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

PROTOCOL NUMBER:	**CC-10004-PSOR-025**
ORIGINAL DATE:	**31 Oct 2018**
AMENDMENT No. 1.0 DATE:	**22 May 2019**
AMENDMENT No. 2.0 DATE:	**01 May 2020**
AMENDMENT No. 3.0 DATE	**03 Mar 2021**
EudraCT NUMBER:	**2018-002608-15**
NCT NUMBER:	**NCT03777436**
IND NUMBER:	**070270**
SPONSOR NAME/ ADDRESS:	**Amgen Inc.** **One Amgen Drive** **Thousand Oaks, CA 91320**

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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, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Apremilast (CC-10004) in Subjects with Moderate to Severe Genital Psoriasis

Indication

The indication is moderate to severe genital psoriasis.

Objectives

Primary Objective

- To evaluate the clinical efficacy of oral apremilast 30 mg twice daily (BID), compared to placebo, in subjects with moderate to severe genital psoriasis during the 16-week Placebo-controlled Phase.

Secondary Objectives

- To evaluate the safety and tolerability of apremilast 30 mg BID, compared with placebo, in subjects with moderate to severe genital psoriasis
- To evaluate the effect of apremilast 30 mg BID compared with placebo on genital psoriasis symptoms
- To evaluate the effect of apremilast 30 mg BID compared with placebo on Health-related Quality of Life (HRQoL)

Study Design

This Phase 3, multicenter, randomized, placebo-controlled, double-blind study is designed to evaluate the efficacy and safety of apremilast (CC-10004) in subjects with moderate to severe genital psoriasis (modified Static Physician Global Assessment of Genitalia (sPGA-G) ≥ 3, moderate or severe).

Approximately **286** subjects will be enrolled and randomized 1:1 to receive either apremilast 30 mg BID or placebo for the first 16 weeks. Subjects will be randomized based on a permuted block randomization using a centralized Interactive Response Technology (IRT).

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

The study will consist of four phases:

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

  - Subjects will be randomly assigned in a 1:1 ratio to either apremilast 30 mg BID or placebo.

- Apremilast Extension Phase – Weeks 16 to 32
  - All subjects will be switched to (or continue to) receive apremilast 30 mg BID. All subjects will maintain this dosing through Week 32.
- Observational Follow-up Phase – 4 weeks
  - Four-week Post-Treatment Observational Follow-up Phase for all subjects who complete the study or discontinue the study prematurely.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 data restriction will be performed; the primary data analysis will be conducted and a Week 16 Clinical Study Report (CSR) will be generated. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Week 16 CSR. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

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

Study Population

Approximately **286** adult subjects ≥ 18 years of age with chronic moderate to severe genital psoriasis (modified sPGA-G ≥3 [moderate or severe]) will be randomized. Only subjects who are inadequately controlled with or intolerant of topical therapies for the treatment of genital psoriasis will be eligible for the study.

Length of Study

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

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

Study Treatments

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

From Weeks 0 to 16, subjects will be dispensed blister cards with 10, 20, or 30 mg apremilast tablets or identically appearing 10, 20, or 30 mg placebo tablets.

Investigational product will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. As in prior Phase 3 studies, dose titration will be implemented in order to mitigate potential gastrointestinal-related adverse events (AEs). During Week 0 (Days 1-7), subjects will be dispensed dose titration blister cards with 10, 20, and 30 mg

apremilast tablets or identically appearing placebo for the dose titration. Starting at Week 16, subjects originally randomized to apremilast will continue with apremilast. Subjects originally randomized to placebo at Week 0 will be switched to apremilast at Week 16. Dose titration blister cards will be used for subjects switching from placebo to apremilast; dummy titration blister cards (dosing at 30 mg BID directly) will be used for subjects initially randomized to receive apremilast 30 mg BID. Starting at the Week 20 Visit through Week 32, all subjects will receive open-label apremilast (APR) 30 mg BID tablets in high-density polyethylene (HDPE) bottles.

Dose modifications are not permitted in this study.

Overview of Key Efficacy Assessments

Primary Efficacy Assessment

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

Additional Efficacy Assessments

- Static Physician Global Assessment (sPGA)
- Body Surface Area (BSA)
- Genital Psoriasis Symptoms Scale (GPSS)
  - Genital Psoriasis Itch Numeric Rating Scale (GPI-NRS)
- Dermatology Life Quality Index (DLQI)

Overview of Key Safety Assessments

Safety assessments will include:

- Adverse events
- Vital signs
- Pregnancy tests for females of childbearing potential (FCBP)
- Clinical laboratory tests

Statistical Methods

[redacted]

It is assumed that modified sPGA-G response will be similar to historic sPGA response. With a total of approximately **286** subjects and a randomization ratio of 1:1, Study PSOR-025 will randomize approximately **143** subjects to apremilast (APR) 30 BID and **143** subjects to placebo. This sample size will provide **85%** power to detect a treatment difference of 15% at Week 16 (25% for APR 30 BID and 10% for placebo) for the primary endpoint using a chi-square test at a 2-sided significance level of 0.05 after adjusting for a 20% dropout rate.

The analyses of efficacy endpoints will be based on the intent-to-treat (ITT) population, defined as all subjects who are randomized. Statistical comparisons will be made between APR 30 BID and placebo for the Placebo-controlled Phase (Weeks 0 to 16). All statistical tests will be at the 2-sided 0.05 significance level and the corresponding p-values will be reported.

The treatment difference for the primary endpoint will be compared between APR 30 BID and placebo using a Cochran Mantel–Haenszel (CMH) test adjusting for the stratification factor. 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 stratification factor with the CMH weights, along with the associated 2-sided 95% confidence intervals (CIs) using a normal approximation to the weighted average will be provided. Missing values at Week 16 will be imputed using multiple imputation (MI) as the primary method, with sensitivity analysis using the nonresponder imputation (NRI) method.

The continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM) as the primary method. The MMRM model will use the change or percent change from baseline as the response variable and include treatment group, visit time, treatment-by-time interaction, and stratification factor as fixed effects, and the baseline value as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted maximum likelihood (REML) to make proper statistical inference. Within-group least-squares (LS) means and the associated standard errors (SEs) and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model. A sensitivity analysis will be conducted using the analysis of covariance (ANCOVA) model with treatment and stratification factor as the fixed effects, the baseline value as the covariate and the last observation carried forward (LOCF) method to impute the missing data at Week 16.

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

To control the overall type I error rate, a fixed-sequence testing procedure will be used to test the primary and secondary endpoints in a predefined order. The test will be performed in sequence and significance of all preceding endpoints is required in order to proceed to the next one. The proposed sequence of testing for the primary and secondary efficacy endpoints is specified in Section 9.6.1.3.

The safety analyses will be performed using the safety population, defined as all subjects who are randomized and receive at least one dose of investigational product. Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, and vital signs; no inferential testing for statistical significance will be performed.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity and relationship to investigational product. TEAEs leading to death or to discontinuation from treatment and serious adverse events (SAEs) will be summarized and listed separately.

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

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

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1. INTRODUCTION

1.1. Disease Background

Psoriasis is a chronic, systemic, immunological disease involving the skin and/or joints that may profoundly affect quality of life and result in a significant socioeconomic burden (World Health Organization [WHO] Global Report on Psoriasis, 2016; Van Voorhees, 2016). Genital psoriasis, defined as psoriasis in the peri-vaginal region, penis, scrotum and perineum (Menter, 2018) has been reported as the most stigmatizing form of psoriasis, regardless of overall disease severity (Schmid-Ott, 1999). Genital involvement has been shown to have a profound impact on quality of life and sexual health (Meeuwis, 2011; Meeuwis, 2015; Ryan, 2015). In addition, patients with genital psoriasis report high levels of itching, pain and discomfort (Meeuwis, 2011; Ryan, 2015).

Involvement of genital skin has been reported to occur in 29-46% of psoriasis patients (Meeuwis, 2015), but underreporting of genital skin involvement has been a concern. In an observational, multicenter study of 354 consecutive psoriasis patients by Ryan (2015), 63% of patients reported genital involvement currently and/or previously during the course of their disease.

Genital psoriasis is characterized as plaque psoriasis, although lesions may differ in appearance from those in other body areas. Genital plaques are more likely to be thinner and less scaly than psoriatic plaques located elsewhere (Menter, 2008; Papp, 2009; Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis, 2005). Local conditions in the genital area such as warmth, moisture and friction from clothing may lead to maceration, fissuring and chafing, and may impede both accurate diagnosis and treatment as well as healing (Guglielmetti, 2012).

1.2. Compound Background

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

In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies, apremilast (OTEZLA®) is approved in approximately 50 countries worldwide for the treatment of adult patients with active psoriatic arthritis and the treatment of **adult** patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. **Apremilast is also approved in several countries for the treatment of adult patients with oral ulcers associated with Behçet's disease.**

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

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

1.3. Rationale

1.3.1. Study Rationale and Purpose

Topical therapies are the first line of treatment for genital psoriasis. However, topical treatment may be limited by short treatment durations, poor treatment compliance, limited efficacy and significant adverse effects such as tachyphylaxis, skin atrophy, striae, telangiectasia, and hypothalamic-pituitary-adrenal (HPA) axis suppression (Chan, 2009; Kragballe, 2013). Evaluation of systemic therapies for the treatment of genital psoriasis has been limited (Guglielmetti, 2012; Meeuwis 2015). To date only the IL-17 inhibitor ixekizumab has demonstrated both dermatologic and psychosocial improvements in patients with moderate to severe genital psoriasis (Ryan, 2017; Cather, 2018). Other systemic therapies used to treat moderate to severe plaque psoriasis have not been studied in moderate to severe genital psoriasis. Therefore, the benefit-risk profile of these agents in patients with genital psoriasis has not been well defined.

There remains an unmet medical need for an effective, convenient treatment for moderate to severe genital psoriasis that is well tolerated compared to the currently available treatment options.

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

Evaluation of apremilast in a randomized clinical study of genital psoriasis will provide robust analysis of the benefit-risk of a systemic therapy in this difficult to treat population. Apremilast may offer patients with moderate to severe genital psoriasis an effective oral therapy with a novel mechanism of action and a favorable safety profile.

1.3.2. Rationale for the Study Design

This Phase 3, multicenter, randomized, placebo-controlled, double-blind study is designed to evaluate the efficacy and safety of apremilast (CC-10004) in subjects with moderate to severe genital psoriasis, who are inadequately controlled with or intolerant of topical therapy. The enrolled adult subjects will have a modified static Physician Global Assessment of Genitalia (sPGA-G) score of ≥ 3 (moderate or severe) and evidence of plaque psoriasis (Body Surface Area [BSA] ≥ 1%) in a non-genital region and static Physician Global Assessment (sPGA) ≥ 3 (moderate or severe). This is a 32-week study comprised of a 16-week Placebo-controlled Phase followed by a 16-week Apremilast Extension Phase where all subjects will receive apremilast (APR) 30 twice daily (BID). The primary endpoint is the proportion of subjects with a modified

sPGA-G score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16.

The efficacy and safety of apremilast in subjects with moderate to severe plaque psoriasis have been demonstrated across multiple clinical trials. In the pivotal Phase 3 studies (PSOR-008 and PSOR-009), significant improvement in difficult to treat areas of psoriasis such as nail, scalp and palmoplantar were observed in subjects treated with apremilast, however, genital manifestations were not assessed in these trials. Study PSOR-025 will be the first study to investigate use of apremilast in the treatment of moderate to severe genital psoriasis.

The sample size estimation of approximately **286** subjects with a randomization ratio of 1:1 is based on extrapolation of results from Phase 3 and 4 studies with apremilast, where an sPGA treatment effect of [redacted] compared to placebo was demonstrated.

Study PSOR-025 will enroll adult subjects with chronic plaque psoriasis of at least 6 months duration, and evidence of plaque psoriasis BSA ≥ 1% in a non-genital region and sPGA ≥ 3 (moderate or severe). Subjects will have moderate or severe genital psoriasis with a modified sPGA-G score of ≥ 3 (moderate or severe), who are inadequately controlled with or intolerant of topical therapy. Prior treatment for psoriasis will be stopped for specified durations before randomization as follows: Topical therapy at least 2 weeks, phototherapy and conventional systemic therapy at least 4 weeks, biologic therapy with a TNF or IL-17 blocker at least 12 weeks and anti-IL-12 or IL-23 monoclonal antibodies at least 24 weeks before randomization, and no concomitant psoriasis therapy (topical, photo or systemic) will be permitted during the active treatment period of the study (except for a non-medicated moisturizer such as Eucerin® or non-medicated shampoo).

The primary endpoint will be the proportion of subjects with a modified sPGA-G score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline at Week 16. Based on health authority feedback, the sPGA-G described by Merola has been modified from a 6-point to a 5-point scale ranging from 0 (clear) to 4 (severe). The modified sPGA-G score incorporates an assessment of the severity of the 3 primary signs of the disease: erythema, scaling and plaque elevation at a given time point, and was developed as an efficacy outcome measure in the clinical assessment of the severity of genital psoriasis, based on sPGA scales used in clinical studies (Merola, 2017; Menter, 2018). Assessment of sPGA-G response was the primary endpoint in a recent ixekizumab genital psoriasis study (Cather, 2018).

In the proposed study population of subjects with a baseline of modified sPGA-G of ≥ 3 (moderate or severe), who are inadequately controlled with or intolerant of topical therapy. Amgen believes that achieving a modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16 will represent a clinically meaningful benefit in subjects with limited treatment options.

Further supporting the decision to use modified sPGA-G, the CHMP Guidelines (2005) recognize that Psoriasis Area and Severity Index (PASI) has not been adapted for difficult to treat manifestations of psoriasis such as the scalp or in the genital region and recommend the use of a PGA to assess efficacy. Similar to the development of a Scalp Physician Global Assessment (ScPGA), the modified sPGA-G serves as a clinical outcome measure of severity in genital psoriasis.

Study PSOR-025 will enroll subjects with total body plaque psoriasis ranging in skin involvement (BSA ≥ 1%). Unlike the PASI scoring system, modified sPGA-G is not limited by a decrease in sensitivity in less extensive disease. Stratification by psoriasis-affected BSA will be performed (BSA < 10% or ≥ 10%) **and the strata with BSA ≥ 10% will take ≥ 40% of the total enrollment** to allow an assessment of efficacy in subjects with greater or lesser overall skin involvement.

The first secondary endpoint will be proportion of subjects achieving an overall sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline.

Other secondary endpoints of response will include the proportion of subjects with a 4-point reduction (improvement) from baseline in the Genital Psoriasis Itch Numeric Rating Scale (GPI-NRS) score at Week 16. The GPI-NRS is one of eight components of the validated Genital Psoriasis Symptoms Scale (GPSS) which was developed to assess symptoms that are particularly burdensome to subjects with genital psoriasis (Gottlieb, 2018). The GPSS was modeled after the Whole Body Itch numeric rating scale (NRS) instrument, which has been previously validated in subjects with moderate to severe plaque psoriasis (Naegeli, 2015). While all eight components of the GPSS and total symptoms score will be included as a secondary endpoint, the significant impact of itch on quality of life in subjects with genital psoriasis warrants additional attention. Pruritus is a common and frequently reported symptom of plaque psoriasis, occurring on a daily basis in 77% of subjects with extensive psoriasis (Yosipovitch, 2000). In an observational, multicenter study of 354 subjects with current and/or previous genital psoriasis, itch was reported by 86% of participants (Ryan, 2015). In study PSOR-025, assessment of genital itch will be conducted from baseline (Visit 2) through the Apremilast Extension Phase. In addition to GPI-NRS, change from baseline in affected BSA, change from baseline in Dermatology Life Quality Index (DLQI) total score, and change from baseline in GPSS total score and individual items scores will be assessed at Week 16.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

In a Phase 2 dose finding study (CC-10004-PSOR-005), a clear dose response was demonstrated with statistically significant improvement in apremilast 30 mg BID, but not the apremilast 10 mg BID treatment groups, compared with placebo. The safety and tolerability profiles of the apremilast 30 mg BID treatment group were acceptable with no clinically significant safety signals. 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 subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Since the outcome of apremilast treatment on genital psoriasis has not been evaluated previously, this study will directly investigate the safety and efficacy of this dosing regimen in the treatment of subjects with moderate to severe genital psoriasis.

1.3.4. Rationale for Choice of Comparator Compounds

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

1.3.5. 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 subjects (Schafer, 2016). Apremilast has been found to reduce Th17 and Th22 cytokine expression in the lesional skin and peripheral blood of psoriasis subjects (Gottlieb, 2013; Krueger, 2016). In subjects 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. These in vitro and clinical data demonstrate that the beneficial effects of apremilast on known inflammatory mediators are associated with its clinical efficacy. However, the efficacy of apremilast has not yet been tested in the moderate to severe genital psoriasis population, and predictors of clinical response to apremilast have not yet been identified. [redacted] These data will define the mechanism of action of apremilast in subjects with moderate to severe genital psoriasis and may inform on the subset of subjects 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 subjects. [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the clinical efficacy of oral apremilast 30 mg BID, compared to placebo, in subjects with moderate to severe genital psoriasis during the 16-week Placebo-controlled Phase.
Secondary Objective(s)
The secondary objectives are: • To evaluate the safety and tolerability of apremilast 30 mg BID, compared with placebo, in subjects with moderate to severe genital psoriasis • To evaluate the effect of apremilast 30 mg BID compared with placebo on genital psoriasis symptoms • To evaluate the effect of apremilast 30 mg BID, compared with placebo, on Health-related Quality of Life (HRQoL)
Exploratory Objective(s)
The exploratory objectives are: [redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Static Physician Global Assessment of Genitalia (sPGA-G) 0/1 (modified)	Proportion of subjects with a modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	Week 16
Secondary	Static PGA (sPGA) 0/1	Proportion of subjects achieving an overall sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline	Week 16
	Genital Psoriasis Itch Numeric Rating Scale (GPI-NRS)	Proportion of subjects with at least a 4-point improvement in GPI-NRS item score within the Genital Psoriasis Symptoms Scale (GPSS) for subjects with a baseline score of ≥ 4	Week 16
	Body Surface Area (BSA)	Change from baseline in affected BSA	Week 16

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Dermatology Life Quality Index (DLQI)	Change from baseline in DLQI total score	Week 16
	Genital Psoriasis Symptoms Scale (GPSS)	Change from baseline in GPSS total score and individual items scores	Week 16
Exploratory	[redacted]		
Safety	Type, frequency, severity and relationship of adverse events to IP	Day 0 through end of Observational Follow-up	Study duration

3. OVERALL STUDY DESIGN

3.1. Study Design

This Phase 3 multicenter, randomized, placebo-controlled, double-blind study is designed to evaluate the efficacy and safety of apremilast over 32 weeks of treatment in approximately **286** subjects with moderate to severe genital psoriasis (modified sPGA-G ≥ 3, moderate or severe). Subjects will be randomized 1:1 based on a permuted block randomization using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline psoriasis-involved body surface area (BSA) (< 10% or ≥ 10%). **No more** than **60**% of subjects with BSA < 10% will be enrolled.

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

The study will consist of four phases (Figure 1):

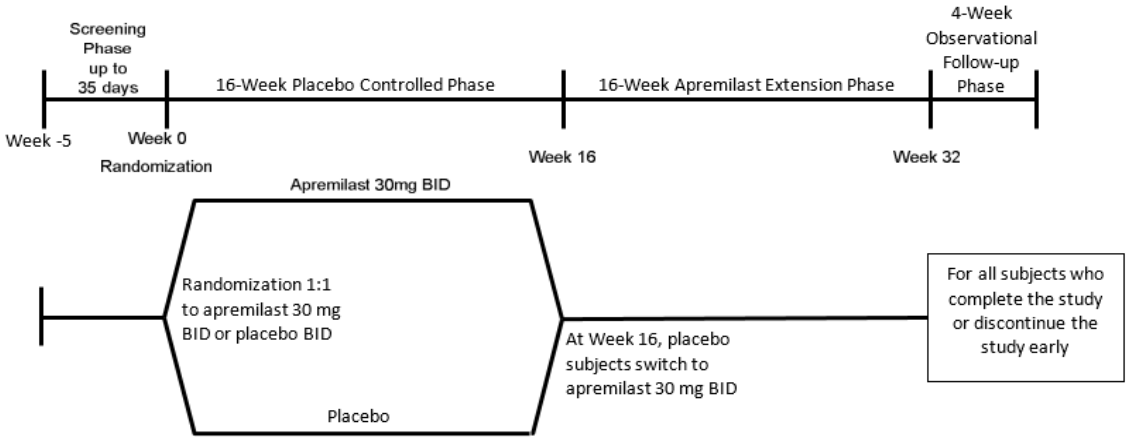
- Screening Phase – up to 35 days
- Double-blind Placebo-controlled Phase – Weeks 0 to 16
  - Subjects will be randomly assigned in a 1:1 ratio to either apremilast 30 mg BID or placebo.
- Apremilast Extension Phase – Weeks 16 to 32
  - All subjects will be switched to (or continue to) receive apremilast 30 mg BID. All subjects will maintain this dosing through Week 32.
- Observational Follow-up Phase – 4 weeks
  - Four-week Post-Treatment Observational Follow-up Phase for all subjects who complete the study or discontinue the study early

The blind should be maintained for persons responsible for the ongoing conduct of the study. Blinded persons may include but are not limited to: Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, and Clinical Research Associates.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 data restriction will be performed; the primary data analysis will be conducted and a Week 16 Clinical Study Report (CSR) will be generated. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Week 16 CSR. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

The study will be conducted in compliance with 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: Study Design



3.2. Study Duration for Subjects

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

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

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

Approximately **286** adult subjects ≥ 18 years of age with moderate to severe genital psoriasis will be randomized worldwide.

4.2. Inclusion Criteria

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

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have a diagnosis of chronic plaque psoriasis for at least 6 months prior to signing the ICF.
5. Subject must have a diagnosis of moderate or severe psoriasis of the genital area at Screening and Baseline as defined by having a modified sPGA-G score of ≥ 3 (moderate or severe).
6. Subject must have a diagnosis of moderate or severe psoriasis at Screening and Baseline as defined by having a sPGA score of ≥ 3.
7. Subject must have plaque psoriasis (BSA ≥ 1%) in a non-genital area at both Screening and Baseline.
8. Subject must have been inadequately controlled with or intolerant of topical therapy for the treatment of psoriasis affecting the genital area.
9. Subject must be in good health (except for psoriasis) as judged by the investigator, based on medical history, physical examination, clinical laboratories, and urinalysis.
10. Subject must meet the following laboratory criteria:
    a. White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L)
    b. Platelet count ≥ 100,000/μL (≥ 100 x 10^9/L)
    c. Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
    d. Total bilirubin ≤ 2 mg/dL (≤34 μmol/L)
    e. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤ 2 x upper limit of normal (ULN)
11. Females of childbearing potential (FCBP)† must have a negative pregnancy test at Screening and Baseline. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which

conception is possible must use one of the approved contraceptive[§] options described below:

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

OR

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

4.3. Exclusion Criteria

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

1. Subject has any significant medical condition or laboratory abnormality, that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject is pregnant or breast feeding.
5. Subject has positive Hepatitis B surface antigen or anti-hepatitis C antibody at Screening.
6. Subject has active tuberculosis (TB) or a history of incompletely treated TB.
7. Subject has history of positive human immunodeficiency virus (HIV), or has congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
8. Subject has active substance abuse or a history of substance abuse within 6 months prior to Screening.
9. Subject has bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of Screening. Any treatment for such infections must have been completed at least 4 weeks prior to Screening.

[†]A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).
[§]The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).
[*]Option 2 may not be an acceptable contraception option in all countries per local guidelines/regulations.

10. Subject has malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas and treated [ie, cured] cervical intraepithelial neoplasia [CIN] or carcinoma in situ of the cervix with no evidence of recurrence).
11. Subject has prior history of suicide attempt at any time in the subject's life time prior to signing the informed consent and randomization, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent.
12. Subject has psoriasis flare/rebound (defined as a sudden worsening of body psoriasis or psoriasis of the genitalia which requires administration of prohibited medications) within 4 weeks of Screening or between the Screening and Baseline Visit.
13. Subject has current or planned concurrent use of the following therapies that may have a possible effect on psoriasis of the body and/or genital area during the course of the treatment phase of the trial:
    a. Topical therapy within 2 weeks prior to randomization (including but not limited to topical corticosteroids, vitamin D analog preparations, calcineurin inhibitors).
        - Exceptions: unmedicated emollients (eg, Eucerin®) for body and genital lesions and non-medicated shampoos for scalp 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, fumaric acid esters).
    c. Phototherapy treatment of body within 4 weeks prior to randomization (ie, ultraviolet B [UVB], psoralen and ultraviolet A radiation [PUVA]).
    d. Biologic therapy:
        i. TNF or IL-17 blockers such as adalimumab, brodalumab, certolizumab pegol, etanercept, infliximab, ixekizumab, secukinumab (or biosimilars for each) within 12 weeks prior to randomization
        ii. Anti-IL-12 or anti-IL-23 monoclonal antibodies such as ustekinumab, guselkumab, or tildrakizumab, within 24 weeks prior to randomization
    e. Use of any investigational drug beginning 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
14. Subject has evidence of skin conditions that would interfere with clinical assessments.
15. Subject has prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources.

16. Subject had prior treatment with apremilast.
17. Subject has history of allergy or hypersensitivity to any components of the IP.

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening	Placebo-controlled Treatment Phase						Active Treatment Phase			Observational Follow-up
Visit Number	**1**	**Baseline[a] 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10/ET[b]**	**11**
Week	**-5 to 0**	**0 (Day 1)**	**2 (± 4 days)**	**4 (± 4 days)**	**8 (± 4 days)**	**12 (± 4 days)**	**16 (± 4 days)**	**20 (± 4 days)**	**24 (± 4 days)**	**32 (± 4 days)**	**4 Weeks After Last Dose (± 2 weeks) [c]**
Administrative/Demographics											
Informed consent[d]	X	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion criteria	X	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-
Prior psoriasis medications	X	-	-	-	-	-	-	-	-	-	-
Prior / concomitant medications or therapies	X	X	X	X	X	X	X	X	X	X	X
Clinical and Laboratory Assessments											
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Psychiatric evaluation[e]	-	-	-	-	-	-	-	-	-	-	-
Pregnancy test and contraception education[f]	X	X	-	-	-	-	-	-	-	X	-
Hepatitis B and C [g]	X	-	-	-	-	-	-	-	-	-	-
Vital signs	X	X	-	X	X	-	X	-	-	X	-
Height	X	-	-	-	-	-	-	-	-	-	-
Weight	X	X	-	-	X	-	X	-	X	X	X
Complete physical examination	X	-	-	-	-	-	-	-	-	X	-

Table 3: Table of Events (Continued)

	Screening	Placebo-controlled Treatment Phase						Active Treatment Phase			Observational Follow-up
Visit Number	**1**	**Baseline[a] 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10/ET[b]**	**11**
Week	**-5 to 0**	**0 (Day 1)**	**2 (± 4 days)**	**4 (± 4 days)**	**8 (± 4 days)**	**12 (± 4 days)**	**16 (± 4 days)**	**20 (± 4 days)**	**24 (± 4 days)**	**32 (± 4 days)**	**4 Weeks After Last Dose (± 2 weeks)[c]**
Clinical laboratory evaluations[h]	X	X	-	-	-	-	X	-	-	X	-
Psoriasis Flare Assessment[i]	-	-	-	-	-	-	-	-	-	-	-
[redacted]											
Subject Rated Outcome and Health-related Quality of Life Assessment											
[redacted]											
Optional Assessment(s) at Selected Investigative Sites											
Photographs	-	X	-	-	X	-	X	-	-	X	-
[redacted]											
IP											
Dispense IP	-	X	-	X	X	X	X	X	X	-	-
Return and count IP tablets	-	-	-	X	X	X	X	X	X	X	-

Abbreviations: [redacted] ET = Early Termination Visit; FCBP = females of childbearing potential; IP = investigational product; [redacted]

a All baseline assessments must be completed prior to randomization and dispensing of IP.
b Visit 10 will serve as the Early Termination Visit for any subject who prematurely discontinues from the study.
c All subjects who complete the study or discontinue the study early will be asked to enter the Four-week Post-Treatment Observational Follow-up Phase.
d Written informed consent will be obtained by the Principal Investigator or designee prior to performing any study assessments.
e Should be performed at any time during the study when suicidal thoughts or a suicide attempt is identified. See Section 6.5 Psychiatric Evaluation
f FCBP: Serum pregnancy tests will be performed at the Screening and Early Termination/Last Treatment Visit. Urine dipstick pregnancy test(s) will be performed at the site at baseline, prior to dosing. An unscheduled serum pregnancy test should be administered if the subject has missed a menstrual period or a positive urine dipstick test. The investigator will educate all FCBP about the options for and correct use of contraceptive methods at the Screening and Baseline Visits and at any time when a FCBP's contraceptive measures or ability to become pregnant changes.
g Hepatitis B surface antigen and anti-hepatitis C antibody.
h Refer to Section 6.5, Clinical Laboratory Evaluations for details regarding hematology, clinical chemistries, and urinalysis parameters to be tested.
i At any time during the study, a psoriasis flare may be reported as an adverse event, provided it meets the protocol definition. See Section 6.5, Psoriasis Flare Assessments.

6. PROCEDURES

The following administrative/demographic procedures will be conducted as outlined in the Table of Events, Table 3.

Informed Consent

An informed consent form (ICF) must be signed by the subject before any study-related assessments are performed. For study-related assessments that are optional, additional ICFs will also be signed before these are performed. Details of the informed consent process may be found in Section 13.3.

Inclusion/Exclusion Criteria

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

Medical and Disease History

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

Prior/Concomitant Medications and Therapies

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

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

6.1. Screening Period

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

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

Safety laboratory analyses 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, after re-consenting to the study.

Efficacy assessments may be performed by the investigator or qualified designee at any time during the Screening Visit.

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

- Demographics (date of birth, sex, race, and ethnicity-if allowed by local regulations)
- Prior disease therapies: includes topical, systemic, and phototherapies
- Complete medical history (all relevant medical conditions diagnosed/ occurring prior to screening should also be included)
- Height
- Weight
- Complete physical examination
- Vital signs (including blood pressure, temperature, and heart rate)
- Modified sPGA-G
- sPGA
- BSA
- Hematology panel
- Chemistry panel
- Urinalysis
- Hepatitis B and C screening
- Serum pregnancy test is required for all female subjects of childbearing potential. Counseling about pregnancy precautions and the potential risks of fetal exposure
- Adverse event assessment (begins when the subject signs the informed consent form)

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. For visits within the Placebo-controlled Phase and Apremilast Extension Phase, an administrative window of ± 4 days is permitted. For the Observational Follow-up visit, an administrative window of ± 2 weeks from the last dose of investigational product (IP) is permitted.

During the treatment period, every effort must be made to ensure that subjects complete the subject questionnaires prior to any other study procedure being performed. Subjects questionnaires must always be completed prior to any efficacy assessments by the investigator or qualified designee.

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

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

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

- Subject reported outcomes or health-related quality of life (HRQoL)
- Concomitant medications and therapies evaluation
- Vital signs
- Weight
- Pharmacodynamic blood sampling
- Hematology panel
- Chemistry panel
- Urinalysis
- Adverse event assessments (continuously)
- Efficacy assessments (see Section 6.4)
- Urine dipstick pregnancy test and contraception education (prior to dosing on Day 1)
- IP dispense, return, and IP tablets count
- Photographs (optional, refer to Section 6.8)

6.2.1. End of Treatment

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

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

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

- Subject reported outcomes or health-related quality of life (HRQoL)
- Concomitant medications and therapies evaluation
- Complete physical examination
- Vital signs
- Weight
- Hematology panel
- Chemistry panel

- Urinalysis
- Adverse event evaluation
- Efficacy assessments (see Section 6.4)
- Serum pregnancy test
- IP return and IP tablets count
- Photographs (optional, refer to Section 6.8)

6.3. Observational Follow-up Period

All subjects will be followed for 28 days 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 following evaluations will be performed at the Follow-up Visit as specified in the Table of Events, Table 3.

- Concomitant medications or therapies evaluation
- Weight
- Adverse event evaluation

6.4. Efficacy Assessments

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

  The modified sPGA-G is the assessment by the investigator of the subject's psoriasis lesions' overall severity in the genital area (labia majora, labia minora, and perineum in females; penis, scrotum, and perineum in males) at the time of evaluation. The modified sPGA-G is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the 3 primary signs of the disease: erythema, plaque elevation, and scaling. It is not necessary that all 3 criteria be fulfilled. The sPGA of Genitalia score is based on a combination of erythema and the secondary features (plaque elevation and/or scale). Since erythema is the most robust finding, it should be the dominant feature influencing the sPGA of Genitalia rating in the majority of cases (Merola, 2017). See Appendix A for grading criteria.

- **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 (Appendix B) for grading criteria.

- **Body Surface Area (BSA)**

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

6.5. Safety Assessments

- **Contraception Education**

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

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

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

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

  A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP subjects at screening and at the Early Termination Visit or Visit 10. In addition, a local urine pregnancy test kit will be provided by the central laboratory and will be performed at the site on all FCBP subjects at the Baseline Visit, prior to dosing. An unscheduled serum pregnancy test should be performed if the FCBP subject has missed a menstrual period or has a positive urine dipstick test.

- **Hepatitis B and C**

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

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

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

- **Complete Physical Examination**

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

- **Psychiatric Evaluation**

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

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

- **Clinical Laboratory Evaluations**

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

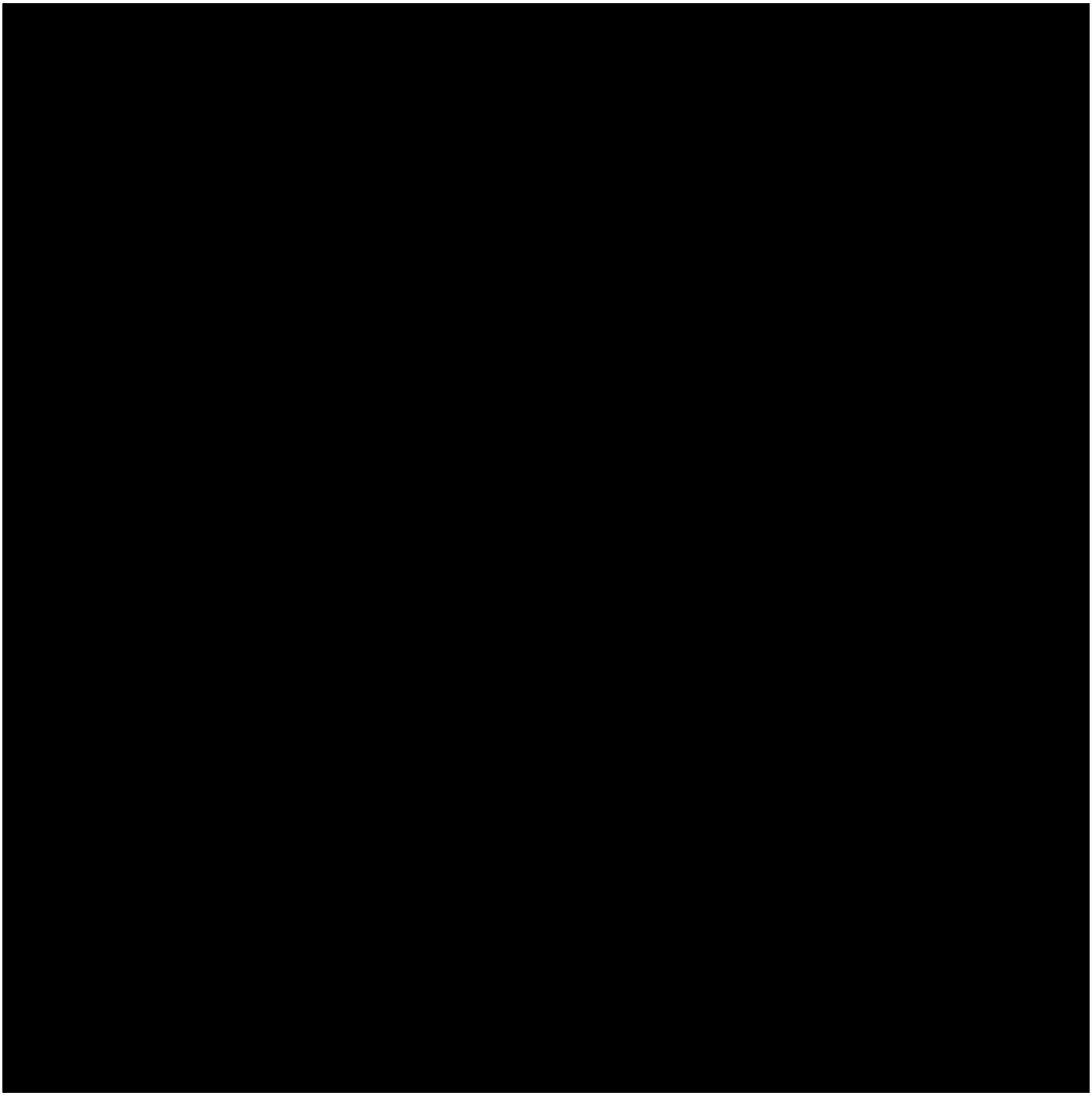
  Fasting is not required. However, if significant elevation of serum lipid(s) is observed, a fasting retest should be requested to determine whether or not elevation was caused by eating.

- **Psoriasis Flare Assessments**

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

- **Adverse Events**

  Details of AE reporting may be found in Section 10.1.



[redacted]

6.7. Subject Reported Outcomes

6.7.1. Genital Psoriasis Symptoms Scale (GPSS)

The GPSS is a patient-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Numeric rating scales (NRS) are used to assess the self-reported overall severity of each of the 8 symptoms individually in the genital area on an 11-point horizontal scale anchored at 0 (no) and 10 (worst imaginable). The overall severity for each individual symptom from patient's genital psoriasis is indicated by selecting the number from 0 to 10 that best describes the worst level of each symptom in the genital area in the past 24 hours. The symptom severity scores, ranging from 0 to 10, are the values of the selected numbers indicated by the patient on the instrument's horizontal scale. Each of the 8 individual items will receive a score of 0 to 10 and will be reported as item scores for itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. In addition, a total score ranging from 0 (no genital psoriasis symptoms) to 80 (worst imaginable genital psoriasis symptoms) will be reported (Gottlieb, 2018). See (Appendix D).

6.7.2. Dermatology Life Quality Index (DLQI)

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

The DLQI total score has a possible range from 0 to 30, with 30 corresponding to the worst health-related quality of life, and 0 corresponding to the best score. The developers suggest that the DLQI can be grouped into six subscales: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and

personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores correspond to poorer health-related quality of life. See Appendix C.

6.8. Photography

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

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

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

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

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

Apremilast will be provided as 10, 20, or 30 mg tablets in blister cards through Week 20. Placebo will be provided as identically appearing 10, 20, or 30 mg tablets in blister cards. Beginning at Week 20, apremilast will be provided as 30 mg tablets in high-density polyethylene (HDPE) bottles with child-resistant caps.

Apremilast, the investigational product (IP), will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To mitigate potential gastrointestinal (GI) side effects, dose titration will be implemented in the first week of this study (see Table 4).

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

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 1:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline psoriasis-involved body surface area (BSA) (< 10% or ≥ 10%). No more than **60**% of subjects with BSA < 10% will be enrolled. IP will be dispensed as indicated below.

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

Starting at Week 16, all subjects will be switched to, or will continue with apremilast. Subjects originally randomized to placebo at Week 0 will be switched to apremilast 30 mg BID at Week 16. Dose titration blister cards will be used for subjects switching from placebo to apremilast; dummy titration blister cards (dosing at 30 mg BID directly) will be used for subjects initially randomized to receive apremilast 30 mg BID. Beginning with the Week 20 visit, all subjects will receive high-density polyethylene (HDPE) bottles containing APR 30 mg tablets. All subjects will receive open-label APR 30 mg BID from Week 20 through Week 32.

The treatment schema for dose titration at baseline is shown in Table 4.

Table 4: Treatment Schema for Dose Titration at Visit 2 (Week 0)

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

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

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

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

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

7.2. Treatment Administration and Schedule

Investigational product will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To mitigate potential gastrointestinal (GI) side effects, dose titration will be implemented in this study. During Week 0 (Days 1-7) and Week 16 (when placebo subjects are switched to receive apremilast 30 mg BID), subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo for the dose titration. The treatment schema for dose titration at baseline and Week 16 is shown in Table 4 and Table 5. Blister card configurations are pictured in Appendix E, Appendix F and Appendix G. At Week 20 through Week 32, all subjects will receive apremilast 30 mg tablets in open-label HDPE bottles with child-resistant caps.

7.3. Overdose

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

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

7.4. Method of Treatment Assignment

At Visit 2 (Week 0), subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 1:1 to receive either apremilast 30 mg BID or placebo, using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline psoriasis-involved body surface area (BSA) (< 10% or ≥ 10%). No more than **60**% of subjects with BSA < 10% will be enrolled. Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to enter the IRT to randomize subjects.

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

Confirmation of the randomization will be sent to the investigational site, 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 will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot

number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

All IP tablets, including apremilast and identically-appearing placebo, will be supplied by Amgen. Investigational product for dose titration at Baseline and at Week 16 will be supplied in blister cards. Investigational product tablets at Week 20 and through Week 32 will be supplied in open-label HDPE bottles with child-resistant caps.

7.6. Investigational Product Accountability and Disposal

The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study.

The investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP accountability form. The investigator(s) or Pharmacist(s) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and record a copy in the IRT. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

The IP should be stored as directed on the package label.

Amgen (or designee) will review with the investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Amgen (or designee).

7.7. Investigational Product Compliance

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

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) are protocol deviations and should be discussed with 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 Phase and Apremilast Extension Phases) of the study.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments. Supportive care may be administered at the discretion of the investigator.

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 and would not be expected to interfere with the conduct of the study or affect assessments. Chronic medication should be dosed on a stable regimen.

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

The following topical therapies will be permitted during the study:

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

8.2. Concomitant Medications Not Recommended

Co-administration of the strong cytochrome P450 3A4 (CYP3A4) enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of strong CYP3A4 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with apremilast is not recommended during the study.

8.3. Prohibited Concomitant Medications and Procedures

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

- Topical therapy
  - Topical therapy, including, but not limited to, topical corticosteroids, retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol for body lesions; coal tar, salicylic acid preparations, or medicated shampoos for scalp lesions, or as specified in Section 8.1.

- Intralesional corticosteroid injections for psoriasis lesions
- Conventional systemic therapy
  - Systemic therapy including but not limited to cyclosporine, corticosteroids, methotrexate, retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, or fumaric acid esters
- Phototherapy
  - UVB or PUVA
- Biologic agents, including:
  - TNF or IL-17 blockers, anti-IL-12 or anti-IL-23 monoclonal antibodies or biosimilars for each
- Use of any investigational drug or device
- Prolonged sun exposure or any use of tanning booths or other ultraviolet light sources

Note: During the Placebo-controlled Phase, the use of antifungal and antiseptic treatment for the genital area is prohibited.

8.4. Required Concomitant Medications and Procedures

Not applicable

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 3, multicenter, randomized, placebo-controlled, double-blind study of the efficacy and safety of apremilast (CC-10004) in subjects with moderate to severe genital psoriasis (modified sPGA-G ≥ 3, moderate or severe). Treatment assignment will be stratified by baseline psoriasis-involved body surface area (BSA) (< 10% or ≥ 10%). No more than **60**% of subjects with BSA < 10% will be enrolled.

The objective of the statistical analysis is to evaluate the efficacy and safety of apremilast 30 mg BID versus placebo for 16 weeks, and to evaluate the effects of apremilast 30 mg BID as a treatment for up to 32 weeks in subjects with moderate to severe genital psoriasis.

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

9.2. Study Population Definitions

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

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

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

9.3. Sample Size and Power Considerations

[redacted] With a total of approximately **286** subjects and a randomization ratio of 1:1, Study PSOR-025 will randomize approximately **143** subjects to APR 30 BID and **143** subjects to placebo. This sample size will provide **85**% power to detect a minimum treatment difference of 15% at Week 16 (25% for APR 30 BID and 10% for placebo) for the primary endpoint using a chi-square test at a 2-sided significance level of 0.05 after adjusting for a 20% dropout rate. The sample size calculation was done using nQuery.

9.4. Background and Demographic Characteristics

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

9.5. Subject Disposition

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

9.6. Efficacy Analysis

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

For the Placebo-controlled Phase (Weeks 0-16), the analyses for efficacy endpoints will be based on the intent-to-treat (ITT) population, defined as all subjects who are randomized. Statistical comparisons will be made between apremilast 30 mg BID and placebo. All statistical tests will be at the 2-sided 0.05 significance level and the corresponding p-values and 95% confidence intervals (CIs) will be reported.

9.6.1.1. Primary Efficacy Endpoint

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

The primary endpoint will be analyzed using the CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization. The 2-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided.

Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc., 2011) based on similar subjects who remained in the study as the primary method. Details of the MI method will be provided in the Statistical Analysis Plan (SAP). Sensitivity analysis will be conducted to account for missing data using the non-responder imputation (NRI) method. The last observation carried forward (LOCF) method will only be used for the exploratory purpose.

9.6.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on the ITT population. The 2-sided p-values and 2-sided 95% confidence intervals (CIs) will be reported for treatment difference between apremilast and placebo arms. Multiplicity adjustment will be specified in the next section.

The continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM) as the primary method. The MMRM model will use the change or percent change from baseline as the response variable and include treatment group, visit time, treatment-by-time interaction, and stratification factor as fixed effects, and the baseline value as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted maximum likelihood (REML) to make proper statistical inference. Within-group least-squares (LS) means and the associated SEs and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model. A sensitivity analysis will be conducted using the analysis of covariance (ANCOVA) model with treatment and stratification factor as the fixed effects, the baseline value as the covariate and the LOCF method to impute the missing data.

The binary endpoints will be analyzed similarly as the primary endpoint using the CMH test adjusting for the stratification factor at randomization. The 2-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided. Missing values at Week 16 will be imputed using the multiple imputation (MI) method (SAS Institute Inc., 2011) based on similar subjects who remained in the study as the primary method. Sensitivity analysis will be conducted to account for missing data using the last observation carried forward (LOCF) method and the non-responder imputation (NRI) method.

9.6.1.3. Multiplicity Adjustment

The primary and secondary efficacy endpoints will be hierarchically ranked for testing in order to control the overall type I error rate in claiming statistical significance at the 2-sided 0.05 significance level. Specifically, for the primary efficacy endpoint (modified sPGA-G 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 any secondary endpoint, statistical significance will be claimed only if its 2-sided p-value is below 0.05 and tests for the primary endpoint and all previous secondary endpoints are significant at the 2-sided 0.05 level. The proposed test sequence for the primary and secondary efficacy endpoints is listed as the following:

- Proportion of subjects with modified sPGA-G score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects achieving an overall sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects with at least a 4-point improvement in GPI-NRS item score within the GPSS for subjects with a baseline score of ≥ 4 at Week 16
- Change from baseline in affected BSA at Week 16
- Change from baseline in DLQI total score at Week 16
- Change from baseline in GPSS total score and individual items scores at Week 16

9.6.1.4. Exploratory Endpoints

[redacted]

9.6.1.5. Subgroup Analysis

Subgroup analyses for modified sPGA-G response at Week 16 based upon baseline demographic (age, gender, race, etc.) or baseline disease characteristics will be provided to determine the robustness of the treatment effect.

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

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

9.7. Safety Analysis

The safety analyses will be performed using the safety population, defined as all subjects who are randomized and receive at least one dose of investigational product. Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, and vital signs; no inferential testing for statistical significance will be performed. Data from safety assessments will be summarized descriptively for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast Exposure Period when subjects receive apremilast treatment. For safety analyses in the Placebo-controlled Phase, baseline will be relative to the first dose date following randomization at Week 0. For safety analyses in Apremilast Exposure Period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the Apremilast Extension Phase (Weeks 16-32).

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 investigational product. TEAEs leading to death or to discontinuation from treatment and serious adverse events will be summarized and listed separately.

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

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

9.8. Interim Analysis

No interim analysis will be conducted.

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

9.9. Other Topics

[redacted]

9.9.2. Investigational Product Compliance

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

9.9.3. Concomitant Therapy

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

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE/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 7.3 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF and the paper SAE report form. The overdose itself should not be reported as an AE.

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

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

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as all SAEs made known to the investigator at any time following the protocol-required reporting period or after end of study. All adverse events (serious/non-serious) will be recorded on the CRF, the paper SAE report form (for SAEs) and in the subject's source documents. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event by recording on the CRF and submitting the SAE information using the paper Serious Adverse Event Report Form by facsimile/email 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.

All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event by recording them on the CRF and submitting the SAE information using the paper Serious Adverse Event Report Form by facsimile/email directly to Amgen Global Patient Safety.

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

10.2.2. Severity/Intensity

For all AEs, the investigator must assess the severity/ intensity of the event.

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

Not suspected:	a causal relationship of the 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 each AE, the investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

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

10.2.6. Outcome

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

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

10.3. Abnormal Laboratory Values

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

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

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

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE on the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in females of childbearing potential are immediately reportable events.

10.4.1. Females of Childbearing Potential – Collection of Pregnancy Information

Pregnancies and suspected pregnancies (including elevated β-subunit of human chorionic gonadotropin [β-hCG] or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Global Patient Safety immediately by email or facsimile, or other appropriate method, using the Pregnancy Notification Form or approved equivalent form (refer to Appendix I). 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 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 by facsimile, email or other appropriate method, within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in-utero exposure to the IP should also be reported to 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 I). 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 J) 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 relevant CRFs and the paper SAE report form. All SAEs must be reported to Amgen Global Patient Safety by recording them on the CRF and sending the SAE data/information using the paper SAE report

form within 24 hours of the Investigator's knowledge of the event. In This instruction pertains to the initial reporting of an SAE as well as reporting any follow-up information.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) and all SAEs 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) will be collected/recorded and reported.

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 H).
- 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 H).

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated/generated 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's Brochure.

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

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 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 H, Appendix I, Appendix J).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

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

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

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

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

11.2. Study Discontinuation

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

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

- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

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

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the investigator should 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 unblinded dose information.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

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

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 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 sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

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

The information contained in the protocol and amendments (with the exception of the information provided by 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 caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

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

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

13.4. Confidentiality

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 subject's signed ICF, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the 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/EC approval but will be submitted to the IRB/EC for information purposes.

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

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

IP can only be supplied to an investigator by 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 CD-ROM.

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 ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the investigator, 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. The 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, 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 product, 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 2 and 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

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
APR	Apremilast
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CMH	Cochran-Mantel-Haenzel
CO_2	Carbon dioxide
CRO	Contract research organization
eCRF	Electronic case report form
CRF	Case report form
CSR	Clinical Study Report
CYP3A4	Cytochrome P450 3A4
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
EC	Ethics Committee
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End of treatment
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
GI	Gastrointestinal
GPI-NRS	Genital Psoriasis Itch Numeric Rating Scale
GPSS	Genital Psoriasis Symptoms Scale
HDPE	High-density polyethylene
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Integrated Response Technology
ITT	Intent-to-treat
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect model for repeated measures
NRI	Non-responder imputation
NRS	Numeric rating scale
PASI	Psoriasis Area and Severity Index
PDE4	Phosphodiesterase type 4
PO	By mouth
PP	Per protocol
PC	Product Complaint

Abbreviation or Specialist Term	Explanation
PUVA	Psoralen and ultraviolet A
RBC	Red blood cell count
REML	Restricted maximum likelihood
[redacted]	
SAE	Serious adverse event
SAP	Statistical Analysis Plan
ScPGA	Scalp Physician Global Assessment
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
sPGA-G	Static Physician Global Assessment of Genitalia
sPGA	Static Physician Global Assessment
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosing factor
TNF-α	Tumor necrosis factor alpha
ULN	Upper limit of normal
UV	Ultraviolet
UVB	Ultraviolet B
WBC	White blood cell count
WHO	World Health Organization

APPENDIX A. THE MODIFIED STATIC PHYSICIAN GLOBAL ASSESSMENT OF GENITALIA (sPGA-G)

Score	Category	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:** coarse scale on most lesions
4	Severe	**Erythema:** severe, bright red or deep red erythema **Plaque elevation:** substantial elevation, hard and sharp edges **Scaling:** coarse scale on most to all lesions

Adapted from source: Merola, 2017.

APPENDIX B. STATIC PHYSICIAN GLOBAL ASSESSMENT (sPGA) OF WHOLE BODY PSORIASIS

Score	Category	Description
0	Clear	**Plaque Elevation** = 0 (no elevation over normal skin) **Scaling** = 0 (no evidence of scaling) **Erythema** = 0 (except for residual hyperpigmentation/ hypopigmentation)
1	Almost Clear	**Plaque Elevation** = ± (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. THE DERMATOLOGY LIFE QUALITY INDEX (DLQI)

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

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	_ Very much _ A lot _ A little _ Not at all	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	_ Very much _ A lot _ A little _ Not at all	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
7.	Over the last week, has your skin prevented you from **working** or **studying**?	_ Yes _ No	_ Not relevant
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	_ A lot _ A little _ Not at all	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example, by making your home messy, or by taking up time?	_ Very much _ A lot _ A little _ Not at all	_ Not relevant

Finlay, 1994.

APPENDIX D. GENITAL PSORIASIS SYMPTOMS SCALE (GPSS)

*Please answer the questions based on your psoriasis symptoms in the genital area within **the past 24 hours.** Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (are between the penis and anus) for males.*

1. Please rate your itching severity due to your genital psoriasis by selecting 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
No itch										Worst itch imaginable

2. Please rate your pain severity due to your genital psoriasis by selecting the number that best describes your worst level of pain in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable

3. Please rate your discomfort severity due to your genital psoriasis by selecting the number that best describes your worst level of discomfort in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No discomfort										Worst discomfort imaginable

4. Please rate your stinging severity due to your genital psoriasis by selecting the number that best describes your worst level of stinging in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No stinging										Worst stinging imaginable

5. Please rate your burning severity due to your genital psoriasis by selecting the number that best describes your worst level of burning in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No burning										Worst burning imaginable

6. Please rate your redness severity due to your genital psoriasis by selecting the number that best describes your worst level of redness in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No redness										Worst redness imaginable

7. Please rate your scaling severity due to your genital psoriasis by selecting the number that best describes your worst level of scaling in the past 24 hours.

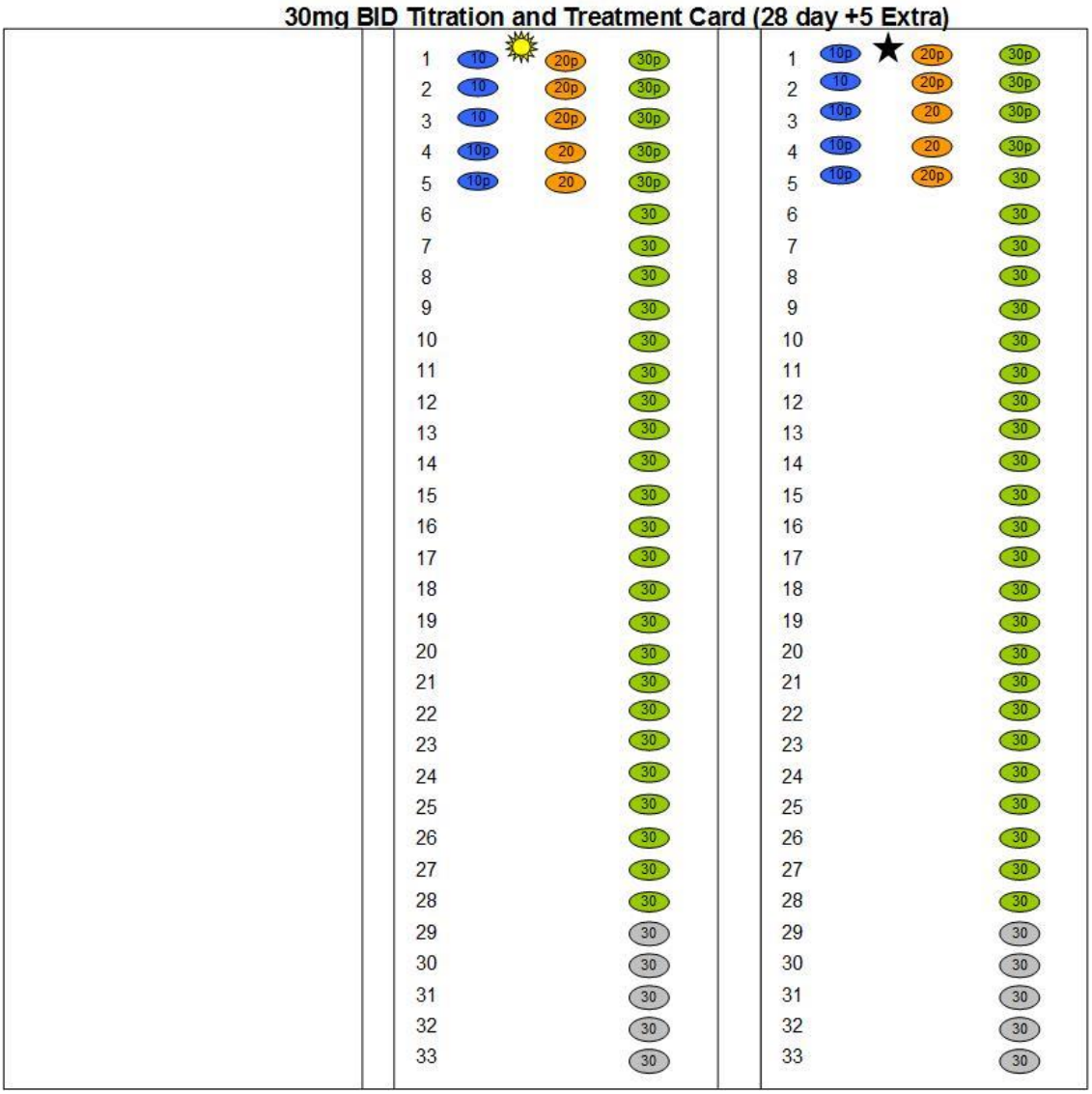
0	1	2	3	4	5	6	7	8	9	10
No scaling										Worst scaling imaginable

8. Please rate your cracking severity due to your genital psoriasis by selecting the number that best describes your worst level of cracking in the past 24 hours.

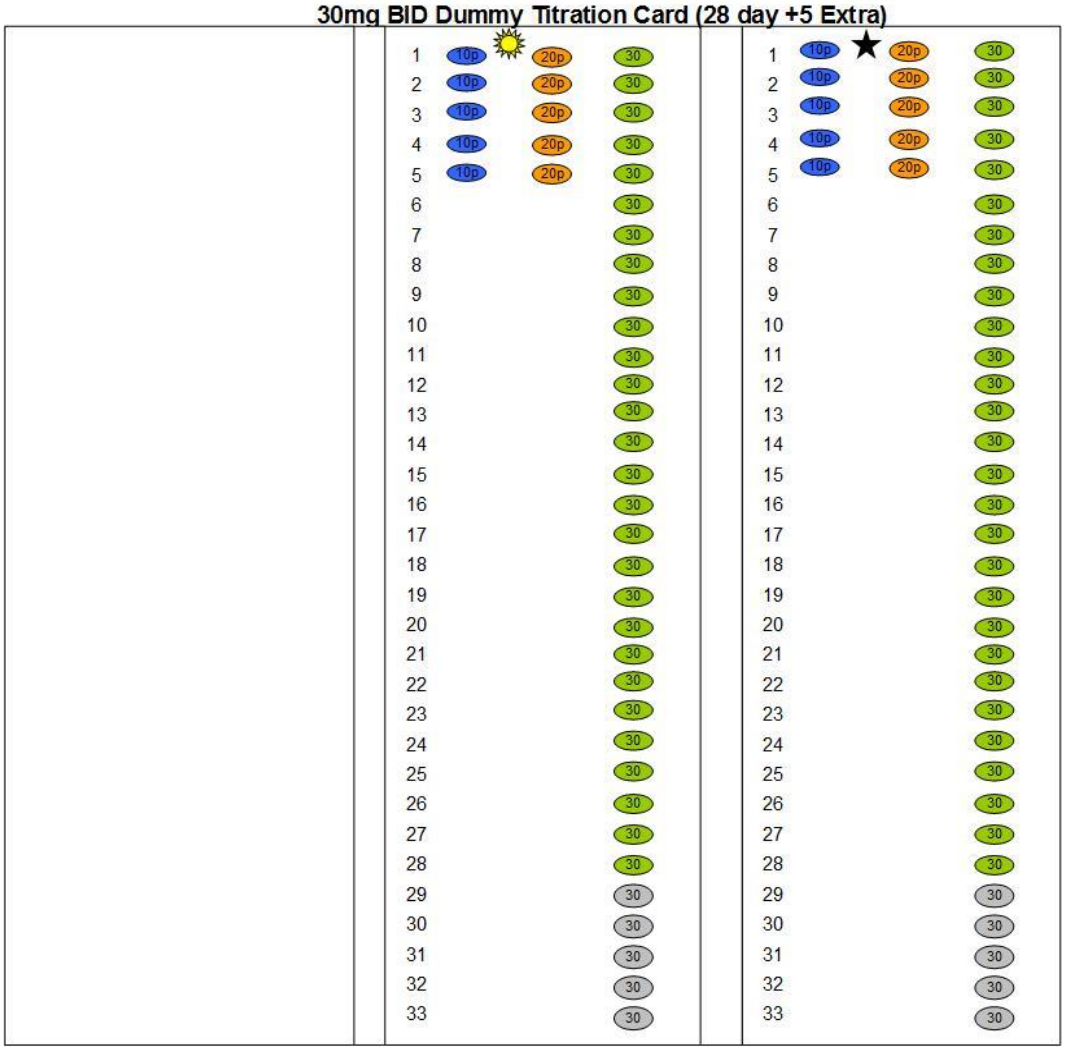
0	1	2	3	4	5	6	7	8	9	10
No cracking										Worst cracking imaginable

Gottlieb, 2018

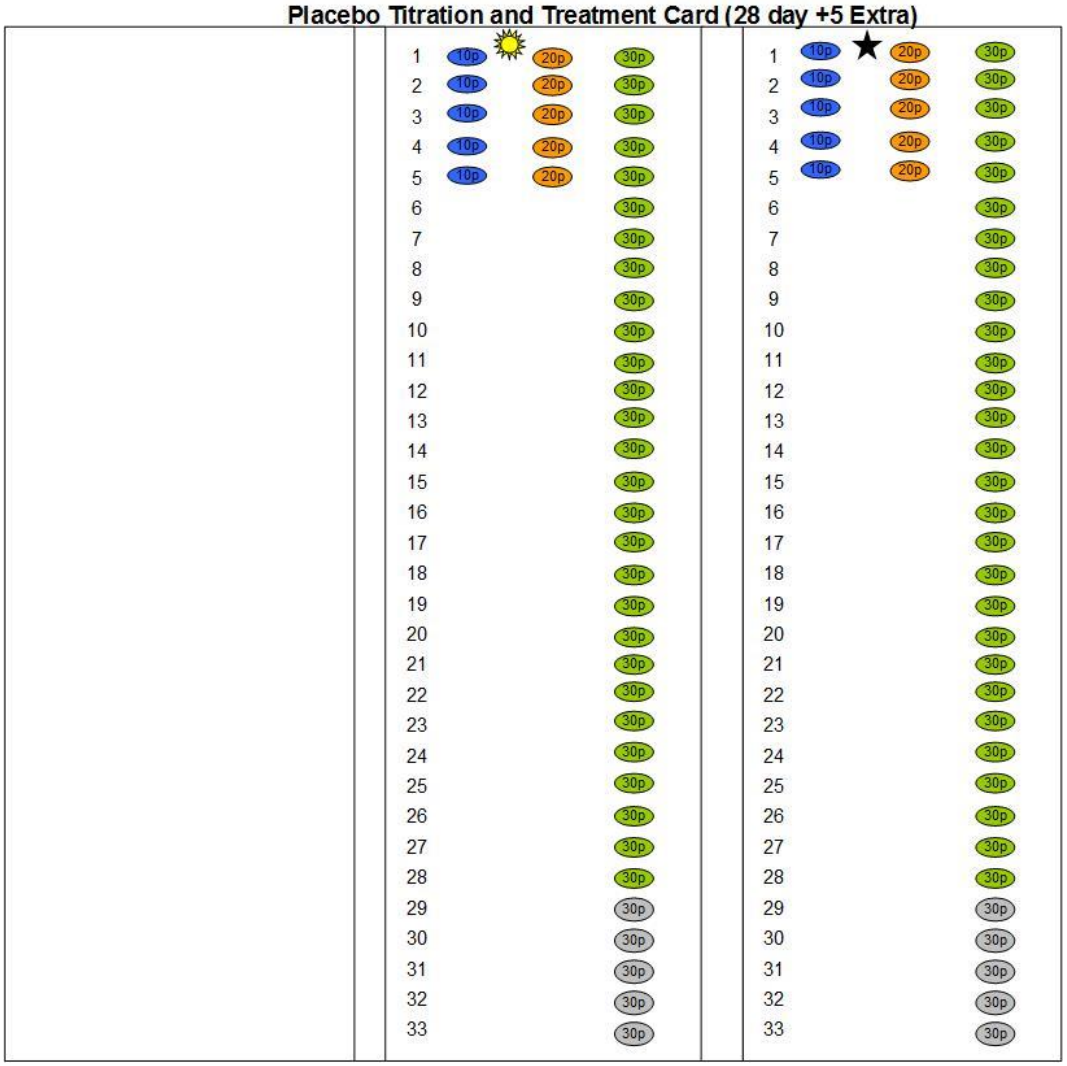
APPENDIX E. TITRATION BLISTER CARD CONFIGURATION



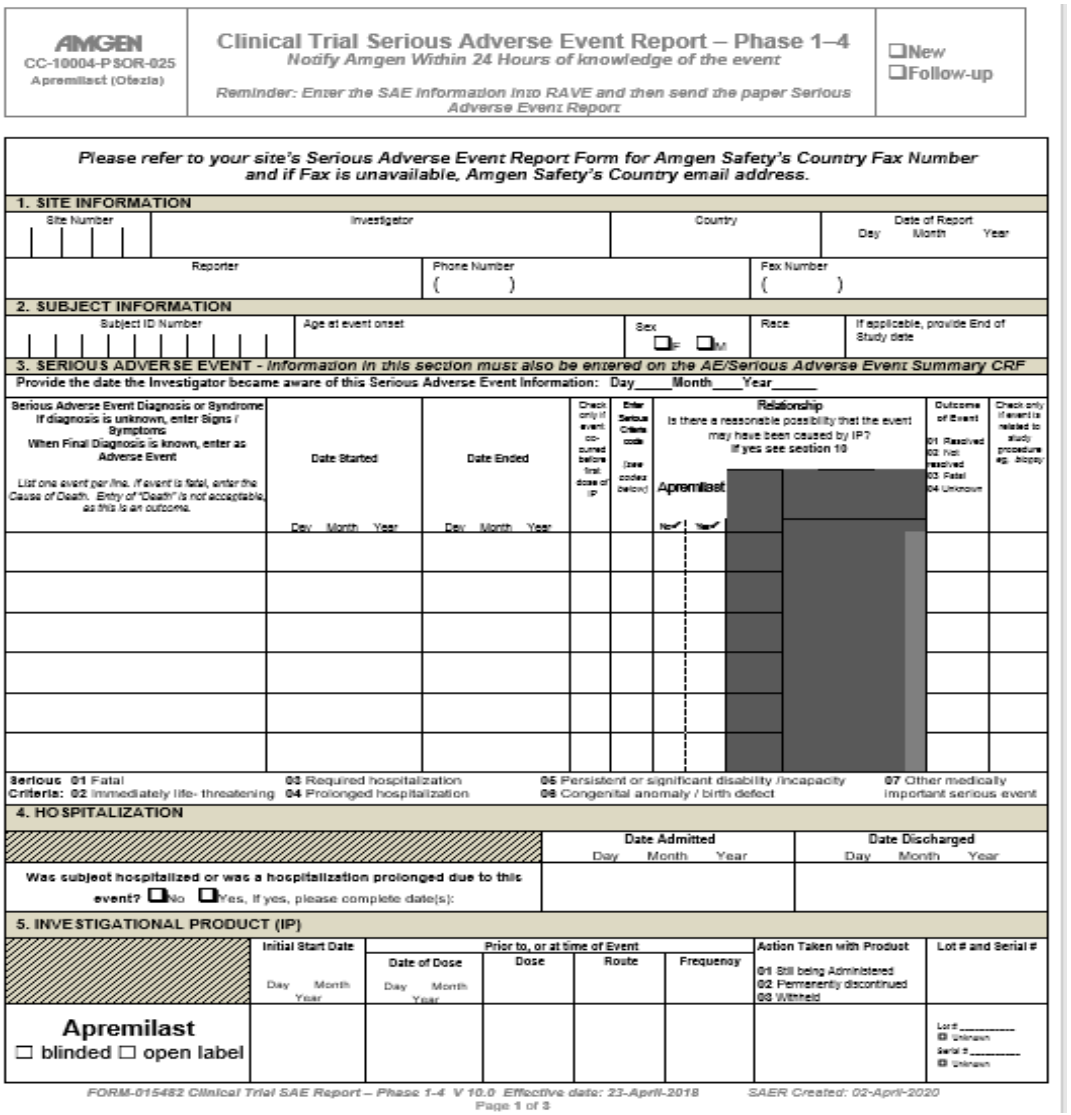
APPENDIX F. ACTIVE TREATMENT DUMMY TITRATION BLISTER CARD CONFIGURATION



APPENDIX G. PLACEBO TREATMENT BLISTER CARD CONFIGURATION



APPENDIX H. SAMPLE SERIOUS ADVERSE EVENT REPORT FORM



AMGEN
CC-10004-PSOR-025
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 ☐F ☐M	Race	If applicable, provide End of Study date

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-PSOR-025 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:

Date (Day Month Year) / Test / 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-PSOR-025 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

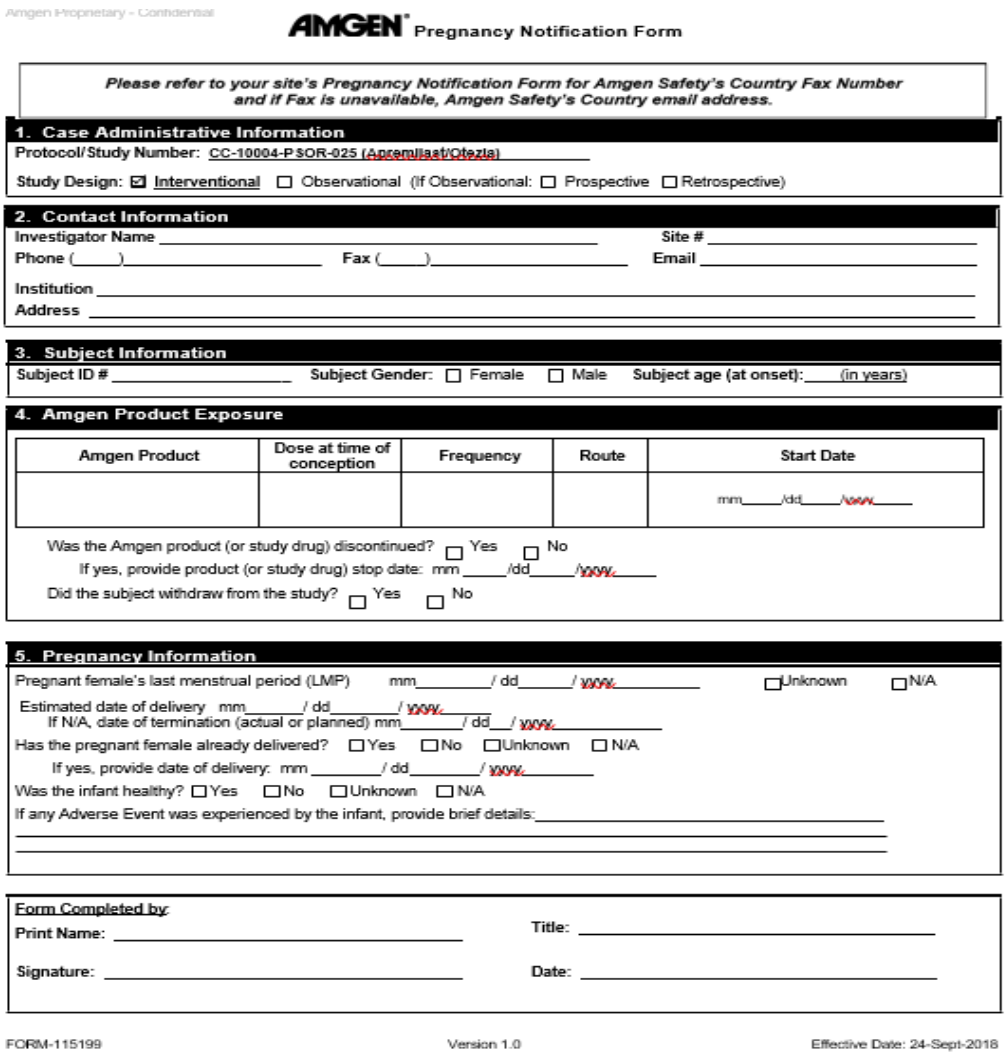
	Site Number	Subject ID Number	

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 *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.*	Title	Date

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 SAER Created: 02-April-2020
Page 3 of 3

APPENDIX I. PREGNANCY NOTIFICATION FORM



Amgen Proprietary – Confidential

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-PSOR-025 (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 J. 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-PSOR-025 (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

– SUMMARY OF CHANGES –

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

AMENDMENT NO. 3.0

PROTOCOL NUMBER:	**CC-10004-PSOR-025**
ORIGINAL DATE:	**31 Oct 2018**
AMENDMENT No. 1.0 DATE:	**22 May 2019**
AMENDMENT No. 2.0 DATE:	**01 May 2020**
AMENDMENT No. 3.0 DATE:	**03 Mar 2021**
EudraCT NUMBER:	**2018-002608-15**
NCT NUMBER:	**NCT03777436**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], MD, PhD
Title:	Clinical Research Medical Director
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 facilitate study enrollment. The following changes were made to the protocol, dated 03 March 2021:

- Specified that the strata with BSA ≥ 10% will take ≥ 40% of the total enrollment in Section 1.3.2 Rationale for the Study Design
- Updated % of subjects with BSA < 10% that will be enrolled in Section 3.1 Study Design, Section 7.1 Description of Investigational Product(s), Section 7.4 Method of Treatment Assignment, and Section 9.1 Overview
- Updated sample size in Section 1.3.2 Rationale for the Study Design, Section 3.1 Study Design, Section 4.1 Number of Subjects, and Section 9.3 Sample Size and Power Considerations
- Updated the approximate number of subjects that will be randomized to each treatment group based on the revised sample size and how the sample size calculation was done in Section 9.3 Sample Size and Power Considerations
- Updated the power calculation based on the change in sample size in Section 9.3 Sample Size and Power Considerations
- Provided minor updates to Section 1.2 Compound Background
- Provided updates to the Medical Monitor/Emergency Contact Information
- 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. 2.0

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

INVESTIGATIONAL PRODUCT (IP):	**CC-10004 (apremilast)**
PROTOCOL NUMBER:	**CC-10004-PSOR-025**
ORIGINAL DATE:	**31 Oct 2018**
AMENDMENT No. 1.0 DATE:	**22 May 2019**
AMENDMENT No. 2.0 DATE:	**01 May 2020**
EudraCT NUMBER:	**2018-002918-12**
NCT NUMBER:	**NCT03777436**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], MD
Title:	Senior Director, Global 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)

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, Primal Kaur

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, Recording 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 H Sample Serious Adverse Event Form was added
- Appendix I Pregnancy Notification Form was added
- Appendix J Lactation Notification Form was added

– SUMMARY OF CHANGES –

AMENDMENT NO. 1.0

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

INVESTIGATIONAL PRODUCT (IP):	**CC-10004 (apremilast)**
PROTOCOL NUMBER:	**CC-10004-PSOR-025**
ORIGINAL DATE:	**31 Oct 2018**
AMENDMENT No. 1.0 DATE:	**22 May 2019**
EudraCT NUMBER:	**2018-002608-15**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], MD
Title:	Senior Director, Clinical Research and 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

In addition to administrative updates, changes in this amendment include requests from the Federal Institute for Drugs and Medical Devices (Bundesinstitut fur Arzeneimittel und Medizinprodukte [BfArM]) that are summarized below:

- Administrative change to be consistent with the document

  Revised Section: Protocol Summary, Study Population

- Revised sentence to reflect citations.

  Revised Section: Section 1.3.1 Study Rationale and Purpose

- Removed wording "for whom topical therapy is inappropriate"

  Revised Sections: Section 1.3.2, Rationale for Study Design and Section 4.2, Inclusion Criterion 8

- Removed reference to a Study Manual

  Revised Section: Section 6, Procedures

- Added a footnote for contraception Option 2 which states that Option 2 may not be an acceptable contraception option in all countries per local guidelines/regulations

  Revised Section: Section 4.2, Inclusion Criterion 11

- Added section to include language about strong cytochrome P450 3A4 inducers

  Added Section: Section 8.2, Concomitant Medications Not Recommended

- Removed blinded language in reference to the Apremilast Extension Phase and added dispensation of bottles at Week 20

  Revised Sections: Protocol Summary, Section 7.1, Description of Investigational Product; Section 7.2, Treatment Administration and Schedule; and Section 7.5, Packaging and Labeling

- Added note to include prohibitive use of antifungal and antiseptic treatment in the genital area

  Revised Section: Section 8.3, Prohibited Concomitant Medications and Procedures

- Removed 'non-adherent'

  Revised Appendix A, The Modified Static Physician Global Assessment of Genitalia (sPGA-G)