDLQI) and family dermatological life quality index (FDLQI). The subject's caregiver/family member may complete the FDLQI when not assisting the subject. The same caregiver/family member that completes the first FDLQI questionnaire at the Baseline visit, should complete all subsequent FDLQI questionnaires at the required visits.

The Columbia Suicide Severity Rating Scale questionnaire will also be administered at treatment visits as designated in Table 3 by the investigator or authorized site staff.

During the treatment period, efficacy assessments may be performed by the investigator or qualified designee at any time during a study visit but only after the subject has completed the whole body itch NRS and health-related quality of life (HRQoL) assessments, when required. The investigator performing efficacy assessments shall make independent observations at a given study visit and shall not review assessments or subject-derived data in advance of conducting the assessments. When conducting the efficacy assessments, the investigator must complete these assessments in the following order when applicable: 1) sPGA; 2) BSA; 3) PASI; 4) scalp physician global assessment (ScPGA); 5) modified static physician global assessment-genital (sPGA-G).

The following evaluations will be performed at the frequency specified in the Table of Events, Section 5.

- Whole body itch NRS, CDLQI, and FDLQI – Patient reported outcomes and Health-related quality of life (HRQoL)
- Concomitant medications and procedures evaluation
- Physical examination (abbreviated from Baseline to Visit 15 and complete exam at Visit 16)
- Vital signs (including blood pressure, temperature, respiratory rate and pulse)
- Body weight, height and BMI
- Apremilast or placebo morning dose to be taken at study site for Visits 4, 7 and 9

- Hematology and chemistry panels as well as urinalysis

- Columbia-Suicide Severity Rating Scale
- Tanner Staging (Baseline and Visit 16)
- Stool Diary review (completed at home and reviewed at study visits)
- Adverse event evaluation (continuously)
- Psoriasis flare/rebound assessment
- Efficacy assessments (sPGA, PASI, BSA, ScPGA, sPGA-G)
- Investigational product dispensation and accountability
- Urine pregnancy test is required at Baseline for all female subjects of childbearing potential as defined in Section 6.5.3. Counselling about pregnancy precautions and the potential risks of fetal exposure.

6.2.1. End of Treatment

An Early Termination visit will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. The Investigator should make every attempt possible to have the subject evaluated at the Early Termination Visit within 4 days of the last intake of IP.

At the Early Termination Visit, subjects must complete the whole body itch NRS and subject questionnaires prior to any other study procedure being performed and in the following order when applicable: 1) Modified Whole body itch NRS; 2) CDLQI and FDLQI. The subject's caregiver/family member may complete the FDLQI when not assisting the subject. The same caregiver/family member that completes the first FDLQI questionnaire at the Baseline visit, should complete all subsequent FDLQI questionnaires at the required visits.

The Columbia Suicide Severity Rating Scale questionnaire will also be administered at this visit by the investigator or authorized site staff.

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

The following evaluations will be performed as specified in the Table of Events, Section 5:

- Modified Whole body itch NRS, CDLQI, and FDLQI – Patient reported outcomes and Health-related quality of life (HRQoL)
- Concomitant medications and procedures evaluation
- Physical examination (complete)
- Vital signs including height and weight
- Body Mass Index (BMI)
- Hematology and chemistry panels as well as urinalysis

- Columbia-Suicide Severity Rating Scale
- Tanner Staging
- Stool Diary collection (completed at home and reviewed at study visits)
- Adverse eventevaluation (continuously)
- Psoriasis flare/rebound assessment
- Efficacy assessments (sPGA, PASI, BSA, ScPGA, sPGA-G)
- Investigational product accountability
- Urine pregnancy test required for all females of child bearing potential as defined in Section 6.5.3. Counselling about pregnancy precautions and the potential risks of fetal exposure.

6.3. Observational Follow-up Period

6.3.1. Observational Follow-up

All subjects that complete Week 52 treatment and opt not to continue into the Long-term Study or discontinue treatment early, will be followed for 98 days (14 weeks) after the last dose of IP for AE reporting, as well as any serious adverse events (SAEs) made known to the Investigator at any time following the protocol-required reporting period or end of study-as described in Section 10.1. The follow up period consists of three visits, one 4 weeks after last dose of IP, one 8 weeks after last dose of IP, and one 14 weeks after the last dose of IP.

During the follow-up period, efficacy assessments may be performed by the investigator or qualified designee at any time during a study visit.

The following evaluations will be performed at all three Observational Follow-up Visits as specified in the Table of Events, Section 5.

- Concomitant medications and procedures evaluation
- Physical examination (abbreviated)
- Vital signs
- Height and weight
- Hematology panel (only at 4-week post-last dose follow-up visit)
- Chemistry panel (only at 4-week post-last dose follow-up visit)
- Urinalysis (only at 4-week post-last dose follow-up visit)
- Stool Diary collection (only at 4-week post-last dose follow-up visit)
- Adverse event evaluation (continuously)
- Efficacy assessments (sPGA, PASI, BSA, ScPGA)
- Urine pregnancy test required for all females of child bearing potential as defined in Section 6.5.3.

- Psoriasis flare/rebound assessments

6.4. Efficacy Assessments

The following assessments, when applicable, will be conducted as outlined in the Table of Events, Section 5:

- **Static Physician Global Assessment (sPGA)**

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

In the event of different severities across disease signs, the sign that is the predominant feature of the disease should be used to help determine the sPGA score. See details in Appendix B.

- **Psoriasis Area Severity Index (PASI)**

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.

The PASI scores range from 0 to 72, with higher scores reflecting greater disease severity (Frederiksson, 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 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. See details in Appendix C.

- **Body Surface Area (BSA)**

BSA is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand, which equates to approximately 1% of total body surface area.

- **Scalp Physician Global Assessment (ScPGA)**

The ScPGA is the Investigator's assessment of severity of psoriasis of the scalp, if present at baseline. When making the assessment of overall severity, the Investigator should factor in areas that have already been cleared (ie, have scores of 0 and not just evaluate remaining lesions for severity, ie, the severity of each sign is averaged across all areas of involvement, including cleared lesions. See details in Appendix D.

- **Modified Static Physician Global Assessment of Genitalia (sPGA-G)**

The sPGA-G is the Investigator's assessment of severity of psoriasis of the genitals, if present at baseline. See details in Appendix E.

6.5. Safety Assessments

6.5.1. 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 10. All AEs will be monitored and recorded from the time the subject signs the ICF until 98 days (14 weeks) after the last dose of investigational product for subjects that discontinue the study early or opt not to continue into the long-term study. Any Serious adverse events (SAEs) made known to the Investigator at any time will be monitored, recorded and reported following the protocol-required reporting period or after the end of study.

6.5.2. 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 4.2 while on investigational product and for at least 28 days after administration of the last dose of the investigational product. If a female subject is considered a FCBP when entering the study, the chosen form of contraception must be effective by the time the female subject is randomized in to the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

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.

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

A serum pregnancy test with a sensitivity of ≤ 25 mI U/mL will be required for all FCBP at Screening and as confirmation of any positive urine test. Urine pregnancy testing will be performed on all FCBP at Screening, Baseline, and at each visit, except Visit 3, during the Placebo-controlled and Apremilast Extension Phases as well as at the 4, 8 and 14 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.

6.5.4. Complete Physical Exam

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 and the Week 52 visit or any early termination visit.

6.5.5. Abbreviated Physical Exam

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.

6.5.6. Hepatitis B and C Testing

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

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

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

Blood pressure 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.

6.5.8. 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.

The amount of blood taken from subjects at each visit and cumulatively over the course of the entire study is within the safety limits as described in a bulletin published by the World Health

Organization (WHO). (Howie, 2011). The volume of blood drawn will not exceed 11 mL at any visit.

6.5.9. Hematology

Hematology laboratory evaluations will include red blood cells (RBCs), hemoglobin, hematocrit, white blood cells (WBCs), absolute and differential and platelet count. Approximately 2 mL of blood will be taken to complete hematology evaluations at each visit as designated in Table 3. An additional 5 mL of blood will be collected at the Screening visit to screen for hepatitis.

6.5.10. 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. Approximately 3.5 mL of blood will be taken to complete serum chemistry evaluations at each visit as designated in Table 3.

6.5.11. 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.

6.5.12. Psychiatric Evaluation

Psoriasis has been associated with an increased risk of developing psychiatric disorders, including depression and anxiety in pediatric patients (Kimball, 2012). Apremilast prescriber information (eg, Summary of Product Characteristics, Package Insert) includes a warning regarding depression and suicidal thoughts. 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.

All subjects will complete the Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix F) 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 up to Week 16 and then approximately every other visit thereafter. Any subject that answers ‘Yes’ to any question on the C-SSRS at any time 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 at four, eight and fourteen weeks after Early Termination.

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

6.5.13. Stool Diary

Diarrhea is the passage of three or more watery/liquid stools per day (WHO, 2017).

Subjects and their parent/guardian will be supplied with diaries (either paper or electronic) that will be filled out daily to record and describe any diarrhea, including duration, frequency, and associated symptoms (Appendix G). 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 Observational Follow-up visit (Visit 17). The investigator will review diary entries with the subject and his/her caregiver at each study visit.

6.5.14. Tanner Staging

Assessments of sexual maturity (Tanner Staging) will be performed at Baseline and Week 52 (Visit 16) or the Early Termination visit for subjects that do not complete the study. A description of each Tanner stage is provided in Appendix H (WHO, 2010).

6.5.15. Worsening of Psoriasis and Rebound Assessments

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

Rebound is an AE and is defined as a severe and sudden worsening of disease that occurs after treatment had been discontinued. This exacerbation is characterized by a PASI $\geq$ 125% of baseline or a new generalized pustular, erythrodermic, or more inflammatory psoriasis after stopping therapy (Gordon, 2005).

6.5.16. 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 blood pressure) and weight
- Record concomitant medications/procedures and AEs
- Drug accountability and dispensation if needed
- sPGA and PASI
- Psoriasis flare/rebound
- C-SSRS questionnaire

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 (Table 3)

- Perform abbreviated physical examination

6.6. Pharmacokinetics

All enrolled subjects who take at least one dose of apremilast should have one blood specimen drawn at four visits (Weeks 4, 8, 16, and 24) for measurement of apremilast in plasma. A small amount of blood (approximately 2 mL) will be drawn before the morning apremilast dose at Weeks 4, 16, and 24. The Week 8 blood specimen, also approximately 2 mL, will be drawn at least 30 minutes after the morning apremilast dose. The evaluable PK data from CC-10004-PPSO-003 will be pooled with those from CC-10004-PPSO-001 and the studies in adults with moderate-to-severe plaque-type psoriasis for the population PK analysis.

The blood samples will be taken through an indwelling venous cannula by direct venipuncture at the following nominal times shown in Table 4. Concentrations of apremilast in plasma will be measured using a validated liquid chromatography tandem mass spectrometry assay.

Table 4: Acceptable Time Windows for Pharmacokinetic Blood Sampling

Scheduled PK Blood Draw Time	Acceptable Time Window
Pre-dose (Weeks 4, 16, and 24)	Within 60 minutes prior to dosing
Post-dose (Week 8)	At least 30 minutes post-dose

The date and time of the last evening dose (for pre-dose blood draw) on the day prior to the clinical visit and the current morning dose (for post-dose blood draw) on the day of visit will be recorded in the source documents and eCRF. Actual PK blood sample collection date and time will also 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 4. Specific details regarding collection, handling, processing, storage, and shipment of PK samples can be found in Appendix I.

6.7. Biomarkers, Pharmacodynamics, Pharmacogenomics

- **Pharmacodynamic Peripheral Blood RNA Gene Expression**

PDE4 is highly overexpressed in the peripheral blood of a subset of psoriasis patients (Schafer, 2016). Furthermore, apremilast has been found to reduce Th17 and Th22 cytokine expression in the lesional skin and peripheral blood of psoriasis patients (Gottlieb, 2013; Krueger, 2016). By optional consent, peripheral blood (approximately 2.5 mL) will be drawn to measure RNA expression at baseline and during the treatment period.

Whole blood will be used for the analysis. The expression of specific RNAs, such as but not limited to PDE4A, PDE4B, PDE4C, PDE4D, IL17A, IL17F, IL22, and TNF-α, will be analyzed at Baseline (Week 0) and during the Placebo-controlled Treatment Phase at Week 16. These data will further define the mechanism of action of apremilast in this patient population, and may inform on the subset of patients who are responding well to apremilast treatment.

- **Pharmacogenetic DNA Analysis**

By optional consent, a buccal swab will be collected at Visit 2 (Baseline Visit; day of randomization) for the purposes of analyzing the genetic polymorphisms that are associated with

clinical and pharmacodynamic interaction with apremilast. Deoxyribonucleic acid (DNA) will be examined for the presence of polymorphisms in the genes encoding the targets of apremilast (PDE4A, PDE4B, PDE4C, and PDE4D), and in genes associated with psoriasis, including but not limited to HLA-Cw6, TNF-α, LCE3B/3C, IL12B, IL23A, IL23R, LCE, TNIP1, IFHIH1, and NFKBIA. Subjects at selected sites will have the option to participate in the Pharmacogenetic Analysis sub-study and must sign a separate consent form specific to the Pharmacogenetic Analysis sub-study at Visit 1 (Screening Visit). Detailed instructions for sample preparation and handling will be contained in the separate laboratory manual prepared for the sites.

- **Skin Microbiome Analysis**

By optional consent, the microbial species (bacterial and fungal) present on the patients' skin will be assessed by swabbing the affected and unaffected skin and subjected the swabbed material to 16S and ITS ribosomal RNA gene amplification and sequencing. Affected and unaffected skin will be analyzed at Baseline (Week 0) and during the Placebo-controlled Treatment Phase at Week 16.

6.8. Subject Reported Outcomes or Health Related Quality of Life

- **Children's Dermatology Life Quality Index (CDLQI)**

  The CDLQI is designed to measure the impact of skin disease on children's quality of life. It is a self-explanatory questionnaire that can be handed to the subject to fill out with the help of a parent or guardian, See details in Appendix J.

- **Family Dermatology Life Quality Index (FDLQI)**

  This is a self-explanatory questionnaire designed for adults (more than 16 years of age), that must be handed to a subject's caregiver/family member for completion. The FDLQI will assess the impact of skin disease experienced by a family member. See details in Appendix K.

- **Modified Whole Body Itch Numeric Rating Scale (NRS)**

  The pruritus NRS whole body assessment is a tool designed to measure the amount of whole body itch due to psoriasis in the previous 24-hour period by circling a number on a scale from 0 to 10. See details in Appendix L.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product

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

Investigational product will be provided in blister cards and bottles, depending on the phase of the study. Apremilast will be provided as 10, 20, and 30 mg tablets. Placebo will be provided as identically appearing 10, 20, and 30 mg tablets. Investigational product will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To reduce potential gastrointestinal (GI) symptoms, dose titration will be implemented during Week 0 and Week 16 of this study (see Table 5).

7.2. Treatment Administration and Schedule

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 2:1 to receive either apremilast or placebo treatment, using a centralized IRT. Randomization to apremilast arm or placebo arm will be stratified by baseline age group (6 to 11 years or 12 to 17 years). Subjects with baseline weight between 20 kg to < 50 kg will receive apremilast 20 mg BID or placebo BID and subjects with baseline weight ≥ 50 kg will receive apremilast 30 mg BID or placebo BID.

During Week 0 visit, subjects will be dispensed dose titration blister cards with 10, 20, and 30 mg apremilast tablets, depending on baseline weight, or identically appearing placebo tablets. The blister cards will contain all IP required for 4 weeks of treatment, and the titration supplies or matching placebo are in the 1st week (see Table 5 Treatment Schema for Dose Titration at Visit 2 [Week 0]). Investigational product will be administered as indicated below:

- Weeks 0 to 16: Placebo-controlled Treatment Phase: Apremilast 20 mg BID, Apremilast 30 mg BID or placebo BID.
  - Week 0: subjects will be dose titrated as described in Table 5.
- Weeks 16 to 52: Apremilast Extension Phase: Apremilast 20 mg BID and apremilast 30 mg BID.
  - Week 16: subjects will be dose titrated as described in Table 6.

Table 5: Treatment Schema for Dose Titration at Visit 2 (Week 0)

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

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

At Week 16, subjects who were originally randomized to placebo at Week 0 will be switched to receive apremilast treatment, where dose levels (either 20 mg BID or 30 mg BID) would have been determined at Week 0 using their baseline weight categories (20 kg to < 50 kg, or ≥ 50 kg). Subjects randomized to the apremilast arm at Week 0 will remain on their assigned apremilast dose levels (either 20 mg BID or 30 mg BID).

During Weeks 16 to 52, study investigators and study subjects will remain blinded to the initial IP assignments. To maintain the blind, all subjects will receive dose titration cards at the Week 16 visit. Although only subjects initially randomized to placebo will be dose titrated during their first week of the Apremilast Extension Phase, all subjects entering the Apremilast Extension Phase will receive identically-appearing titration/treatment cards. The treatment schema for dose titration at Week 16 is shown in the tables below.

Table 6: Treatment Schema for Dose Titration at Visit 7 (Week 16)

	Week 16											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6-7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Apremilast 30 mg BID	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	20 mg P 30 mg A	20 mg P 30 mg A	20 mg P 30 mg A	20 mg P 30 mg A	30 mg A	30 mg A
Apremilast 20 mg BID	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	10 mg P 20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A
Placebo to Apremilast 30 mg BID	10 mg A 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg P 20 mg A 30 mg P	20 mg A 30 mg P	20 mg A 30 mg P	20 mg A 30 mg P	20 mg P 30 mg A	30 mg A	30 mg A
Placebo to Apremilast 20 mg BID	10 mg A 20 mg P	10 mg P 20 mg P	10 mg A 20 mg P	10 mg A 20 mg P	10 mg A 20 mg P	10 mg P 20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A	20 mg A

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

Investigational product will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To reduce potential gastrointestinal (GI) symptoms, dose titration will be implemented in this study (Table 5 and Table 6). Apremilast dose titration will be provided in blister cards as 10, 20, and 30 mg tablets or identically appearing placebo tablets. Blister card configurations are pictured in Appendix M. The Apremilast Extension Phase begins with a titration period where IP will be supplied in blister cards. After completion of the Apremilast Extension Phase titration period, IP will be distributed in bottles containing 20 or 30 mg tablets for the remainder of the study.

7.3. Overdose

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

Overdose for this protocol, on a per dose basis, is defined as ingestion of greater than 100 mg of apremilast (or matching placebo) tablets in any 24-hour period whether by accident or intentionally. On a schedule or frequency basis, an overdose is defined as dosing more than 4 times during any 24-hour period.

7.4. Method of Treatment Assignment

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized to receive either apremilast or placebo (2:1), using a centralized interactive response technology (IRT). Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to enter the IRT to randomize subjects.

The system will present a menu of questions by which the research center personnel will identify the subject and IRT will assign a randomization identification number.

Confirmation of the randomization will be sent to the investigational site, Amgen, and/or its representative. The confirmation reports should be maintained as source documents.

During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization number assigned by the IRT.

7.5. Packaging and Labeling

The label(s) for IP may include, but may not be limited to, Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.6. Investigational Product Accountability and Disposal

The Investigator(s) or 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 designee(s), will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and record the information in the IRT.

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 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.

Amgen (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 Amgen (or designee).

7.7. 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 Amgen'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 blister cards and bottles, 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 four or more consecutive days of dosing, Amgen 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 Amgen. Overall compliance with the study treatment regimen is defined as taking between 75% and 120% of the expected doses during a subject's participation while in the treatment phases (Placebo-controlled Treatment Phase and Apremilast Extension Phase) of the study.

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.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

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

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

8.1. Permitted Concomitant Medications and Procedures

Subjects may take any medication that is not restricted by the protocol, 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 36-week Apremilast Extension Phase.

All medications (prescription and non-prescription), treatments and therapies taken by the subject from Screening throughout the Placebo-controlled Treatment Phase and Apremilast Extension Phase and the 4-, 8-, and 14-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.
- An unmedicated skin moisturizer (eg, Eucerin®) will also be permitted for body lesions only

* Subjects should not use these topical treatments within 24 hours of a study visit.

From Week 8 through Week 16, subjects who meet the criteria for early escape (PASI increase ≥ 50% from baseline) will be allowed to commence treatment with moderate-to-high potency topical steroid preparations and continue receiving IP.

At Week 32, subjects who did not achieve a 50% improvement in psoriasis area severity index (PASI-50) from baseline, can add topical standard of care therapy and continue to receive apremilast.

8.2. 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.

- 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, guselkumab, tildrakizumab, ixekizumab, brodalumab, or ustekinumab
- Use of tanning booths or other ultraviolet light sources
- Use of an investigational drug

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

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 3, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of apremilast (CC-10004) in pediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis. Integrated Response Technology (IRT) will be utilized to ensure a central randomization based on a parallel permuted block randomization scheme. Randomization to the apremilast arm or the placebo arm will be stratified by age group (6 to 11 years or 12 to 17 years), with a minimum of 75 subjects for each age group. Subjects randomized to apremilast will receive weight-based apremilast dose which will provide comparable exposure to the adult subjects treated with 30 mg BID. Therefore, the apremilast arm will include both 20 mg BID and 30 mg BID for the statistical analysis.

9.2. Study Population Definitions

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

The intent-to-treat (ITT) population will consist of all subjects who are randomized regardless of whether or not the subject received IP. Subjects will be included in the treatment group to which they are randomized.

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

9.3. Sample Size and Power Considerations

At least **230** pediatric subjects (ages from 6 through 17 years) will be randomized to receive either apremilast or placebo (2:1) at Week 0. The sample size estimation is based on the results of the adult Phase 3 and 3b studies with apremilast (CC-10004-PSOR-008, CC-10004-PSOR-009 and CC-10004-PSOR-010) which demonstrated positive treatment effects between apremilast and placebo in the proportion of subjects achieving sPGA response and PASI-75 response at Week 16.

With a total of **230** patients and a randomization ratio of 2:1, the study will have **90**% power to detect a 15% difference (20% versus 5%) between apremilast arm and placebo arm for the proportion of subjects achieving sPGA response at Week 16, based on a Chi-square test at a two-sided significance level of 0.05. The study will **also** have **more than 95**% power to detect a 20% difference (30% versus 10%) between apremilast and placebo for the proportion of subjects achieving PASI-75 response at Week 16.

9.4. Background and Demographic Characteristics

Subject's age, height (as measured with stadiometer), weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency

tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for the Placebo-controlled Treatment Phase (Weeks 0 to 16) and the Apremilast Extension Phase (Weeks 16 to 52). A summary of subjects enrolled by site will be provided. Protocol deviations and important protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

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

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

9.6.1.1. Primary Efficacy Endpoint

The primary endpoint is the proportions of subjects achieving sPGA response at Week 16 (defined as sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16). The estimand of primary interest is defined in terms of the following four attributes:

A. The population is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval (eg, ITT Population);

B. The variable is the proportion of subjects who achieve sPGA response at Week 16. Subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 will be assigned as non-responders.

C. Potential intercurrent events are captured through the variable definition (B).

D. The summary measure is the difference in response proportions.

Missing values at Week 16 for this estimand will be imputed using the multiple imputation (MI) method (SAS Institute Inc, 2011) based on similar subjects who remained in the study as the primary method. With this missing data handling approach, the estimand answers a clinically relevant question that compares the number of subjects who achieve the defined response criteria at Week 16 in the ITT population.

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

Sensitivity analysis will be conducted to account for missing data using the last observation carried forward (LOCF) method, the non-responder imputation (NRI) method and the tipping point analyses. A sensitivity analysis using the PP population will also be performed.

For the multiple imputation method, the SAS procedure MI will be used to impute missing sPGA scores at the scheduled analysis visits in the Placebo-controlled Treatment Phase (Weeks 0 to 16) to create M=25 complete data sets. The sPGA assessment data will not be included in multiple imputation steps from subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16. The missing data patterns will be checked at the scheduled analysis visits, ie, Baseline (Week 0), and Weeks 2, 4, 8, 12 and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used with a single chain to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary. The seed will be set to 17813721. The imputed scores will be rounded to the nearest integer. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest sPGA scores.

In the second step, the predictive mean matching method will be used to impute the remaining missing scores for the 25 data sets with monotone missing patterns. The imputation procedure will use monotone statement to create one complete data set for each of the monotone data set from the first step, and the variables will include treatment arm, stratification factor, and sPGA scores at scheduled analysis visits from Baseline to Week 16. The seed will be set to 55218163.

After the completion of imputation, sPGA response at Week 16 will be derived based on both observed and imputed scores. Data from subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 as non-responders will be added to the 25 imputed data sets. The same CMH method will be used to analyze the 25 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences. This study is a multicenter study and planned to have more than 100 study sites to enroll at least **230** subjects. A single site may not have a sufficient number of subjects to allow a meaningful within-site analysis; therefore, study sites will be pooled for the analysis. The primary endpoint will be further analyzed adjusting for the stratification factor and the pooled site and examining whether the treatment differences are consistent with those from the primary analysis. In addition, the consistency of the treatment effect across individual study sites (or pooled sites) will also be assessed by performing a subgroup-type analysis with individual study sites (or pooled sites) treated as subgroups. Listings of response rates will be provided by individual study site and by pooled site. The treatment difference for each of the individual study sites (or pooled sites) will be reviewed to evaluate the effect among the individual study sites (or pooled sites).

9.6.1.2. Major Secondary Efficacy Endpoint

The major secondary efficacy endpoint is the proportions of subjects who achieving PASI-75 response at Week 16 (defined as at least a 75% reduction in total PASI score from baseline at

Week 16), which will be analyzed using the same approaches as the primary endpoint. The estimand of primary interest is defined in terms of the following four attributes:

A. The population is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval (eg, ITT Population);

B. The variable is the proportion of subjects who achieving PASI-75 response at Week 16. Subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 will be assigned as non-responders.

C. Potential intercurrent events are captured through the variable definition (B).

D. The summary measure is the difference in response proportions.

Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc, 2011) based on similar subjects who remained in the study. With this missing data handling approach, the estimand answers a clinically relevant question that compares the number of subjects who achieve the defined response criteria at Week 16 in the ITT population

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

Sensitivity analysis will be conducted to account for missing data using the last observation carried forward (LOCF) method, the NRI method, and tipping point analyses. A sensitivity analysis using the PP population will also be performed.

For using the multiple imputation method, the SAS procedure MI will be used to impute missing total PASI scores at the scheduled analysis visits in the Placebo-controlled Treatment Phase (Weeks 0-16) to create M=25 complete data sets. The PASI assessment data will not be included in multiple imputation steps from subjects who terminate early due to lack of efficacy or who added moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16. The missing data patterns will be checked at the scheduled analysis visits, ie, Baseline (Week 0), and Weeks 2, 4, 8, 12 and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the MCMC method will be used to impute missing scores by treatment and stratification factor to create M=25 imputed data sets with monotone missing patterns. In case there are convergence issues, a simple model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor in imputation model if necessary. The minimum and the maximum values for imputation will be 0 and 72, which correspond to the lowest and the highest total PASI scores. The seed will be set to 17813721 and a single chain will be used to produce imputations. The imputed scores will be rounded to numbers with one digit.

In the second step, the predictive mean matching method will be used to impute the remaining missing scores for the 25 data sets with monotone missing patterns. The imputation procedure will use monotone statement to create one complete data set for each of the monotone data set

from the first step, and the variables will include treatment arm, stratification factor, and total PASI scores at scheduled analysis visits from baseline to Week 16. The seed will be set to 55218163.

After the completion of imputation, PASI-75 response at Week 16 will be derived based on both observed and imputed scores. Data from subjects who early terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 as non-responders will be added to the 25 imputed data sets. The same CMH method will be used to analyze the 25 complete data sets and the SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

The major secondary endpoint will also be further analyzed adjusting for the stratification factor and the pooled site and examining whether the treatment differences are consistent with those from the primary analysis. In addition, the consistency of the treatment effect across individual study sites (or pooled sites) will also be assessed by performing a subgroup-type analysis with individual study sites (or pooled sites) treated as subgroups. Listings of response rates will be provided by individual study site and by pooled site. The treatment difference for each of the individual study sites (or pooled sites) will be reviewed to evaluate the effect among the individual study sites (or pooled sites).

9.6.1.3. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints will be analyzed similarly as the primary and the secondary endpoints. The main analysis will be based on the ITT population with missing values imputed using multiple imputation methods. The 2-sided p-values and 2-sided 95% CIs will be reported for treatment difference between apremilast and placebo arms.

The binary endpoint (PASI-50, CDLQI [0/1] response) will be analyzed similarly as the primary endpoint. The treatment difference between apremilast arm and placebo arm will be compared using CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization. The 2-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided. Subjects who terminate early due to lack of efficacy or add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16 will be considered non-responders. Missing values will be imputed using the similar MI method as the primary and major secondary endpoints, with sensitivity analysis using the LOCF method and NRI method.

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

will estimate treatment effect without additional psoriasis medications, ie, data from assessments after adding those medications will be removed before using MI method for subjects who add moderate-to-high potency topical steroid preparations (early escape) or other protocol prohibited medications prior to Week 16. A sensitivity analysis will be performed with all available data using MI method regardless whether subjects add moderate-to-high potency topical steroid preparations (early escape) or any protocol prohibited medications prior to Week 16.

9.6.1.4. Multiplicity Adjustment

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

- Proportions of subjects who achieve sPGA response at Week 16 (defined as sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16)
- Proportion of subjects who achieve PASI-75 response at Week 16 (defined as at least a 75% reduction in total PASI score from baseline at Week 16)

For the other secondary efficacy endpoints, multiplicity adjustment will not be applied and statistical significance will not be claimed.

9.6.1.5. Exploratory Endpoints

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

9.6.1.6. Subgroup Analysis

Subgroup analyses for sPGA and PASI-75 responses at Week 16 based upon baseline demographic (age, gender, race, etc.) or baseline disease characteristics will be provided to determine the robustness of the treatment effect. These two endpoints will also be evaluated in patients using or not using low potency topical corticosteroids in the phase as two subgroups.

9.6.2. Efficacy Evaluation – Apremilast Extension Phase (Weeks 16 to 52)

Efficacy endpoints for time points in the Apremilast Extension Phase (Weeks 16 to 52) will be summarized for subjects who continue apremilast treatment or who switch to apremilast from placebo according to the treatment arms assigned at randomization. For all subjects, changes in measurements will be calculated relative to measurements obtained at Baseline (Week 0). Descriptive summary statistics or proportion of subjects achieving specified criteria will be summarized by treatment group. For continuous variables, descriptive statistics for baseline and

changes or percent changes from baseline will be provided. Categorical variables will be summarized with frequency tabulations. Two-sided 95% CIs will be provided for changes or percent changes and response rates.

9.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 9.2. Safety will be assessed by clinical review of all relevant parameters, including treatment-emergent adverse events (TEAEs), laboratory tests, and vital signs; no inferential testing for statistical significance will be performed. Data from safety assessments will be summarized descriptively for the Placebo-controlled Treatment Phase (Weeks 0 to 16) and the Apremilast Exposure Period when subjects receive apremilast treatment. For safety analyses in the Placebo-controlled Treatment Phase, baseline will be relative to the first dose date following randomization at Week 0. For safety analyses in Apremilast Exposure Period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the Apremilast Extension Phase.

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

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

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

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

9.8. Interim Analysis

No interim analysis will be conducted.

After all subjects have completed Week 16 (Visit 7), or discontinued from the study, a Week 16 database lock will be performed; the primary data analysis will be conducted and a Week 16 Clinical Study Report will be generated. Study investigators and subjects will remain blinded to treatment assignments until the final database lock at the conclusion of the study. At the end of the study, after all subjects have either completed the Observational Follow-up Phase or have been discontinued from the Apremilast Extension Phase (Weeks 16 to 52) or the Observational Follow-up Phase, the final analysis will be performed and a final Clinical Study Report will be generated.

9.9. Other Topics

9.9.1. 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 clinical trialists and one independent external biostatistician for whom there is no identified conflict of interest. The DMC will meet as outlined in the DMC charter. 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.

9.9.2. Scientific Steering Committee

Guidance in protocol development and interpretation of data analysis will be provided by a Scientific Steering Committee (SSC). The SSC will serve in an advisory capacity to the Sponsor. Details for the SSC are pre-specified in a SSC charter.

[redacted]

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

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

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE/SAE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on the AE/SAE CRF and the paper SAE report form. The overdose resulting in the SAE should not be reported as an SAE itself.

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

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

All AEs will be recorded by the Investigator from the time the subject's legal guardian signs informed consent until 98 days (14 weeks) after the last dose of IP for those subjects that early terminate or choose not to enroll in the Long-term Study. All SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study will also be reported for these subjects. Subjects entering the Long-term Study will not complete the 14-week follow up period and therefore will report any AE or SAE occurring after Visit 16 in the Long-term Study CRF. AEs and SAEs for either study will be recorded on the AE/SAE page of the CRF, the paper SAE report form and in the subject's source documents associated with that particular study.

All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event using the paper Serious Adverse Event Report Form by facsimile/email of the paper SAER Form directly to Amgen Global Patient Safety.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

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

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

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

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

If an AE is considered serious, the AE/SAE page/screen of the eCRF must be completed in EDC and the paper SAE report form.

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

10.2.2. Severity/Intensity

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

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

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

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

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

10.2.4. Duration

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

10.2.5. Action Taken

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

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

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

10.3. Abnormal Laboratory Values

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

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

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

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

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

10.4. Pregnancy

All pregnancies or suspected pregnancies are immediately reportable events.

10.4.1. Females of Childbearing Potential – Collection of Pregnancy Information:

Pregnancies and suspected pregnancies (including elevated β-subunit of chorionic gonadotropin [βhCG] or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Global Patient Safety immediately by facsimile, email or other appropriate method, using the Pregnancy Notification Form or approved equivalent form (refer to Appendix O). The Pregnancy Notification Form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking IP through 28 days of the subject's last dose of IP. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted 12 months after the birth of the child (if applicable).

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

The Investigator will follow the female subject until completion of the pregnancy and must notify Amgen Global Patient Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Amgen Global Patient Safety using the paper Serious Adverse Event Report Form within 24 hours of the Investigator's knowledge of the event.

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

10.4.2. Male Subjects With Partners Who Become Pregnant

In the event a male subject fathers a child during treatment, and for an additional 28 days after discontinuing IP, the information will be recorded on the Pregnancy Notification Form (refer to Appendix O). The form must be submitted to Amgen Global Patient Safety with 24 hours of the investigator's/site's awareness of the pregnancy (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

10.4.3. Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking IP through 28 days post last dose of IP.
- Information will be recorded on the Lactation Notification Form (refer to Appendix P) and submitted by facsimile or email to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking IP through 28 days after discontinuing IP.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of the AE/SAE page/screen of the eCRF and the completion of the paper Serious Adverse Event Report Form (refer to Appendix N). All SAEs must be reported to Amgen Global Patient Safety by facsimile or email via the paper Serious Adverse Event Report form within 24 hours of the Investigator's

knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the legal guardian signs informed consent and subject signs assent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time following the protocol-required reporting period or after end of study. Serious adverse events occurring prior to treatment (after signing the ICF/assent) will be collected/recorded/reported.

Any follow-up data to the existing SAE should be resubmitted to Amgen Global Patient Safety.

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

Serious Adverse Event Reporting transmitted via paper Serious Adverse Event Report Form:

- Facsimile transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information. If facsimile is unavailable, the email method to transmit this information is acceptable (refer to Appendix N).
- In rare circumstances and in the absence of facsimile equipment, this form may be sent via email, or notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form in English language sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting timeframes.
- Once the study has ended, serious adverse events (regardless of causality) should be reported to Amgen Global Patient Safety if the investigator becomes aware of them and may use the paper Serious Adverse Event Report Form (refer to Appendix N).

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Amgen Global Patient Safety to the site via Amgen's safety query paper process**,**or other appropriate method.

10.6. Expedited Reporting of Adverse Events

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

In the US, 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 (EEA), Amgen or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (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.

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

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

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

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

Amgen Global Patient Safety Contact Information (fax/email):

For Amgen Global Patient Safety contact information, please refer to your site's paper Serious Adverse Event Report Form, paper Pregnancy Notification Form and/or paper Lactation Notification Form (Appendix N, Appendix O, Appendix P*)*.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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 8.1) 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 lack of efficacy. 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. Any subject whose calculated BMI falls below the 5th percentile on the CDC growth chart (CDC, 2000) at any visit will be discontinued from the study.

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

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

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

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

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

11.2. Study Discontinuation

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

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

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

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should use their medical judgement to provide appropriate medical care of clinical trial subjects. The Investigator may also 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, the Investigator may also contact the Amgen Medical Information number at 1-800-77-AMGEN (1-800-772-6436). The representatives are responsible for obtaining your call-back information and contacting the on-call Amgen/contract research organization Medical Monitor, who will then contact you promptly.

12.2. Emergency Identification of Investigational Products

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

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

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

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

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

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

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Amgen staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff. The specific study-appropriate qualifications of each investigator are assessed during the site feasibility and selection process.

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 Amgen 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 complete the informed consent/assent process and are screened for entry into the study. Subjects who fail Screening must have the reason(s) recorded in the subject's source documents.

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

The information contained in the protocol and amendments (with the exception of the information provided by Amgen on public registry websites) is considered Amgen confidential information. Only information that is previously disclosed by Amgen on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Amgen 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 Amgen. Information proposed for posting on the Investigator's or their institution's website must be submitted to Amgen 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, Amgen 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 legal guardian as agreed by the subject.

13.3. Subject Information and Informed Consent

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 (assent), subject's legal guardian (ICF), and by the person facilitating the process (assent and ICF), 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.

13.4. Confidentiality

Amgen 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). Amgen requires the Investigator to permit Amgen'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 signed ICF and assent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

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

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

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

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

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

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

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

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

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

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

13.8. Termination of the Study

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

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

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Amgen 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.

14.3. Record Retention

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

- Signed legal guardian ICFs and assents 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, Amgen, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Amgen 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 Amgen prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Amgen for permission to make alternative arrangements. Details of these arrangements should be documented.

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

15.1. Study Monitoring and Source Data Verification

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

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

15.2. Audits and Inspections

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

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, 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 Amgen immediately.

15.3. Product Complaint

A product complaint (PC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product or device after they are released for distribution to market or clinic by either Amgen or by distributors, and partners with whom Amgen manufactures the material. This includes any drugs, devices, or combination products provisioned and/or repackaged/modified by Amgen. Drugs or devices include investigational

product. Any product complaints associated with an investigational products, or non-investigational products or devices supplied by Amgen are to be reported according to the instructions provided in the Investigational Product Instruction Manual or equivalent.

If you become aware of a suspected PC, you are obligated to report the issue within 24 hours of discovery or notification of the concern or irregularity. Amgen requires notification of any concern or irregularity at any stage of the study.

How to Report a Product Complaint to Amgen

- Complete Amgen's paper Clinical Product Complaint Intake Form and email the form to the following Amgen email address: Clinical-Complaint-Intake@amgen.com

16. PUBLICATIONS

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

Amgen will ensure Amgen-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 authorship will be in alignment with ICMJE authorship criteria and be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis and contribution to abstract, presentation and/or publication development.

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance (model)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
AUC_{ss}	Area under the curve steady state
AUCtau	Area under the curve dosing interval
β-hCG	β-subunit of human chorionic gonadotropin
BID	Twice Daily
BMI	Body Mass Index
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CDC	Centers for Disease Control
CDLQI	Children's Dermatological Life Quality Index
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
C_{max}	Peak observed plasma concentration of drug
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
DCR	Disease control rate
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EDC	Electronic Data Capture
EEA	European Economic Area
EU	European Union
EOT	End of treatment
FCBP	Female of Childbearing Potential
FDA	Food and Drug Administration
FDLQI	Family Dermatological Life Quality Index
GCP	Good Clinical Practice
GI	Gastrointestinal
GM	Geometric Mean
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IL	Interleukin
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Integrated Response Technology
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LS	Least Square
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NRI	Non-responder Imputation
NRS	Numeric Rating Scale
PASI	Psoriasis Area Severity Index
PASI-50	50% reduction in Psoriasis Area Severity Index

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PASI-75	75% reduction in Psoriasis Area Severity Index
PCQ	Product Complaint
PDE4	Phosphodiesterase type 4
PD	Pharmacodynamic
PG	Pharmacogenomic
PK	Pharmacokinetics
PP	Per protocol
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SOP	Standard operating procedure
sPGA	Static Physician Global Assessment
sPGA-G	Static Physician Global Assessment-Genitalia
SSC	Scientific Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Event
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor-α
ULN	Upper limit of normal
US	United States (of America)
UVB	Ultraviolet B
WBC	White blood cell count
WHO	World Health Organization

Appendix B: 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 C: Psoriasis Area Severity Index (PASI)

Psoriasis Area and Severity Index (PASI)

* Round all calculations to 1 decimal place

STEP A. Please write in the appropriate number for rows 1 - 3 using the scale below:

0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe

	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
1. Erythema				
2. Thickness				
3. Scaling				
4. TOTAL Each Column				

STEP B. Enter the number of hands the psoriasis covers on each body area

	HEAD	TRUNK	UPPER LIMBS	LOWER LIMBS
5. Number of Hands				
6. Area (% of total BSA)	10	30	20	40

STEP C. Calculate % of involvement:

7. % of each region involved [**(Row 5 ÷ Row 6) x 100*]**				
8. TOTAL BSA (sum of # of hands from row 5)				

STEP D. Select Degree of Involvement using value in Row 7:

0 = No involvement

1 = <10%

2 = 10 < 30%

3 = 30 < 50%

4 = 50 < 70% 5 = 70 < 90% 6 = 90 < 100%				
9. Degree of Involvement (0-6) of each region				
STEP E. Calculate PASI (Row 4 x Row 6 x Row 9) ÷ 100*				
10. PASI for each body region				
11. TOTAL PASI (sum of Row 10 subscores)				

Appendix D: Scalp Physician Global Assessment (ScPGA)

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

Appendix E: Modified Static Physician Global Assessment of Genitalia (sPGA-G)

Score	Category	Description
0	Clear	**Erythema:** no erythema (except for residual hyperpigmentation/hypopigmentation) **Plaque Elevation:** no elevation **Scaling** = no scale
1	Almost clear	**Erythema:** faint, light pink erythema **Plaque Elevation:** elevation is very slight and difficult to confirm **Scaling** = some fine, white surface dryness
2	Mild	**Erythema:** mild, pink erythema **Plaque Elevation:** slight elevation with sloped edges **Scaling** = fine scale on some or most lesions
3	Moderate	**Erythema:** moderate, red erythema **Plaque Elevation:** moderate elevation with definite edges that are either sloped or rough **Scaling** = course scale on most lesions
4	Severe	**Erythema:** severe, bright red or deep red erythema **Plaque Elevation:** substantial elevation, hard or sharp edges **Scaling** = course, non-adherent scale on most to all lesions

Adapted from source: Merola, 2017.

Appendix F: 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., 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 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* _____

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: **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** ☐ ☐
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 G: Stool Diary

DAILY STOOL DIARY

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

2. 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 H: Tanner Staging

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 I: Pharmacokinetic Sample Processing Instructions

PK Blood and Plasma Sample Labeling

Labels will contain, at minimum, the following information:

- Protocol No.: **CC-10004-PPSO-003**
- Subject ID number
- Nominal Time Point: eg, Week 4, Pre-dose or Week 8, Post-dose
- 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.

PK Blood Sample Collection for Apremilast

- Fill an ice bucket with a sufficient amount of wet ice to pre-chill all collection tubes before blood draw.
- Collect approximately 2 mL of whole blood into a pre-chilled **lithium heparin** tube. Blood can be collected via direct vein puncture or indwelling catheter.
- Accurately record the time of blood collection.
- Gently invert the tube 3 to 5 times and immediately immerse it into ice to prevent possible compound degradation.

PK 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 minutes at 4°C to obtain plasma.
  - Immediately record the time of sample entry into and out of the centrifuge.
- Transfer approximately 0.5 mL of plasma into each of the two pre-labeled, pre-chilled, **citric acid-containing polypropylene storage tubes** (one primary and one back-up).
- Gently invert the tube 3 to 5 times.

  Note: Amgen will provide these tubes.

  - Keep storage 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 –70°C freezer, where they will remain stored until shipping.
  - Immediately record the time of sample entry into the freezer.

PK Sample Shipment

- All PK sample label information on the storage tubes have to check against requisition form and then the samples must be shipped frozen and on dry ice to QPS.
- QPS must be contacted via email PRIOR TO shipping, and confirmation of receipt from QPS must be documented at the site.

Attn: [redacted]

QPS
Three Innovation Way; Suite 240
Newark, Delaware 19711
Office: [redacted]
Facsimile: [redacted]
Email: [redacted]

PK Sample Collection Documents to Accompany Shipment(s)

A copy of the completed shipment manifest must accompany the shipment, an electronic copy of the shipping manifest (EXCEL format preferred), and must list the following information at minimum:

- Sponsor name: Amgen Inc.
- Amgen Study Number: **CC-10004-PPSO-003**
- **Subject ID Numbers**
- Collection Date: **eg, 10 Oct 2018**
- Nominal collection time point for plasma samples: eg, Week 4, Pre-dose

Sample type (**eg, *primary* plasma** or ***back-up* plasma**)

Appendix J: The Children's Dermatology Life Quality Index (CDLQI)

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

1.	Over the last week, how **itchy**, "**scratchy**", **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out, playing,** or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time**? **OR** was it **holiday time**?	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your **enjoyment** of the **holiday**?	Prevented school ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐

Please check that you have answered EVERY question. Thank you.

Appendix K: Family Dermatology Life Quality Index (FDLQI)

- The questions relate to the impact of your relative/partner's skin disease on your quality of life over the last month.
- Please read the questions carefully and tick one box for each.

1. Over the last month how much emotional distress have you experienced due to your relative/partner's skin disease (e.g. worry, depression, embarrassment, frustration)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

2. Over the last month how much has your relative/partner's skin disease affected your physical well-being (e.g. tiredness, exhaustion, contribution to poor health, sleep/rest disturbance)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

3. Over the last month how much has your relative/partner's skin disease affected your personal relationships with him/her or with other people?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

4. Over the last month how much have you been having problems with other peoples' reactions due to your relative/partner's skin disease (e.g. bullying, staring, need to explain to others about his/her skin problem)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

Snip

5. Over the last month how much has your relative/partner's skin disease affected your social life (e.g. going out, visiting or inviting people, attending social gatherings)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

(Please turn over)

6. Over the last month how much has your relative/partner's skin disease affected your recreation/leisure activities (e.g. holidays, personal hobbies, gym, sports, swimming, watching TV)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

7. Over the last month how much time have you spent on looking after your relative/partner (e.g. putting on creams, giving medicines or looking after their skin)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

8. Over the last month how much extra house-work have you had to do because of your relative/partner's skin disease (e.g. cleaning, vacuuming, washing, cooking)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

9. Over the last month how much has your relative/partner's skin disease affected your job/study (e.g. need to take time off, not able to work, decrease in the number of hours worked, having problems with people at work)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

10. Over the last month how much has your relative/partner's skin disease increased your routine household expenditure (e.g. travel costs, buying special products, creams, cosmetics)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

Thank you for completing the questionnaire.

Appendix L: Modified Whole Body Itch Numeric Rating Scale (NRS)

Instruction: Please think about **your whole body** when answering the question below.

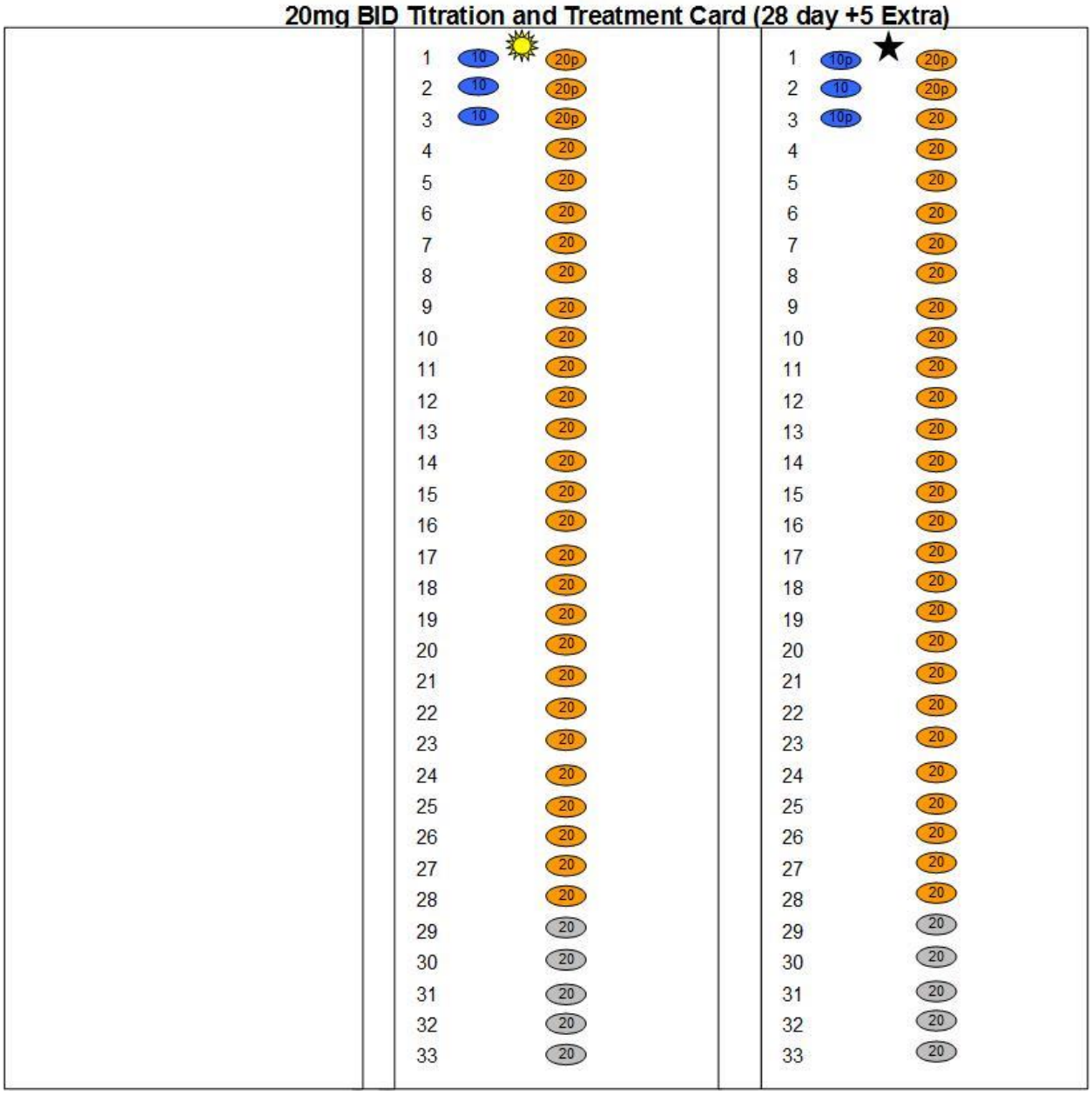
Please rate the itching severity due to your psoriasis by circling the number that best describes your worst level of itching in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

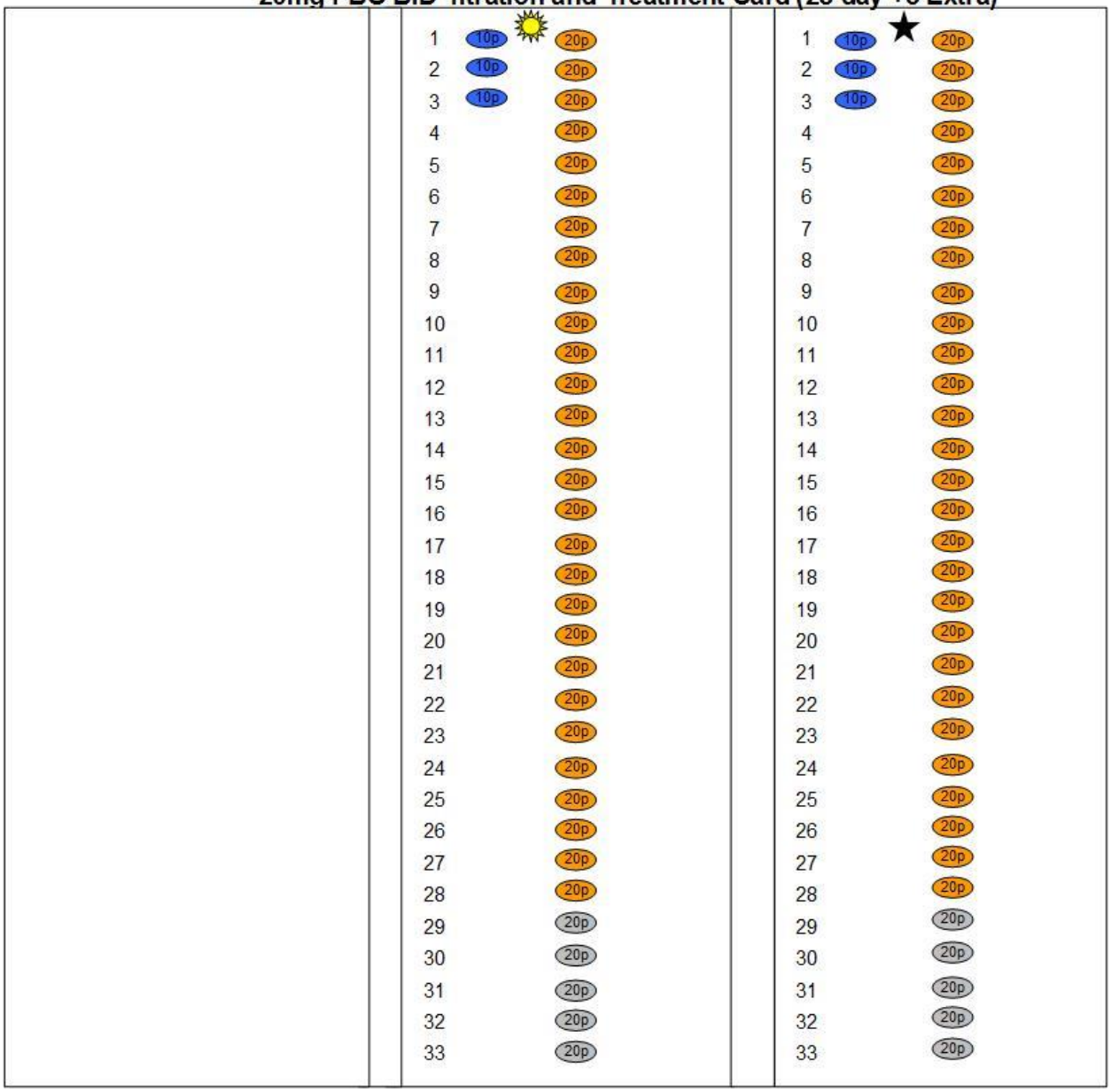
0 = No itching 10 = Worst itch imaginable

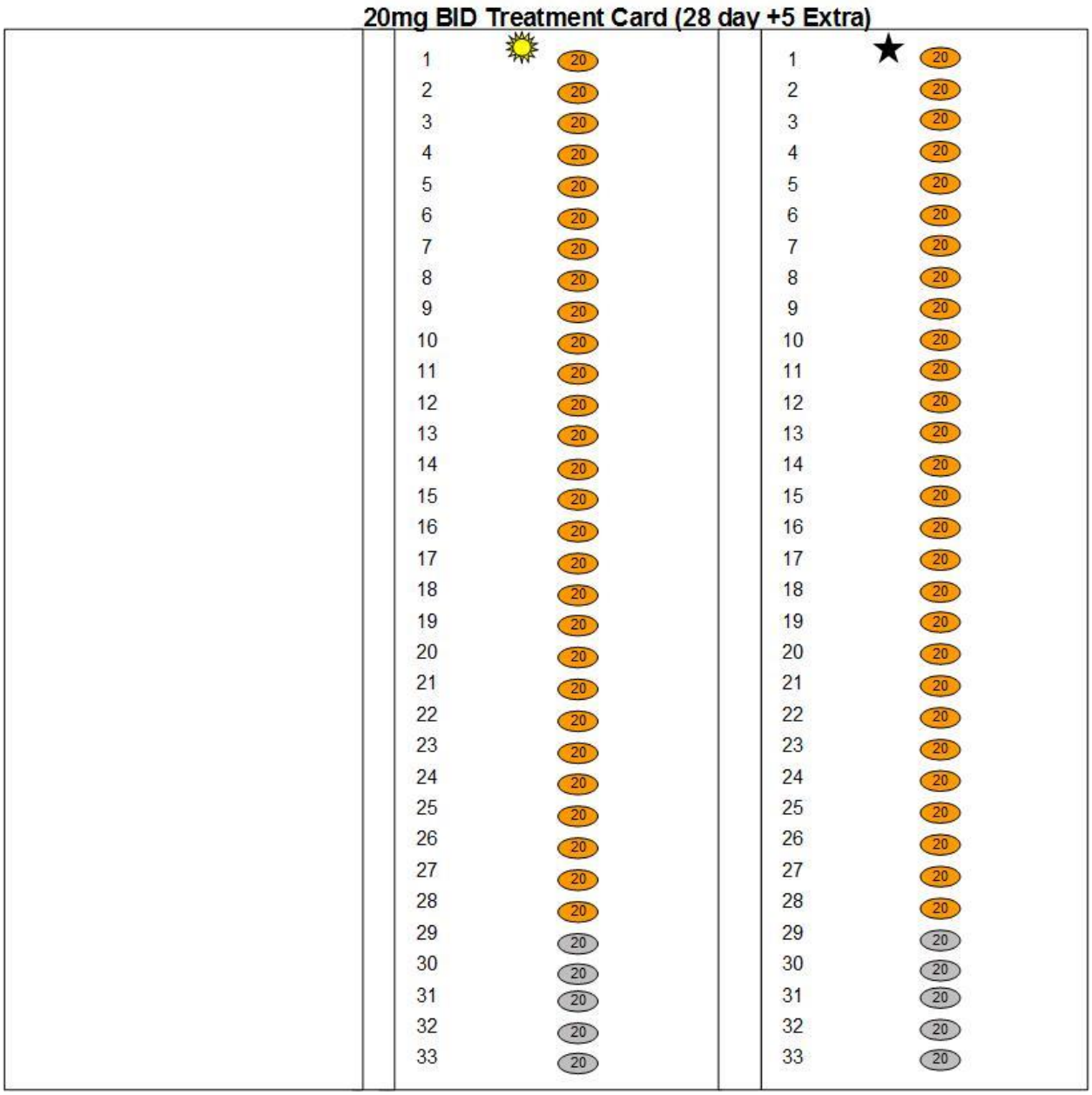
Naegeli, 2015.

Appendix M: Monthly Blister Card Configurations



20mg PBO BID Titration and Treatment Card (28 day +5 Extra)

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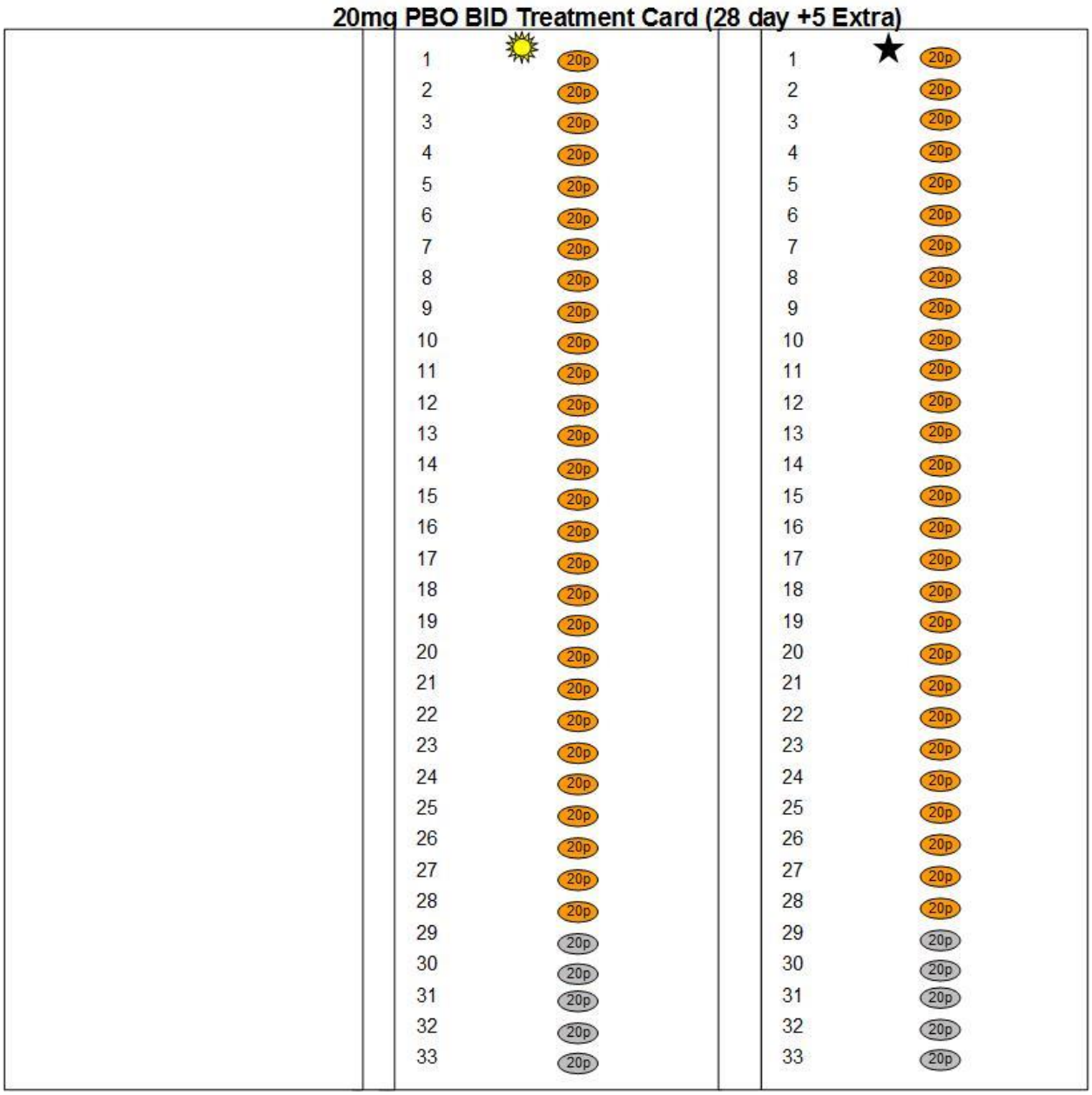
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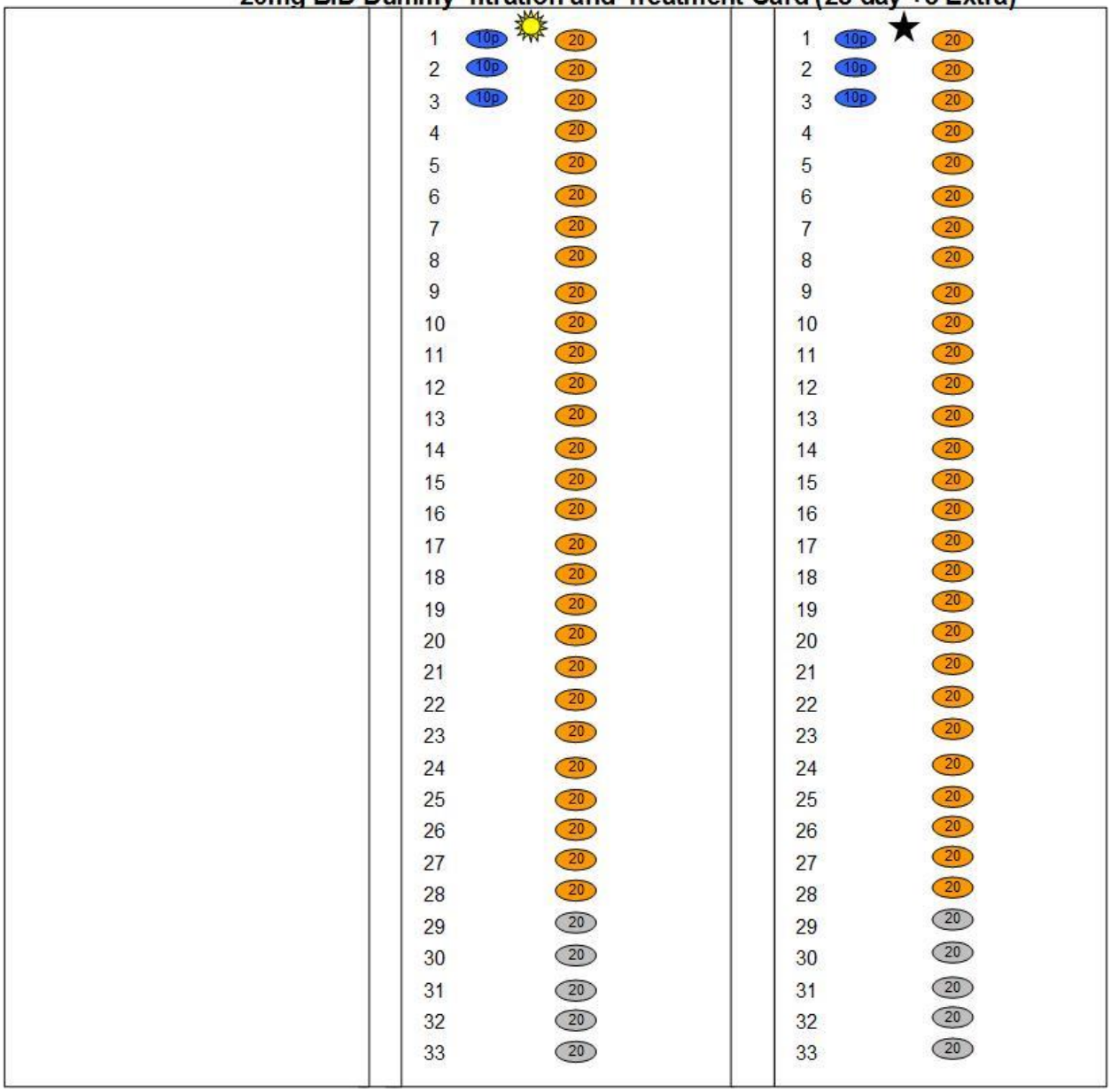

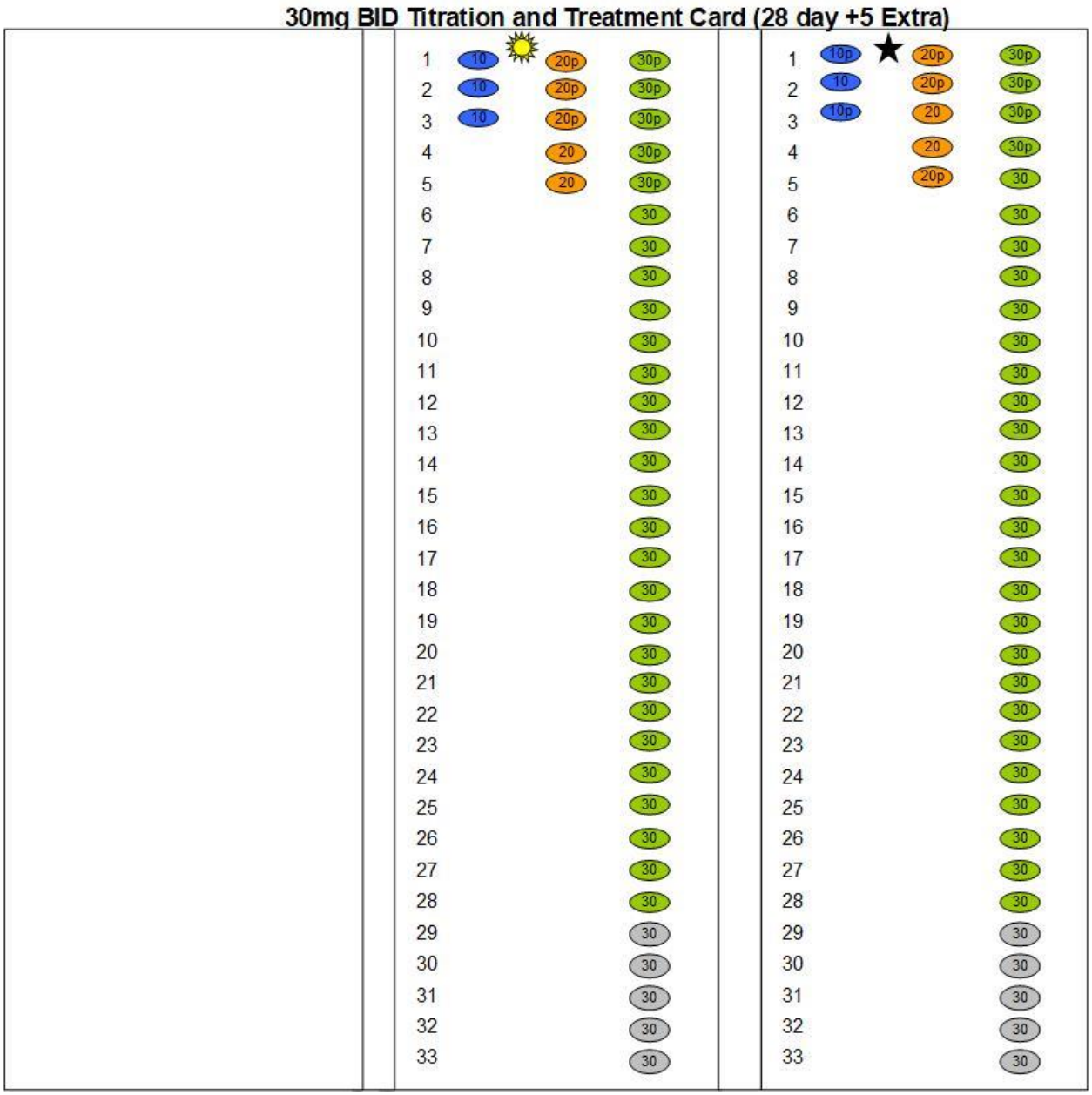
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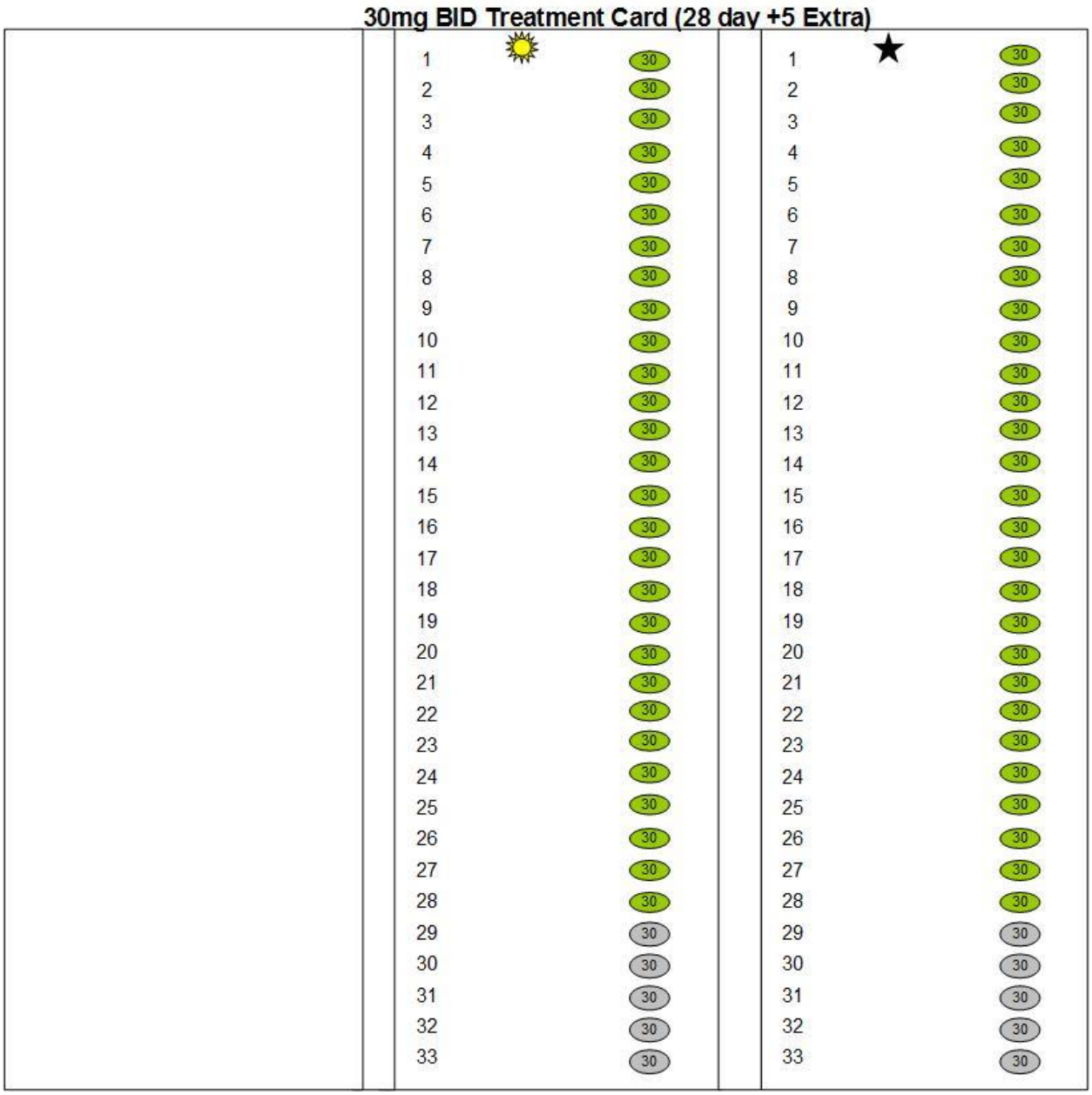
30mg Placebo Titration Card (28 day +5 Extra)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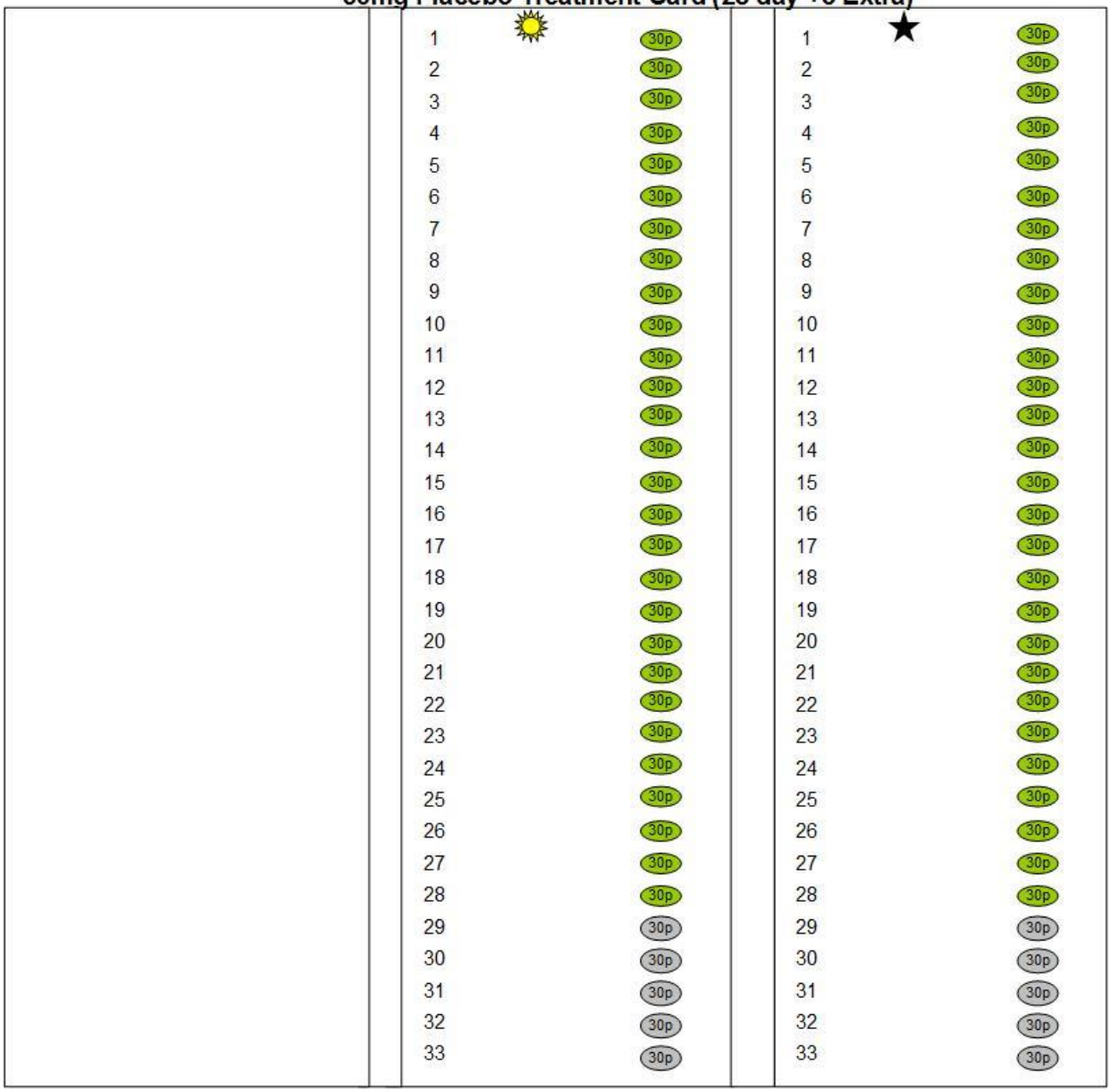

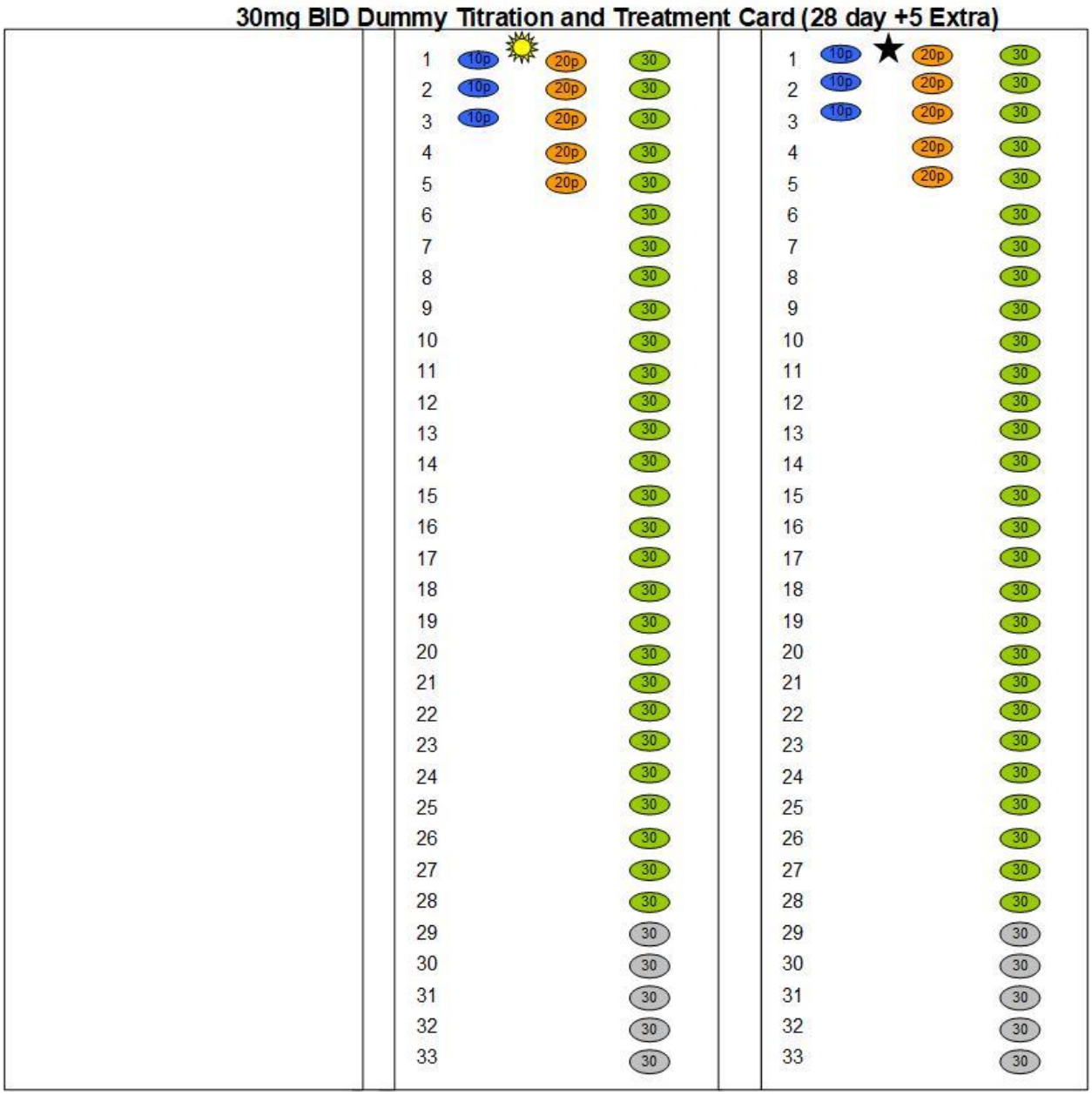
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Appendix N: Sample Serious Adverse Event Report Form

AMGEN CC-10004-PPS0-003 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

Please refer to your site's Serious Adverse Event Report Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		❑F ❑M		

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the AE/Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____Month___Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event co-curred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? If yes see section 10 Apremilast No ✓ Yes ✓	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life- threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Apremilast ☐ blinded ☐ open label							Lot #_____ ☐ Unknown Serial #_____ ☐ Unknown

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 02-April-2020*

Page 1 of 3

AMGEN CC-10004-PPSO-003 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	☐New ☐Follow-up

Site Number | Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Test												
Date Day Month Year	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN CC-10004-PPSO-003 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.		

Appendix O: Pregnancy Notification Form

AMGEN® Pregnancy Notification Form

Please refer to your site's Pregnancy Notification Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. Case Administrative Information

Protocol/Study Number: CC-10004-PPSO-003 (Apremilast/Otezla)

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (___)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Appendix P: Lactation Notification Form

AMGEN Lactation Notification Form

Please refer to your site's Lactation Notification Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. Case Administrative Information

Protocol/Study Number: CC-10004-PPSO-003 (Apremilast/Otezla)

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (_____)_____ Fax (_____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐Yes ☐No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Amendment 5

Protocol Title: A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

Sponsor Number: CC-10004-PPSO-003 (Apremilast 20200056)

EudraCT Number: 2018-002918-12

NCT Number: NCT03701763

Amendment Date: 17 December 2021

Rationale:

The purpose of this protocol amendment is to revert the study sample size from at least 180 randomized subjects to the original protocol goal of at least 230 randomized subjects. This change has been made based on the enrollment progress for the study and advice from the United States Food and Drug Administration.

The following modifications were made to the protocol:

- Updated sample size in the Synopsis, Section 3.1 Study Design, Section 4.1 Number of Subjects, Section 9.3 Sample Size and Power Considerations, and Section 9.6.1.1 Primary Efficacy Endpoint; and,
- Updated the power calculations based on the change in sample size in the Synopsis and Section 9.3 Sample Size and Power Considerations.

– SUMMARY OF CHANGES –

AMENDMENT NO. 04

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

INVESTIGATIONAL PRODUCT (IP):	CC-10004 (apremilast)
PROTOCOL NUMBER:	CC-10004-PPSO-003
ORIGINAL DATE:	15 Aug 2018
AMENDMENT No. 01 DATE:	12 Apr 2019
AMENDMENT No. 02 DATE:	23 Sep 2019
AMENDMENT No. 03 DATE:	01 May 2020
AMENDMENT No. 04 DATE:	26 Aug 2021
EudraCT NUMBER:	2018-002918-12
IND NUMBER:	070270
NCT NUMBER:	NCT03701763

Contact Information:

Name:	[redacted], MD
Title:	Associate Director, Clinical Research & Development
Address:	One Amgen Center Drive, Thousand Oaks, CA 91320
Phone:	[redacted]
E-mail:	[redacted]

Note: Only call Amgen Medical Information if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Amgen Medical Information: +1- 800-77-AMGEN (1-800-772-6436)

JUSTIFICATION FOR AMENDMENT

The purpose of this amendment is to reduce the study sample size from at least 230 subjects to at least 180 subjects. This sample size retains adequate power for the primary and key secondary endpoints while making the overall study more efficient.

The following changes were made to the protocol, dated 26 Aug 2021:

- Updated sample size in the Synopsis, Section 3.1 Study Design, Section 4.1 Number of Subjects, Section 9.3 Sample Size and Power Considerations, and Section 9.6.1.1 Primary Efficacy Endpoint
- Updated the power calculations based on the change in sample size in the Synopsis and Section 9.3 Sample Size and Power Calculations
- Added language in Section 10.5 Reporting of Serious Adverse Events to comply with an Amgen template update
- Deleted Celgene Therapeutic Area Head Signature Page to conform to the Amgen template
- Grammatical and typographical changes were made throughout the protocol.

– SUMMARY OF CHANGES –

AMENDMENT NO. 03

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

INVESTIGATIONAL PRODUCT (IP):	CC-10004 (apremilast)
PROTOCOL NUMBER:	CC-10004-PPSO-003
ORIGINAL DATE:	15 Aug 2018
AMENDMENT No. 01 DATE:	12 Apr 2019
AMENDMENT No. 02 DATE:	23 Sep 2019
AMENDMENT N0. 03 DATE:	01 May 2020
EudraCT NUMBER:	2018-002918-12
IND NUMBER:	070270
NCT NUMBER:	NCT03701763

Contact Information:

Name:	[redacted], MD
Title:	Associate Director, Clinical Research & Development
Address:	One Amgen Center Dr. Thousand Oaks, CA 91320
Phone:	[redacted]
E-mail:	[redacted]

Note: Only call Amgen Medical Information if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Amgen Medical Information: 1- 800-77-AMGEN (1-800-772-6436)

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted], MD – VP and Head of Immunology & Fibrosis Clinical Development
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable. NOTE: Signed by Celgene based on approval from Amgen Therapeutic Head, [redacted]

1. JUSTIFICATION FOR AMENDMENT

The purpose of this amendment is to update the change in Sponsor, as well as key contact and emergency information, and to update safety reporting and product complaints to align with Amgen processes.

Significant changes included in this amendment are summarized below:

- All references to "Celgene Corporation" were removed and replaced with "Amgen Inc." and "Celgene" changed to "Amgen" throughout the protocol.
- Cover Pages were updated with Amgen contact information
- Section 6 Procedures was updated to align with Amgen Global Drug Safety processes
- Section 10.1 Monitoring and Reporting of Adverse Events was updated to align with Amgen Global Drug Safety processes.
- Section 10.4 Pregnancy was modified according to the Amgen Global Drug Safety process:
    - Collection of Pregnancy Information and Infant Health Information
    - Collection of information: Male Subjects with Partners Who Become Pregnant
    - Collection of Lactation Information
- Section 10.5 Reporting of Serious Adverse Events was updated to include instructions for paper reporting of SAEs
- Section 12.1 Emergency Contact was updated with Amgen emergency contact information.
- Section 15.3 Product Complaint section was modified according to the Amgen product complaint reporting process

The amendment also includes addition of forms, minor clarifications and corrections to align with Amgen processes:

- Section 7.6 Investigational Product Accountability and Disposal
- Section 15.2 Audits and Inspections
- Section 16 Publications
- Appendix N Sample Serious Adverse Event Form was added
- Appendix O Pregnancy Notification Form was added
- Appendix P Lactation Notification Form was added

– SUMMARY OF CHANGES –

AMENDMENT NO. 2

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE- BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

INVESTIGATIONAL PRODUCT (IP):	**CC-10004 (apremilast)**
PROTOCOL NUMBER:	**CC-10004-PPSO-003**
ORIGINAL DATE:	**15 Aug 2018**
AMENDMENT No. 1 DATE:	**12 Apr 2019**
AMENDMENT No. 2 DATE	**23 Sep 2019**
EudraCT NUMBER:	**2018-002918-12**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], MD
Title:	Associate Director, Clinical Research & Development
Address:	86 Morris Avenue, Summit, NJ 07901
Phone:	[redacted]
E-mail:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 2 has been written to implement changes to the study for all participating sites. The intent of the amendment is to include descriptions of the redesigned packaging of investigational product (IP) as well as a statement that IP will be supplied during the Apremilast Extension Phase in a blister pack for the first month and then in bottles for the rest of the study.

Significant changes included in this amendment are summarized below:

1. Removed previous depictions of IP blister card packaging and replaced them with depictions of the redesigned versions.

The blister cards were redesigned to address the fact that extra pills included in the old design were superfluous and not needed to ensure protection of the blind.

Revised section: Appendix M

2. Added text that informs of switch from blister card supplied IP to bottles during the Apremilast Extension Phase and provided an updated text description of the redesigned blister cards.

Revised sections: Protocol Summary; Section 7 Description of Study Treatments

3. Revised platelet ranges for subject eligibility.

It was learned during the study that the upper limit of the allowable platelet range was unnecessarily too low and could be raised safely to more closely align with what is typically seen in this disease population.

Revised section: Section 4.2 Inclusion Criteria, Inclusion Criterion number 11

4. Removed pregnancies of partners of male subjects as an event that must be reported.

Safety has updated the standard safety language to remove pregnancies of male subjects as an event that must be reported and followed.

Revised section: Section 10.4 Pregnancy

– SUMMARY OF CHANGES –

AMENDMENT NO. 1

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS FROM 6 THROUGH 17 YEARS OF AGE WITH MODERATE TO SEVERE PLAQUE PSORIASIS

INVESTIGATIONAL PRODUCT (IP):	**CC-10004 (apremilast)**
PROTOCOL NUMBER:	**CC-10004-PPSO-003**
ORIGINAL DATE:	**15 Aug 2018**
AMENDMENT No. 1 DATE:	**12 Apr 2019**
EudraCT NUMBER:	**2018-002918-12**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], MD
Title:	Associate Director, Clinical Research & Development
Address:	86 Morris Avenue, Summit, NJ 07901
Phone:	[redacted]
E-mail:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted], MD – Vice President Clinical Research and Development
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 1 has been written to implement changes to the study for all participating sites. The intent of the amendment is to improve protocol clarity as well as address changes in response to requests from the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]).

Significant changes included in this amendment are summarized below:

1. **Added a new inclusion criterion for baseline minimum allowable body mass index (BMI)**

   The amendment adds a new Inclusion Criterion which provides a specific minimum for subject BMI in order to ensure that no underweight subjects are enrolled. The Otezla® Summary of Product Characteristics (SmPC) mentions "underweight" under special warnings and precautions for use; this new inclusion criterion will exclude underweight subjects from the study.

   Revised Section: Section 4.2 Inclusion Criterion #3

2. **Added a specific BMI parameter as a reason for mandatory subject withdrawal.**

   Loss of weight is a known adverse reaction with apremilast therapy. If any subject, while on treatment, experiences weight loss and their BMI falls below the defined threshold, the subject will be terminated from the study.

   Revised Section: Section 11.1 Treatment Discontinuation

3. **Revised hemoglobin ranges for subject eligibility**

   This was an update made to the allowable upper ranges of entrance hemoglobin values in response to feedback from an active study investigator. The higher limits of the hemoglobin ranges were considered to be too low, which would make enrollment of study subjects unnecessarily challenging. The inclusion hemoglobin ranges were reviewed by the Celgene safety physician (executive director) and new ranges were approved which are wider but still well within established normal ranges for this patient population.

Age (years)	Males (g/dL)	Females (g/dL)
6-11	10.0 – ~~13.5~~15.0	10.0 – ~~13.5~~15.0
12-18	11.0 – ~~14~~16.5	10.5 – ~~14.0~~15.5

   Revised Section: Section 4.2 Inclusion Criterion #11

4. **Added a NOTE under contraception Option 2 for females of childbearing potential (FCBP)**

   The double-barrier methods listed in contraception Option 2 are not considered highly effective methods of contraception in all European Union (EU) countries which follow the "*Recommendations related to contraception and pregnancy testing in clinical trials*" of the Clinical Trial Facilitation Group (CTFG). In these cases, only Option 1 should be utilized as an acceptable contraception method for females of childbearing potential (FCBP) subjects. To make this clear in the protocol, a note was added below Option 2 which states:

NOTE: *Option 2 may not be acceptable as a highly effective contraception option in all countries per local guidelines/regulations*.

Revised Section: Section 4.2 Inclusion Criterion #12

The amendment also includes other minor clarifications:

- Added a sentence to Section 13.2 Investigator Responsibilities in response to a BfArM comment, which confirmed selection of qualified investigators.
- Added a reference for the BMI chart to be used for determination of subject inclusion and possible study discontinuation to the list of References in Section 17:

  Centers for Disease Control (CDC) National Center for Health Statistics Clinical Growth Charts, Modified 2000: https://www.cdc.gov/growthcharts/clinical_charts.htm
- The reference to a Study Manual was removed from Section 6
- A clarification was added to the Table 3 footnotes, indicating that a urine pregnancy test would not be performed at Visit 3
- Added an attribution to Appendix E
- Added a reference to Section 17 in connection with the attribution added to Appendix E:

  Merola JF, Bleakman AP, Gottlieb AB, Menter A, Naegeli AN, Bissonnette R, et al. The static physician's global assessment of genitalia: a clinical outcome measure for the severity of genital psoriasis. J Drugs Dermatol. 2017;16(8):793-9.
- Added completion of the C-SSRS questionnaire to the Unscheduled Visit column in Section 5, Table 3 and Section 6.5.16.
- Added Centers for Disease Control (CDC) to the list of abbreviations (Appendix A)
- Added some text to Section 6.2 to clarify that efficacy assessments performed during the Treatment Period should be completed only after the subject has completed the whole body itch Numeric Rating Scale (NRS) and the health-related quality of life assessments
- Deleted text from Section 6.3.1 that referenced completion of the whole body itch NRS and the health-related quality of life assessments at the observational follow-up visits since these are not actually completed at these visits