A PHASE 4, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE IMPACT OF APREMILAST (CC-10004) ON QUALITY OF LIFE, EFFICACY, AND SAFETY IN SUBJECTS WITH MANIFESTATIONS OF PLAQUE PSORIASIS AND IMPAIRED QUALITY OF LIFE

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SPONSOR NAME / ADDRESS:	AMGEN, INC. One Amgen Center Drive Thousand Oaks, CA 91320

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information
Name: [redacted] MD
Title: Senior Director, Global Development
Address: Amgen Inc. 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
Vice President 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 protocol and find its content to be acceptable.

NOTE: Signed by Celgene based on Approval from Amgen Therapeutic Head [redacted]

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 4, multi-center, randomized, double-blind, placebo-controlled study of the impact of apremilast (CC-10004) on quality of life, efficacy, and safety in subjects with manifestations of plaque psoriasis and impaired quality of life.

Indication

Psoriasis vulgaris is a chronic inflammatory immunologic disorder which manifests primarily in the skin. It is characterized by sharply demarcated areas of affected skin which appear thickened, red, and scaly. The scalp, elbows, knees, lower back, hands, and feet are commonly affected sites. About 80% of affected patients complain of pruritus (Gottlieb, 1998). The psoriatic appearance of the skin is initiated by an antigen presenting cell (APC) – T-cell interaction leading to the release of multiple inflammatory cytokines (Nestle, 2009). In time, this leads to an increased rate of epidermal proliferation with impaired differentiation of keratinocytes, resulting in a thickened epidermis covered by a thickened, parakeratotic stratum corneum. Dermal capillaries become tortuous and dilated, and there is infiltration of both epidermis and dermis with immunologically active cells (Lowes, 2007).

According to a European consensus statement on the definition of treatment goals for patients with plaque psoriasis, mild psoriasis is defined as body surface area (BSA) ≤ 10% and Psoriasis Area Severity Index (PASI) ≤ 10 and Dermatology Life Quality Index (DLQI) ≤ 10. However, patients with mild psoriasis, as indicated by the somatic scores, BSA and PASI, may present with disease manifestations not adequately controlled by topical therapy alone which, in addition, may lead to a significantly impaired quality of life. These manifestations can include the following: involvement of visible areas, involvement of major parts of the scalp, involvement of genitals, involvement of palms and/or soles, onycholysis or onychodystrophy of at least two fingernails, pruritus leading to scratching, and presence of single recalcitrant plaques.

The presence of any of the previously mentioned manifestations alters the classification of mild psoriasis to moderate to severe psoriasis in need of systemic therapy due to significantly impaired quality of life (Mrowietz, 2011).

Objectives

Primary Objective

- To assess the impact of apremilast 30 mg twice daily (BID), compared to placebo, on Health-related Quality of Life (QOL) in subjects with manifestations of plaque psoriasis and impaired quality of life at Week 16

Secondary Objectives

- To assess the efficacy and safety of apremilast 30 mg BID, compared to placebo in subjects with manifestations of plaque psoriasis and impaired quality of life at Week 16
- To assess the long-term effects of apremilast 30 mg BID, with respect to quality of life, efficacy, and safety at Weeks 32 and 52

Study Design

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs). This is a Phase 4, multi-center, randomized, placebo-controlled, double-blind study of the impact of apremilast on quality of life, efficacy, and safety in subjects with manifestations of plaque psoriasis and impaired quality of life.

Approximately 255 subjects will be randomized 2 (apremilast):1 (placebo) in approximately 6 to 10 countries in Western Europe. Subjects will be block-randomized to each of the 5 manifestations of plaque psoriasis. If subjects present with multiple manifestations, they will be allocated to the manifestation which is most severe, as determined by the subject. However, all manifestations will be assessed for efficacy at each study visit.

- After a 5-day titration with apremilast, subjects will receive apremilast 30 mg tablets or matching placebo orally twice daily (BID) for 16 weeks. Subjects randomized to the apremilast treatment group will receive apremilast 30 mg tablets orally twice daily for 52 weeks.
- Subjects randomized to the placebo treatment group will receive placebo tablets (identical in appearance to the apremilast 30 mg tablets) orally twice daily for 16 weeks. Beginning at Week 16 and after a 5-day titration with apremilast, subjects initially randomized to placebo will be switched to receive apremilast 30 mg BID for an additional 36 weeks (52 weeks total).

The study will consist of 4 phases:

- Screening Phase – up to 5 weeks (35 days)
- Double-blind Placebo-controlled Phase – Weeks 0 to 16

  Subjects will receive treatment with either:

  – Apremilast 30 mg tablets orally BID, or

  – Matched placebo tablets orally BID
- Apremilast Extension Phase – Weeks 16 through 52

  – All subjects will be switched to (or continue with) apremilast 30 mg BID at Week 16 (after a 5-day titration for subjects initially randomized to placebo). All subjects will maintain this dosing to Week 52.
- Post-treatment Observational Follow-up Phase

  – 4-week post-treatment observational follow-up for all subjects who complete the 52-week study treatment or discontinue from the study treatment early

Study Population

Adult subjects ≥ 18 years of age with manifestations of plaque psoriasis and impaired quality of life.

Length of Study

The study is designed as a 52-week study, with a 4-week post-treatment observational follow-up. Visits will be scheduled at screening (no more than 5 weeks prior to randomization), Week 0

(baseline/randomization), Weeks 2, 4, 16, 20, 32, 44, and 52. A post-treatment observational follow-up will be conducted by telephone at Week 56 or 4 weeks after subject discontinues from the study treatment.

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

Study Treatments

Subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets, or identically appearing placebo, for the dose titration, at the baseline visit (Week 0). The treatment schema for dose titration at Baseline is shown in Appendix P.

Starting at Week 16, all subjects will be switched to, or will continue with, apremilast. Subjects originally randomized to placebo at Week 0 will be switched to apremilast at Week 16. Dose titration blister cards will be used for subjects switching from placebo to apremilast; blister cards with dummy titration (dosing at 30 mg BID directly) will be used for subjects originally randomized to apremilast. Beginning with the Week 20 visit, all subjects will receive open label high-density polyethylene (HDPE) bottles of investigational product (IP) tablets. All subjects will maintain this dosing through Week 52.

Apremilast tablets will be taken orally twice daily, approximately 12 hours apart, through the last treatment visit.

Overview of Key Efficacy Assessments

Primary Efficacy Endpoint

The primary endpoint will be the proportion of subjects who achieve a $\geq$ 4-point reduction from baseline in the DLQI in subjects receiving apremilast compared to placebo at Week 16.

Secondary Efficacy Endpoints

- Dermatology Life Quality Index (DLQI)
- Itch Numeric Rating Scale (NRS)
- Skin Discomfort/Pain Visual Analog Scale (VAS)
- Body Surface Area (BSA)
- Psoriasis Area and Severity Index (PASI)
- Patient Benefit Index (PBI)
- European Quality of Life 5-Dimension Questionnaire (EQ-5D)
- The Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)

Overview of Key Safety Assessments

Safety assessments will include:

- Adverse events (AE)

- Pregnancy tests for females of childbearing potential (FCBP)
- Vital signs
- Body weight and waist circumference
- Clinical laboratory tests

Statistical Methods

This study will randomize approximately 255 subjects to either apremilast 30 mg BID or placebo in a 2:1 ratio, respectively.

Assuming a placebo DLQI Responder proportion of 0.50 at Week 16, a minimum total sample size of 210 subjects (140 allocated to apremilast 30 mg and 70 allocated to placebo) is needed to detect a 0.20 difference in the DLQI Responder proportions between apremilast and placebo with at least 0.807 power using a two-sided test at the 0.05 level of significance. This sample size calculation was determined using the commercial software EaST, Version 6.3. Allowing for an 18% discontinuation rate prior to Week 16, the sample size was revised from a total of 210 subjects to a final sample size of 255.

The primary analysis for the primary endpoint at Week 16 will be the Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factor at randomization (ie, the 5 manifestation types). This form of the CMH test will use the sample sizes in each of the strata as weights when estimating the adjusted difference in the treatment proportions, constructing 95% Wald confidence intervals for the difference, and conducting a statistical test of no difference between the treatment proportions (ie, H_0: $\pi_{APR} - \pi_{PBO} = 0$ as the null hypothesis).

All reasonable attempts will be made to prevent missing data from occurring in this study, especially at Week 16. However, in the case of missing data at Week 16 a multiple imputation (MI) method will be incorporated into the primary analysis. The aim of the multiple imputation approach is to incorporate a representative random sample in place of the missing data such that unbiased estimation and valid statistical inferences (ie, confidence intervals and hypothesis testing) can be made.

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1. INTRODUCTION

1.1. Disease Background

Psoriasis vulgaris is a chronic inflammatory immunologic disorder which manifests primarily in the skin. It is characterized by sharply demarcated areas of affected skin which appear thickened, red, and scaly. The scalp, elbows, knees, lower back, hands, and feet are commonly affected sites. About 80% of affected patients complain of pruritus (Gottlieb, 1998). The psoriatic appearance of the skin is initiated by an antigen presenting cell (APC) – T-cell interaction leading to the release of multiple inflammatory cytokines (Nestle, 2009). In time, this leads to an increased rate of epidermal proliferation with impaired differentiation of keratinocytes, resulting in a thickened epidermis covered by a thickened, parakeratotic stratum corneum. Dermal capillaries become tortuous and dilated, and there is infiltration of both epidermis and dermis with immunologically active cells (Lowes, 2007).

According to a European consensus statement on the definition of treatment goals for patients with plaque psoriasis, mild psoriasis is defined as body surface area (BSA) ≤ 10% and Psoriasis Area Severity Index (PASI) ≤ 10 and Dermatology Life Quality Index (DLQI) ≤ 10. However, patients with mild psoriasis, as indicated by the somatic scores, BSA and PASI, may present with disease manifestations not adequately controlled by topical therapy alone which, in addition, may lead to a significantly impaired quality of life. These manifestations can include the following: involvement of visible areas, involvement of major parts of the scalp, involvement of genitals, involvement of palms and/or soles, onycholysis or onychodystrophy of at least two fingernails, pruritus leading to scratching, and presence of single recalcitrant plaques. The presence of any of the previously mentioned manifestations may alter the classification of mild psoriasis to moderate to severe psoriasis in need of systemic therapy due to significantly impaired quality of life (Mrowietz, 2011).

1.2. Compound Background

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

In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies, apremilast (OTEZLA) is approved within Europe for the treatment of moderate to severe chronic plaque psoriasis in patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate or psoralens and long-wave ultraviolet radiation (PUVA) and alone or in combination with disease-modifying antirheumatic drugs (DMARDs) for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD.

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

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

1.3. Rationale

1.3.1. Study Rationale and Purpose

Psoriasis vulgaris is a chronic inflammatory immunologic disorder which manifests primarily in the skin. It is characterized by sharply demarcated areas of affected skin which appear thickened, red, and scaly. The scalp, elbows, knees, lower back, hands, and feet are commonly affected sites. About 80% of affected patients complain of pruritus (Gottlieb, 1998). The psoriatic appearance of the skin is initiated by an APC – T-cell interaction leading to the release of multiple inflammatory cytokines (Nestle, 2009). In time, this leads to an increased rate of epidermal proliferation with impaired differentiation of keratinocytes, resulting in a thickened epidermis covered by a thickened, parakeratotic stratum corneum. Dermal capillaries become tortuous and dilated, and there is infiltration of both epidermis and dermis with immunologically active cells (Lowes, 2007).

According to a European consensus statement on the definition of treatment goals for patients with plaque psoriasis, mild psoriasis is defined as BSA $\leq$ 10% and PASI $\leq$ 10 and DLQI $\leq$ 10. However, many patients may present with BSA $\leq$ 10% and PASI $\leq$ 10 but due to the presence of disease manifestations that are difficult to control with topical therapy alone, may have a significantly impaired quality of life (DLQI > 10). These manifestations can include the following: involvement of visible areas, involvement of major parts of the scalp, involvement of genitals, involvement of palms and/or soles, onycholysis or onychodystrophy of at least two, fingernails, pruritus leading to scratching, and presence of single recalcitrant plaques. The presence of any of the previously mentioned manifestations may alter the classification of mild psoriasis to moderate to severe psoriasis in need of systemic therapy due to significantly impaired quality of life (Mrowietz, 2011).

1.3.2. Rationale for the Study Design

This is a Phase 4, multi-center, randomized, double-blind, placebo-controlled study to assess the impact of apremilast on health-related quality of life, efficacy, and safety in patients with manifestations of plaque psoriasis and impaired quality of life. The primary endpoint in this study is the proportion of subjects who achieve a $\geq$ 4-point change in the DLQI at Week 16 compared to placebo. The study population will be very heterogeneous and consist of subjects with a variety of clinical manifestations of psoriasis, such as scalp, nail, palmoplantar, and genital psoriasis and lesions in visible locations. Common among patients with any of these manifestations is a high impairment in Quality of Life (QOL); therefore, assessing the proportion of subjects who achieve a minimal clinically important difference in the DLQI is clinically meaningful. Although the DLQI is the gold standard QOL assessment in psoriasis and other dermatologic diseases, as a patient-reported outcome, it is often associated with a high placebo

response rate. To understand the true impact of apremilast on QOL in patients with manifestations of psoriasis and impaired quality of life, a 16-week placebo-controlled period is necessary. After Week 16, subjects who were randomized to placebo will receive active treatment with apremilast through Week 52.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to assess the impact of apremilast 30 mg twice daily (BID), compared to placebo, on health-related quality of life (qol) in subjects with manifestations of plaque psoriasis and impaired quality of life at Week 16.
Secondary Objective(s)
The secondary objectives are: • To assess the efficacy and safety of apremilast 30 mg BID, compared to placebo in subjects with manifestations of plaque psoriasis and impaired quality of life at Week 16 • To assess the long-term effects of apremilast 30 mg BID, with respect to quality of life, efficacy, and safety at Weeks 32 and 52
Exploratory Objective(s)
The exploratory objectives are: • To assess the efficacy of apremilast 30 mg BID, compared to placebo in subgroups of subjects with specific manifestations [redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Dermatology Life Quality Index (DLQI)	Proportion of subjects who achieve a ≥ 4-point reduction from baseline	Weeks 16
Secondary	DLQI	Proportion of subjects who achieve a ≥ 4-point reduction from baseline	Weeks 32, 52
	DLQI	Mean change from baseline	Weeks 16, 32, 52
	Itch Numeric Rating Scale (NRS)	Mean change from baseline in Itch NRS score	Weeks 16, 32, 52
	Skin Discomfort/Pain Visual Analog Scale (VAS)	Mean change from baseline in skin discomfort/pain VAS	Weeks 16, 32, 52
	Body Surface Area (BSA)	Mean percent change in BSA affected by psoriasis	Weeks 16, 32, 52
	Patient Benefit Index (PBI)	Proportion of subjects who achieve PBI score of ≥ 1	Weeks 16, 32, 52
	Psoriasis Area Severity Index (PASI)	Proportion of subjects who achieve PASI < 3	Weeks 16, 32, 52

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	European Quality of Life 5-Dimension (EQ-5D)	Mean percent change from baseline in EQ-5D score	Weeks 16, 52
	Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)	Mean change in WPAI domain scores	Weeks 16, 52
	Treatment-emergent Adverse events	Frequency and incidence rate of any TEAE by SOC, PT, severity, and relationship of adverse events (AEs) to investigational product (IP).	During double-blinded treatment and throughout the duration of the apremilast treatment
	Clinically significant changes in body weight, waist circumference, vital signs, and/or laboratory findings	Frequency of clinically significant changes in body weight, waist circumference, vital signs, and/or laboratory findings.	During double-blinded treatment and throughout the duration of the apremilast treatment
Exploratory	[redacted]		
	Static Physician Global Assessment (sPGA) of Visible locations	Proportion of subjects who achieve sPGA score of 0 or 1 (among subjects randomized with moderate to severe psoriasis in visible areas, defined as sPGA ≥ 3, which include the dorsal hand, face, neck, or hairline)	Weeks 16, 32, 52
	Scalp Physician Global Assessment (ScPGA)	Proportion of subjects who achieve ScPGA score of 0 or 1 (among subjects randomized with moderate to severe scalp psoriasis, ScPGA ≥ 3)	Weeks 16, 32, 52
	Nail Psoriasis Severity Index (NAPSI)	Proportion of subjects who achieve NAPSI score of 0 in the target fingernail (among subjects randomized with presence of nail psoriasis, defined as onycholysis and onychodystrophy in at least 2 fingernails)	Weeks 16, 32, 52

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Modified Static Physician Global Assessment-Genitalia (sPGA-G)	Proportion of subjects who achieve modified sPGA-G score of 0 or 1 (among subjects randomized with moderate to severe genital psoriasis, modified sPGA-G ≥ 3)	Weeks 16, 32, 52
	Palmoplantar Psoriasis Physician Global Assessment (PPPGA)	Proportion of subjects who achieve PPPGA score of 0 or 1 (among subjects randomized with moderate to severe palmoplantar psoriasis, PPPGA ≥ 3)	Weeks 16, 32, 52

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 4, multi-center, randomized, placebo-controlled, double-blind study of the impact of apremilast on quality of life, efficacy, and safety in subjects with manifestations of plaque psoriasis and impaired quality of life.

Approximately 255 subjects will be randomized 2 (apremilast):1 (placebo) in approximately 6 to 10 countries in Western Europe. Subjects will be block-randomized to each of the manifestations of psoriasis (scalp psoriasis, nail psoriasis, palmoplantar psoriasis, genital psoriasis, and psoriasis in visible locations). If subjects present with multiple manifestations, they will be allocated to the manifestation which is most severe, as determined by the subject. However, all manifestations will be assessed for efficacy at each study visit.

- After a 5-day titration with apremilast, subjects will receive apremilast 30 mg tablets or matching placebo orally twice daily (BID) for 16 weeks. Subjects randomized to the apremilast treatment group will receive apremilast 30 mg tablets orally twice daily for 52 weeks.
- Subjects randomized to the placebo treatment group will receive placebo tablets (identical in appearance to the apremilast 30 mg tablets) orally twice daily for 16 weeks. Beginning at Week 16 and after a 5-day titration with apremilast, subjects initially randomized to placebo will be switched to receive apremilast 30 mg BID for an additional 36 weeks (52 weeks total).

The study will consist of 4 phases:

- Screening Phase – up to 5 weeks (35 days)
- Double-blind Placebo-controlled Phase – Weeks 0 to 16

  Subjects will receive treatment with either

  – apremilast 30 mg tablets orally BID, or

  – matched placebo tablets orally BID
- Apremilast Extension Phase – Weeks 16 through 52

  – All subjects will be switched to (or continue with) apremilast 30 mg BID at Week 16 (after a 5-day titration for subjects initially randomized to placebo). All subjects will maintain this dosing through Week 52.
- Post-treatment Observational Follow-up Phase

  – 4-week post-treatment observational follow-up phase for all subjects who complete the study on treatment or discontinue from the study treatment early

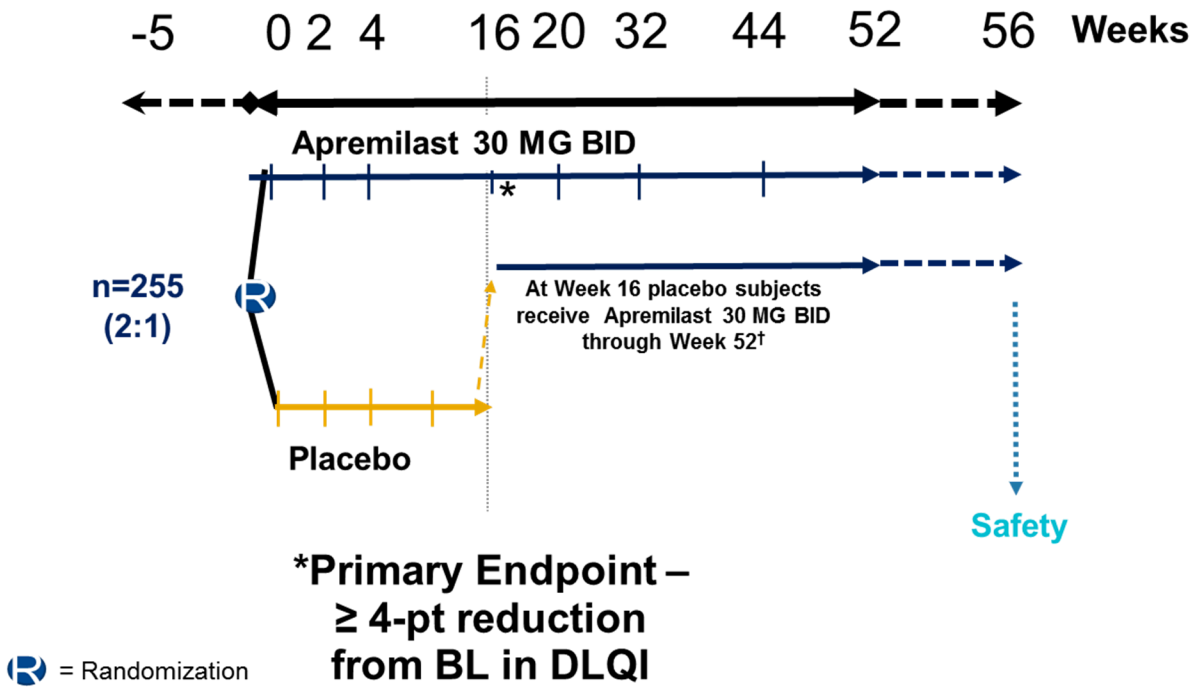
After all subjects complete the Week 16 Visit (or discontinue prematurely from the study), selected members of the Amgen study team and external partner who do not have direct interaction with subjects will be unblinded for the analysis of the Week 16 data. These persons may include but are not limited to the following: Therapeutic Area Head, Study lead, Medical

Director and the Statistician. The results from these analyses may be published prior to the end of the study.

The blind should be maintained for persons responsible for the ongoing conduct of the study. Subjects, Investigators and persons responsible for the ongoing conduct of the study will continue to be blinded to the original treatment assignment until the end of the study. These persons are those individuals who have direct interaction with subjects and/or subject assessments, and may include but are not limited to the following: Clinical Trial Manager, Data Manager, Clinical Research Associates (Amgen and External Partners) and Site Monitors.

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

Figure 1: Overall Study Design



BID = twice daily; BL = baseline; DLQI = Dermatology Life Quality Index.

3.2. Study Duration for Subjects

The study is designed as a 1-year (52-week) study, with a 4-week Post-treatment Observational Follow-up Phase.

Visits will be scheduled at screening (no more than 5 weeks prior to randomization), Week 0 (baseline/randomization), Weeks 2, 4, 16, 20, 32, 44, and 52. Subjects who discontinue before

Week 52 will be asked to attend an Early Termination visit. A post-treatment observational follow-up will be conducted by phone at Week 56 for subjects who complete the 52-week study treatment, or 4 weeks after study treatment discontinuation.

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 255 subjects will be enrolled in the study across approximately 6 to 10 countries in Western Europe.

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 has diagnosis of chronic plaque psoriasis for at least 6 months prior to baseline, that cannot be controlled by topical therapy.
5. Subject has a PASI score ranging from ≥3 to ≤ 10 at baseline.
6. Subject has a DLQI score > 10 at baseline.
7. Subject has presence of ≥ 1 clinical manifestations of plaque psoriasis, defined as at least one of the following:
    a. Moderate to severe scalp psoriasis, defined as Scalp Physician Global Assessment (ScPGA) ≥ 3
    b. Nail psoriasis, defined as onycholysis and onychodystrophy in at least 2 fingernails
    c. Moderate to severe genital plaque psoriasis, defined as modified static Physicians Global Assessment of Genitalia (sPGA-G) ≥ 3
    d. Moderate to severe palmoplantar psoriasis, defined as Palmoplantar Psoriasis Physicians Global Assessment (PPPGA) ≥ 3
    e. Moderate to severe plaque psoriasis in visible locations (dorsal hand, face, neck, and hairline) with static Physicians Global Assessment (sPGA) ≥ 3
8. Subject must be in general good health (except for psoriasis) as judged by the Investigator, based on medical history, physical examination, and clinical laboratories. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions.)
9. Subject must have failed to respond to, or be contraindicated to, or intolerant to other systemic therapy including, but not limited to, cyclosporine, methotrexate, acitretin, psoralen and ultraviolet-A-light (PUVA), fumaric acid esters or biologic therapies.
10. Subjects (**in Italy only**) must be non-responder to, contraindicated to, or intolerant to other systemic therapy (including cyclosporine, methotrexate, or PUVA) **AND** also be contraindicated to, or intolerant to biologics.

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.

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

4.3. Exclusion Criteria

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

1. Subject has any condition, including other inflammatory diseases or dermatologic conditions, which confounds the ability to interpret data from the study, including other types of psoriasis (ie, erythrodermic, or guttate), other than plaque psoriasis or inverse psoriasis.
2. Subject has history of drug-induced psoriasis.
3. Subject has arthritis that requires disease-modifying antirheumatic drug (DMARD) treatment.
4. Subject unable to avoid use of tanning booths for at least 4 weeks prior to baseline and during study.
5. Subject is currently enrolled in any other clinical trial involving an investigational product.
6. Other than psoriasis, subject has history of clinically significant or uncontrolled disease (as determined by the Investigator), including the presence of laboratory abnormalities, cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease, which places the subject at unacceptable risk if he/she were to participate in the study.

[†] A female of childbearing potential is defined as 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).

7. Prior history of suicide attempt at any time in the subject's lifetime prior to signing the informed consent, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent.
8. Subjects with severe renal impairment, defined by eGFR (estimated glomerular filtration rate) or CLcr (creatinine clearance) less than 30 mL/min, are also categorized as having Stage 4 Chronic Kidney Disease (CKD), and are excluded from the study.
9. Malignancy or history of malignancy or myeloproliferative or lymphoproliferative disease within the past 3 years, except for treated (ie, cured) basal cell or squamous cell in situ skin carcinomas.
10. 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 and the infection cured, at least 4 weeks prior to Screening and no new or recurrent infections prior to the Baseline Visit.
11. Subject has received a live vaccine within 3 months of baseline or plans to do so during study.
12. Subject is a pregnant or breastfeeding (lactating) woman.
13. Subject has used topical therapy within 2 weeks of randomization (including, but not limited to, topical corticosteroids, retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, anthralin/dithranol, or moisturizers which contain urea or salicylic acid). Use of phototherapy within 4 weeks prior to randomization. Use of conventional systemic therapy or systemic corticosteroids within 4 weeks prior to randomization, except for conditions other than psoriasis or psoriatic arthritis. Use of biologic therapy within 5 pharmacokinetic half-lives.
14. Prior treatment with apremilast, or participation in a clinical study, involving apremilast.
15. Subject has any condition that confounds the ability to interpret data from the study.
16. Subject has history of allergy or hypersensitivity to any components of the IP (including placebo).
17. Subject has rare hereditary problem of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption.

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening	Placebo-Controlled Phase[a]				Apremilast Extension Phase[b]				Post-Treatment Observational Follow-up[d]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[c]**	
Week	**-35 to 0 days**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**16 (± 3 days)**	**20 (± 4 days)**	**32 (± 4 days)**	**44 (± 4 days)**	**52 (± 4 days)**	**56 weeks (or 4 weeks after study discontinuation)**
Informed consent[e]	X	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion criteria	X	X	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Prior / concomitant medications or therapies	X	X	X	X	X	X	X	X	X	-
Clinical and Laboratory Assessments										
Adverse events[f]	X	X	X	X	X	X	X	X	X	X
Pregnancy test and contraception education[g]	X	X	-	-	-	-	-	-	X	-
Vital signs	X	X	X	X	X	X	X	X	X	-
Height	X	-	-	-	-	-	-	-	-	-
Weight	X	X	X	X	X	X	X	X	X	-
Waist Circumference	X	X	X	X	X	X	X	-	X	-
Body Mass Index	X	-	-	-	-	-	-	-	-	-
Physical Examination	X	-	-	-	-	-	-	-	-	-
Clinical laboratory evaluations[h,i]	X	X	-	-	X	-	X	-	X	-

Table 3: Table of Events (Continued)

	Screening	Placebo-Controlled Phase[a]				Apremilast Extension Phase[b]				Post-Treatment Observational Follow-up[d]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[c]**	**56 (or 4 weeks after study discontinuation)**
Week	**-35 to 0 days**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**16 (± 3 days)**	**20 (± 4 days)**	**32 (± 4 days)**	**44 (± 4 days)**	**52 (± 4 days)**	
Health-related Quality of Life and Efficacy Assessments[j]										
DLQI	X	X	X	X	X	X	X	-	X	-
sPGA of Visible Location[k]	X	X	X	X	X	X	X	-	X	-
ScPGA[k]	X	X	X	X	X	X	X	-	X	-
Nail Assessment[l]	X	X	X	X	X	X	X	-	X	-
NAPSI[k]		X	X	X	X	X	X	-	X	-
Modified sPGA-G[k]	X	X	X	X	X	X	X	-	X	-
PPPGA[k]	X	X	X	X	X	X	X	-	X	-
Itch NRS	-	X	X	X	X	X	X	-	X	-
Skin Discomfort/Pain VAS	-	X	X	X	X	X	X	-	X	-
PASI	X	X	X	X	X	X	X	-	X	-
BSA	-	X	X	X	X	X	X	-	X	-
EQ-5D	-	X	-	-	X	-	-	-	X	-
PNQ	-	X	-	-	-	-	-	-	-	-
PBQ	-	-	-	X	X	-	X	-	X	-
WPAI: PSO	-	X	-	-	X	-	-	-	X	-
Photography[m]	-	X	-	-	X	-	X	-	X	-

Table 3: Table of Events (Continued)

	Screening	Placebo-Controlled Phase[a]				Apremilast Extension Phase[b]				Post-Treatment Observational Follow-up[d]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET[c]**	**56 (or 4 weeks after study discontinuation)**
Week	**-35 to 0 days**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**16 (± 3 days)**	**20 (± 4 days)**	**32 (± 4 days)**	**44 (± 4 days)**	**52 (± 4 days)**	
Dispense IP	-	X	-	X	X	X	X	X	-	-
Return and Count IP Tablets	-	-	-	X	X	X	X	X	X	-

Abbreviations: BMI = body mass index; BSA = body surface area; [redacted] DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life 5-Dimension; FCBP = females of childbearing potential; IP = investigational product; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index; PBQ = Patient Benefit Questionnaire; PNQ = Patient Needs Questionnaire; PPPGA = Palmoplantar Psoriasis Physicians Global Assessment; NRS = Numeric Rating Scale; ScPGA = Scalp Physician Global Assessment; sPGA = static Physicians Global Assessment; sPGA-G = static Physicians Global Assessment of Genitalia; VAS = Visual Analog Scale; WPAI:PSO = Work Productivity and Activity Impairment Questionnaire: Psoriasis.

[a] Visits in the Placebo-controlled Phase to be performed ± 3 days.

[b] Visits in the Apremilast Extension Phase to be performed ± 4 days.

[c] Visit 9 will serve as the Early Termination Visit for any subject who prematurely discontinues from the study, prior to Week 52. 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] Post-treatment observational follow-up will be conducted by telephone.

[e] Written informed consent will be obtained by the Principal Investigator or designee prior to initiation of any study procedures, including washouts from prior medications.

[f] Adverse event review should include new or worsening psychiatric symptoms, suicidal ideation, suicidal attempt, severe diarrhea, nausea and vomiting, and unexplained and clinically significant weight loss. See Section 6.5.

[g] Females of childbearing potential (FCBPs) only. Serum pregnancy tests are performed at Screening, and Early Termination Visit/Last Treatment Visit. Urine pregnancy test kit will also be provided to the site and performed at baseline prior to randomization. The Investigator will educate all FCBP about the different options of contraceptive methods and their correct use at Screening and Baseline visits. The subject will be reeducated every time their contraceptive measures/methods or their ability to become pregnant changes. A pregnancy test(s) should be administered if the FCBP subject misses a menstrual period.

[h] Laboratory assessments will include routine/standard chemistry and hematology panel of tests. A lipid panel will be included in the standard chemistry panel. If screening laboratory assessments are within 7 days of Baseline (Week 0), laboratory assessment does not need to be repeated at Baseline (Week 0). For females of childbearing potential urine pregnancy test will be performed at Baseline (Week 0) to confirm subject eligibility (negative results required for IP administration).

[redacted]

[j] Subject assessments must be completed in the following order: DLQI, Itch NRS, Skin Discomfort/Pain VAS, EQ-5D, PNQ/PBQ, and WPAI: PSO, as scheduled in the Table of Events.

[k] All manifestations should be assessed in all subjects at all visits, so that improvement, worsening, or new onset of any of these manifestations can be assessed.

[l] Nail assessments will evaluate presence of nail psoriasis, defined as onycholysis and onychodystrophy.

[m] Photographs will be obtained from subjects who provide separate consent to be photographed and at select sites only.

6. PROCEDURES

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

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 5 weeks of randomization. Subjects who do not meet eligibility criteria for the study may be re-screened once, after a minimum of 35 days from the date of their first screening.

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

Safety laboratory analyses and all assessments will be performed (locally/centrally). Screening laboratory values must demonstrate subject eligibility, but may be repeated once within the screening window, if necessary.

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

- Demographics (year of birth, sex, and race, if allowed by local regulations, will be collected).
- Complete medical history
- Prior and concomitant medications
- Physical examination, height, weight, waist circumference, body mass index (see Appendix O)
- Vital signs (including blood pressure and heart rate)
- Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC Morphology, mean corpuscular volume (MCV), white blood cell (WBC) count (with differential), and platelet count.
- Chemistry panel including sodium, potassium, calcium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH). A lipid panel will be included in the standard chemistry panel. [redacted]
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72

hours prior to the first administration of IP, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration).

- Contraception education will be performed by the Investigator at screening for 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.
  - A pregnancy test should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed
  - Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.
- Adverse event assessment begins when the subject signs the informed consent form
- Health-related quality of life and efficacy assessments to determine study eligibility, including DLQI, sPGA of visible locations, ScPGA, NAPSI, modified sPGA-G, PPPGA, and PASI

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 35 days (5 weeks) of signing the ICF. An administrative window of ± 3 day is permitted for Visits 3 and 4 and ± 4 days is permitted for Visits 5 through 9.

The following procedures will be conducted as outlined in the Table of Events, Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Inclusion/Exclusion criteria (Baseline/Visit 2)
- Concomitant medications and therapies evaluation
- Vital signs
- Weight, waist circumference
- Adverse event evaluation (continuously and through 28 days after last dose of apremilast)
- Clinical laboratory evaluations [If screening laboratory assessments are within 7 days of Baseline (Week 0), laboratory assessment does not need to be repeated at Baseline (Week 0)]
- Efficacy assessment (see Section 6.4) [In addition to assessments specified in Table 3, investigator will follow country guidelines to monitor therapy outcomes according to clinical routine care and may assess efficacy or safety at any unscheduled visit and document in source documents.]
- Dispense IP
- Return and count IP tablets
- Urine (or serum) pregnancy test (prior to dosing on Day 1)

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 9) assessments will also be performed for subjects who complete the study.

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

- Weight, waist circumference
- Vital signs
- Concomitant medications and therapies evaluation
- Adverse event evaluation (through 28 days past last dose of apremilast)
- Clinical laboratory evaluations
- Serum pregnancy test for females of childbearing potential (β-subunit of human chorionic gonadotropin [Serum β-hCG])
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted
- Return and count IP tablets
- Efficacy assessment

6.3. Follow-up Period

6.3.1. Post-Treatment Observational Follow-up

All subjects will be followed for 28 days after the last dose of apremilast for AE reporting , as well as all SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study, as described in Section 10.1. A 4-week post-treatment observational follow-up will be conducted by telephone at Week 56 for subjects who complete the 52-week study treatment or 4 weeks after study treatment discontinuation.

6.4. Efficacy Assessments

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

6.4.1. The Dermatology Life Quality Index (DLQI)

The DLQI (Finlay, 1994) will be assessed by the subject upon arrival at the site before any other procedures or assessments are performed. The DLQI was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease (Finlay, 1994). The instrument contains 10 items pertaining to 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 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 quality of life. See Appendix B.

6.4.2. Static Physicians Global Assessment (sPGA) of Visible Locations

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. In this study, sPGA is used to evaluate psoriasis **only** in **visible locations**, defined as **dorsal hand, face, neck and hairline**. 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 C for grading criteria.

6.4.3. Scalp Physician Global Assessment (ScPGA)

The ScPGA will assess scalp involvement. See Appendix D for grading criteria. The 5-point ScPGA scale ranges from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe).

6.4.4. Nail Assessments/Nail Psoriasis Severity Index (NAPSI)

The number of fingers with psoriasis nail involvement, defined as onycholysis and onychodystrophy, will be counted.

The NAPSI will assess one target thumb nail or fingernail representing the worst nail psoriasis involvement at Baseline. See Appendix E for grading criteria.

6.4.5. Modified static Physicians Global Assessment of Genitalia (Modified sPGA-G)

The modified sPGA-G is the assessment by the Investigator of the overall disease severity at the time of evaluation of the genital regions. The assessment area includes the vulvar region in women, from the clitoral prepuce to the perineum, and the penis, scrotum, and perineum in men. It does not include the pubis, inguinal folds, peri-anal region, or gluteal cleft; however, in this study, the assessment will be modified to also include the peri-anal region and gluteal cleft. As with the sPGA, it is a 5-point scale, ranging from 0 (clear) to 4 (severe). Note that not all three individual features will always be present on evaluation. Thus, while the total represents a combination of the

three features, it should be primarily determined by the degree of erythema, as that is the dominant feature in the majority of cases of genital psoriasis (Merola, 2017). Appendix F.

6.4.6. Palmoplantar Psoriasis Physicians Global Assessment (PPPGA)

The PPPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation of palms and soles (Leonardi, 2007). The scale ranges from ranging from 0 (clear) to 4 (severe). See Appendix G.

6.4.7. Itch Numeric Rating Scale (NRS)

The Itch NRS is a single-item patient-reported outcome that asks subjects to assess the worst severity of itch over the past 24 hours. Subjects indicate itch severity by circling the number that best describes the worst level of itching due to psoriasis in the past 24 hours on an 11-point scale anchored at 0, representing 'no itching' and 10, representing 'worst itch imaginable' (Naegeli, 2015). See Appendix H.

6.4.8. Skin Discomfort/Pain Visual Analog Scale (VAS)

The subject will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents no skin discomfort/pain, and the right-hand boundary represents skin discomfort/pain as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded. See Appendix I.

6.4.9. Body Surface Area (BSA)

Body surface area is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint"), which equates to approximately 1% of total BSA.

6.4.10. Psoriasis Area Severity Index (PASI)

The PASI will be determined for all subjects throughout the study. The PASI calculation is described in Appendix J.

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

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

6.4.11. Patient Benefit Index (PBI)

The PBI is a validated patient-reported instrument to assess patient-relevant benefits of psoriasis treatment (Feuerhahn, 2012). Prior to starting therapy, subjects are asked to assess their treatment expectations by completing the Patient Needs Questionnaire (PNQ) (See Appendix K). After a period of treatment, subjects are then asked to assess the benefits of treatment by completing the Patient Benefit Questionnaire (PBQ) (See Appendix L). The Patient Benefit Index represents the subject benefits realized as a function of most important subject needs. The PBI score ranges from 0 (no benefit) to 4 (maximum benefit).

6.4.12. The European Quality of Life 5-Dimension Questionnaire (EQ-5D)

EQ-5D (The EuroQol Group, 1990) measures the subject's general health state as a vertical VAS and 5 quality of life domains as multiple-choice questions: mobility, self-care, main activity (work, study, housework, family/leisure activities), pain/discomfort, and anxiety/depression, the combination of which generates 243 possible health states. See Appendix M.

6.4.13. The Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)

The WPAI: PSO questionnaire is a validated, 6-item self-administered instrument used to assess the impact of disease on work productivity in psoriasis due to general health or a specified health problem (Reilly, 2012; Appendix N).

[redacted]

6.4.15. Photography

Photographs will be collected only at selected sites, in subjects who consent, and will be considered as supportive evidence of efficacy. Descriptive summary of photography will be addressed in the statistical analysis plan (SAP) and included in the clinical study report.

Photographs will be taken of all effected manifestations of plaque psoriasis at Weeks 0, 16, 32, and 52. Appropriate protective mechanisms shall be implemented to ensure that the photographs do not contain any subject-specific identifiers (such as tattoos, scars, etc) when shared with the Sponsor.

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 sign a separate consent form specific to photography at Visit 1 (Screening Visit), prior to being photographed.

6.5. Safety Assessments

In addition to safety monitoring conducted by Investigators and individual study personnel, AEs, serious adverse events (SAEs), discontinuations and laboratory findings will be reviewed by the study team. The review follows the Council for International Organizations for Medical Sciences, Working Group VI (CIOMS VI) recommendations.

The study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use/GCP and applicable regulatory requirements.

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

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

A serum pregnancy test with a sensitivity of ≤ 15 mIU/mL will be required for FCBP subjects at Screening and the Week 52 Visit (or at the Early Termination Visit for subjects who prematurely discontinue from the study). Urine pregnancy test will be performed on all FCBP subjects at the Baseline Visit, prior to randomization. A urine pregnancy test kit will be provided by the central laboratory. Pregnancy tests should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed.

6.5.2. Vital Signs, Weight and Waist Circumference

Vital signs, including pulse, and seated blood pressure, will be taken during the visits indicated in Table 3, Table of Events. Weight and waist circumference will be measured and recorded at the Screening Visit and then as indicated in Table 3, Table of Events; Body mass index (BMI) will be calculated programmatically based on the Height measured and recorded at Screening. In the event of unexplained and clinically significant weight loss, the patients should be evaluated by the investigator and discontinuation of treatment should be considered (see Section 11).

6.5.3. Physical Examination

A physical examination includes evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems. A physical examination is done at Screening as indicated in Table 3, Table of Events. Additional physical examinations may be performed during the course of study as deemed necessary per investigator's judgment and recorded in source documents.

6.5.4. Psychiatric Evaluation

Treatment with apremilast is associated with an increase in adverse reactions of depression. Before using apremilast in subjects with a history of depression and/or suicidal thoughts or behavior, the Investigator should carefully weigh the risks and benefits of treatment with apremilast in such patients. Subjects should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact the Investigator.

If a patient suffers from new or worsening psychiatric symptoms, or suicidal ideation is identified, it is recommended to discontinue the subject participation to the study. Subjects who are identified by the Investigator as having attempted suicide must be immediately withdrawn from the study (see Section 11).

6.5.5. Severe Diarrhea, Nausea and Vomiting

There have been post-marketing reports of severe diarrhea, nausea, and vomiting associated with the use of apremilast. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications. Subjects should be monitored for severe diarrhea, nausea and vomiting. If patients develop severe diarrhoea, nausea, or vomiting, discontinuation of treatment may be necessary (see Section 11).

6.5.6. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as indicated in Table 3, Table of Events. These include complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count) and serum chemistries including sodium, potassium, calcium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH). A lipid panel will be included in the standard chemistry panel. [redacted]

6.5.7. Tuberculosis

After an extensive clinical development program, there is no current evidence that apremilast has the potential to activate latent TB. Therefore, no TB testing will be done in this protocol. Investigators can test for TB if clinically indicated, using the site's local or country-specific guidelines. If the subject has active or latent TB, he/she should be treated according to local guidelines. Subjects who require TB treatment at any time during the study must be discontinued.

6.5.8. Adverse Events

All subjects will be monitored for adverse events (AEs) during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, radiological, or surgical findings; physical examination findings; psychiatric evaluation; or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP. Adverse events and serious adverse events (SAEs) will be recorded on the AE page of the electronic case report form (eCRF), the paper SAE reporting form (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 using the paper Serious Adverse Event Report Form by facsimile/email of the paper SAER Form directly to Amgen Global Patient Safety.

Details of AE reporting can be found in Section 10.1 of the protocol.

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 provided by Amgen as 10, 20, or 30 mg tablets in blister cards for dose titration purposes. Apremilast will also be provided as 30 mg tablets in high-density polyethylene (HDPE) bottles (approximately 80 tablets) with child-resistant caps.

Identically-appearing placebo tablets will also be provided by Amgen in blister cards.

7.2. Treatment Administration and Schedule

Subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets, or identically appearing placebo, for the dose titration, at the baseline visit (Week 0) and Week 16.

Starting at Week 16, all subjects will be switched to, or will continue with, apremilast. Subjects originally randomized to placebo at Week 0 will be switched to apremilast at Week 16. At all visits (Week 0 to Week 16), titration / treatment will be dispensed in blister cards with apremilast or placebo tablets and will be identically appearing. Beginning with the Week 20 visit, all subjects will receive open label HDPE bottles of IP tablets. All subjects will maintain this dosing through Week 52.

Apremilast or placebo tablets will be taken orally twice daily, approximately 12 hours apart, through the last treatment visit.

The titration blister card configurations are pictured in Appendix R. The treatment schema for dose titration at Baseline is shown in Appendix P, and at Week 16 is shown in Appendix Q.

Dose modifications are not permissible in this study.

7.3. Method of Treatment Assignment

After the informed consent is signed, subjects will be assigned a subject identification number using a centralized interactive response technology (IRT). At the Baseline Visit, a centralized schema will be applied to assign subjects who meet the eligibility criteria in a 2:1 ratio to receive either apremilast 30 mg tablets orally BID or identically-appearing placebo tablets using the IRT. Subjects will be block-randomized to each of the manifestations of plaque psoriasis specified in the protocol. If subjects present with multiple manifestations, they will be allocated to the manifestation which is most severe, as determined by the subject at the screening and baseline visits. However, all manifestations will be assessed for efficacy at each study visit.

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 subject 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.

7.4. 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 to Week 20 will be supplied in blister cards. Investigational product tablets at Week 20 and through Week 52 will be supplied in open label HDPE bottles with child-resistant caps.

7.5. Investigational Product Accountability and Disposal

The Investigator, or designee, is responsible for taking an inventory of each shipment of oral IP received, and comparing it with the accompanying IP shipping order/packing list.

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

Investigational product will be stored per the storage conditions identified on the IP label. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

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

7.6. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP in tablet form (both blister cards and bottles). 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. At each study visit, subjects will be asked whether they have taken their IP as instructed. 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 Posttreatment 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) should be discussed with Amgen. Compliance is defined as taking between 75% and 120% of dispensed IP.

7.7. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the investigational product(s) (IPs) 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-study drugs 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.

Adverse Events associated with an overdose must be collected on the Adverse Events page of the eCRF (see Section 10.1) for all overdosed subjects, but the overdose itself is not considered an AE.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

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 signing the informed consent throughout their entire participation in the study, including those initiated prior to signing the informed consent and continued through 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.

During the study, the initiation of new concomitant medications or a change of existing concomitant medications may potentially indicate the presence of a new adverse event or the worsening of an existing condition. If appropriate, such events should be recorded in the eCRF.

The following topical therapies will be permitted throughout the study:

- Unmedicated skin moisturizers will be permitted for body lesions only.
  - Permitted skin moisturizers may not contain urea or salicylic acid.

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, unless otherwise specified in Section 8.1 (including, but not limited to topical corticosteroids, retinoids or Vitamin D analog preparations, tacrolimus, pimecrolimus, coal tar, anthralin/dithranol, or urea- and salicylic acid-containing moisturizers)
- Conventional systemic therapy
  - Conventional systemic therapy including but not limited to cyclosporine, methotrexate, retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters, and corticosteroids
- Biologic agents, including:

  - Adalimumab, etanercept, infliximab, or certolizumab pegol, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab

- Phototherapy
  - Ultraviolet light B (UVB) or psoralens and long-wave ultraviolet radiation (PUVA)
- Use of any investigational drug or device
- Use of tanning booths, which may confound the ability to interpret data from the study.

8.4. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

The objective of this study is to evaluate the health-related quality of life, efficacy, and safety of apremilast compared to placebo, for 16 weeks, and evaluate the long-term effects of apremilast on quality of life, efficacy, and safety for up to 52 weeks in subjects with manifestations of plaque psoriasis and impaired quality of life.

9.2. Study Population Definitions

Four analysis populations will be defined for this study. These populations include the safety population, the intent to treat (ITT) population, the per protocol (PP) population, and the apremilast exposure population.

- The Safety population will consist of all subjects who are randomized and receive at least one dose of investigational product (IP). This set of subjects will be included in the treatment group corresponding to the IP they actually receive. This will be the population for all safety analyses on data from the Placebo-controlled Phase.
- The ITT population will consist of all subjects who are randomized. This will be the primary population for the primary endpoint and all other quality of life and efficacy analyses. Baseline summaries will also be based on the ITT population.
- The PP population will consist of all subjects who are in the ITT population, complete the Placebo-controlled Phase, and have no major protocol violations. The PP population will only be used to supplement the primary endpoint ITT analysis.
- The apremilast (APR) exposure population will consist of only those subjects who receive at least one dose of apremilast treatment. The APR exposure population will only be used for the purposes of safety reporting including all safety data during apremilast treatment.

9.3. Sample Size and Power Considerations

Using an exploratory analysis on a subset of subjects meeting the following criteria: 1) ScPGA $\geq$ 3 at baseline or 2) NAPSI $\geq$ 1 at baseline or PPPGA $\geq$ 3 at baseline and DLQI $\geq$ 10 at baseline in the PSOR-008 and PSOR-009 Phase 3 studies, it was estimated that the proportion of subjects who achieved a $\geq$ 4-point reduction from baseline in DLQI was 0.50 (97 responders out of 193 subjects) and 0.83 (337 responders out of 406 subjects) for placebo and apremilast 30 mg, respectively.

Assuming a placebo DLQI Responder proportion of 0.50 at Week 16, a minimum total sample size of 210 subjects (140 allocated to apremilast 30 mg and 70 allocated to placebo) is needed to detect a 0.20 difference in the DLQI Responder proportions between apremilast and placebo with at least 0.807 power using a two-sided test at the 0.05 level of significance. This sample size calculation is based on an unpooled variance, and was determined using the commercial software EaST, Version 6.3. Allowing for a 18% discontinuation rate prior to Week 16, the sample size was revised from a total of 210 subjects to a final sample size of 255. If there are no discontinuations prior to Week 16, then the power with a sample size of 255 subjects would

increase to 0.872. Hence when addressing missing data due to discontinuations with multiple imputations, we would expect the power to be in between the bounds of 0.807 (based on 210 subjects) and 0.872 (based on 255 subjects), as the analysis that incorporates multiple imputation under a missing at random assumption will always be more efficient compared to the observed analysis when the missing data is actually missing completely at random.

9.4. Background and Demographic Characteristics

Subjects' 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. The disease characteristics at baseline will also be summarized using appropriate descriptive statistics. These descriptive statistics will be summarized by the randomized treatment group using the ITT population.

9.5. Subject Disposition

The distribution of enrollment by site will be provided. Subject disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for the Placebo-controlled Phase (Weeks 0 to 16) and the apremilast Extension Phase (Weeks 16 to 52). Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

Statistical comparisons will be made between apremilast and placebo at Week 16. The statistical test on the primary endpoint will be at a 2-sided 0.05 significance level with treatment effect estimates and the corresponding 95% confidence intervals (CIs) being reported. Any p-values reported other than for the primary endpoint analysis will be considered as summary statistics.

Descriptive statistic summaries for the observed data will also be provided by visit and randomized treatment group.

9.6.1. Primary Endpoint

The primary endpoint is the proportion of subjects achieving a ≥ 4 point reduction from baseline in DLQI at Week 16. It will be analyzed using the ITT population. However, a supplemental analysis will be performed using the PP population.

The primary analysis for the primary endpoint at Week 16 will be the Cochran–Mantel–Haenszel (CMH) test adjusted for the stratification factor at randomization (ie, the 5 difficult to treat manifestation types). This form of the CMH test will use the sample sizes in each of the strata as weights when estimating the adjusted difference in the treatment proportions, constructing 95% Wald confidence intervals for the difference, and conducting a statistical test of no difference between the treatment proportions (ie, H_0: $\pi_{APR} - \pi_{PBO} = 0$ as the null hypothesis).

All reasonable attempts will be made to prevent missing data from occurring in this study, especially through Week 16. However, in the case of missing data at Week 16 a multiple imputation (MI) method will be incorporated into the primary analysis. Imputations will be made on the continuous-like scale of the total DLQI score, and then dichotomized according to the primary endpoint definition prior to performing the CMH analysis. The aim of the multiple

imputation approach is to incorporate a representative random sample in place of the missing data such that unbiased estimation and valid statistical inferences (ie, confidence intervals and hypothesis testing) can be made.

Details with respect to the construction of the CMH test statistic, multiple imputation procedure and the terminal analysis method for combining the multiple imputation results, as well as all supportive sensitivity and subgroup analyses involving the stratums for the primary endpoint will be specified in the SAP.

9.6.2. Secondary and Exploratory Efficacy Endpoints

For continuous endpoints at Week 16, an analysis of covariance (ANCOVA) model with treatment and randomization strata as fixed effects and corresponding baseline value as a continuous covariate will be employed. Missing data will be addressed using multiple imputation. The adjusted means and standard errors will be reported for each of the treatment group using the ANCOVA model, as well as the estimated treatment effect (ie, difference in the adjusted treatment means, their standard errors, and 95% confidence intervals). In addition, descriptive statistics will be provided based upon the observed data which will not address missing data. Details regarding the methods of estimation to be performed at Weeks 32 and 52 will be provided in the statistical analysis plan (SAP).

For discrete endpoints, the CMH estimation method stratified by the randomization strata for assessing the difference in proportion between the treatment groups will be conducted. The weights in the CMH estimation method will be same as those used in the primary endpoint analysis. The adjusted difference in the proportions between the treatment groups, their standard errors, and corresponding 95% confidence intervals will be reported. Missing data will be addressed through multiple imputation similar to that of the primary endpoint analysis. In addition, descriptive statistics involving the sample size, the number of responders, and proportion of responders will be summarized by treatment group. Details regarding the methods of estimation to be performed at Weeks 32 and 52 will be provided in the SAP.

9.6.3. Photography

Photographs will be collected only at selected sites in subjects who consent and will be considered as supportive evidence of efficacy. Descriptive summary of photography will be addressed in the SAP and included in the clinical study report.

Photographs will be taken of all effected manifestations of plaque psoriasis at Weeks 0, 16, 32, and 52.

Subjects must sign a separate consent form specific to Photography at Visit 1 (Screening Visit).

[redacted]

9.6.5. Multiplicity Adjustment

There will be no multiplicity adjustment. Only the primary endpoint analysis will be used to declare a statistical significance.

9.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 9.2, 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 16-52).

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. Adverse events will be tabulated by study phase (Double-blind Placebo-controlled Phase or apremilast Exposure Phase). All treatment-emergent adverse events (AEs) will be summarized by system organ class, preferred term, severity, and relationship to IP. Adverse events leading to death or to discontinuation from treatment and serious AEs will also be summarized and listed separately.

Laboratory data will be summarized using shift tables showing the number of subjects with low, normal, and high values based on the normal ranges, pretreatment versus post-treatment.

Vital sign measurements, including weight, will be summarized by visit descriptively (count, mean, median, standard deviation, and range). In addition, shift tables showing the number of subjects with values below, within and above the normal reference ranges pretreatment versus post-treatment will be provided.

The changes and percent changes in body weight will be summarized by visit. In addition, the changes by baseline body mass index (BMI; (< 18.5, 18.5 to < 25, 25 to < 30, 30 to < 35, 35 to < 40, ≥ 40 kg/m^2) will be explored.

9.8. Interim Analysis

No interim analysis is planned for this study.

9.9. Other Topics

9.9.1. Investigational Product Compliance (Tablets)

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

9.9.2. Concomitant Therapy

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

9.9.3. Steering Committee

The conduct of this trial will be overseen by a steering committee (SC), presided over by the coordinating Principal Investigator. The SC will serve in an advisory capacity to the Sponsor. Operational details for the SC will be detailed in a separate SC charter.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE/SAE page of the eCRF 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 eCRF. (See Section 7.7 for definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is a serious adverse event (SAE), then the sequela must be reported on the paper SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the paper SAE report form and eCRF, but should not be reported as an SAE itself.

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

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well 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 eCRF, 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 eCRF 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

A serious adverse event (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 eCRF. Hospitalization or prolonged hospitalization for a complication from such a procedure remains a reportable SAE.
- An elective treatment of, or an elective procedure for, a pre-existing condition unrelated to the studied indication, that has not worsened from baseline.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the paper SAE Report Form must be completed. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event by submitting the SAE information using the

paper Serious Adverse Event Report Form by facsimile/email directly to Amgen Global Patient Safety.

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

10.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event according to the following grading scale:

Mild

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

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with 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 AEs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

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

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

10.2.3. Causality

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

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

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

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

10.2.4. Duration

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

10.2.5. Action Taken

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

10.2.6. Outcome

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

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

10.3. Abnormal Laboratory Values

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

- results in discontinuation from the study;
- requires treatment, modification/interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

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

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

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential – Collection of Pregnancy Information

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately. A female subject with suspected pregnancy may resume IP after a confirmed negative pregnancy test and consultation with the sponsor. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Global Patient Safety , or designee, immediately by email, , facsimile, or other appropriate method, using the Pregnancy Notification Form or approved equivalent form (refer to Appendix T). The Pregnancy Notification Form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

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

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

The Investigator will monitor the progress of the pregnancy of a female subject, 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 or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to 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 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.

10.4.2. Male Subject 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 T). 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 U) 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 serious criterion requires the completion of the relevant eCRFs and the paper SAE report form. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event by sending the SAE data/information using the paper SAE report form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms are 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) are to be collected/recorded/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 information on file including correspondence with Amgen and 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 S).
- 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 S).

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

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

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

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

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

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

For Amgen Global Patient Safety contact information, please refer to your site's paper Serious Adverse Event Report Form, paper Pregnancy Notification Form and/or paper Lactation Notification Form (Appendix S, Appendix T, Appendix U).

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
- Non-compliance with investigational products
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol deviation
- Pregnancy
- Physician decision
- Study terminated by sponsor
- Other (to be specified on the eCRF)

Subjects have the right to withdraw from the study at any time and for any reason. The reason for discontinuation should be recorded in the eCRF 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 investigational product.

The decision to discontinue a subject can be taken at any time and 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 or designee and forward appropriate supporting documents for review and discussion, without identifying the subject.

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 eCRF)

The reason for study discontinuation should be recorded in the eCRF 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 contact IRT for unblinded dose information.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

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

13.2. Investigator Responsibilities

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

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

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

The information contained in the protocol and amendments (with the exception of the information provided by 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. In addition to the main consent for the research study, the subjects will be given the opportunity to consent to two optional sub-studies, ie, the [redacted] and, at selected sites only, photography.

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.

Subjects have the right to withdraw from the study and sub-studies at any time and for any reason. Subject information already obtained as part of the study and sub-studies will be retained for analysis subject to applicable law. The Investigator shall ensure that all appropriate processes regarding research ethics and subject consent have been followed in accordance with applicable law and will notify Amgen in the event that any subject whose data is stored at or otherwise processed by Amgen withdraws consent.

The subject data shall be key-coded (the direct identifiers will have been removed or replaced with a subject code) prior to being transferred to the Sponsor or third parties. In particular, appropriate protective mechanisms shall be implemented to ensure that photographs from the sub-study do not contain any subject identifiers (for example, scars, tattoos, etc) when shared with the Sponsor.

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 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 eCRFs or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Amgen standard operating procedures (SOPs). These 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 for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. 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. Investigator/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 Investigator meeting. Prior to enrolling subjects into the study, a Amgen representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the 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 eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

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, eCRFs, and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact 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.

15.3.1. How to Report a Product Complaint to Amgen

Complete Amgen's paper Clinical Product Complaint Intake Form and email the form to the following Amgen email address:

Clinical-Complaint-Intake@amgen.com

16. PUBLICATIONS

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

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

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

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

17. REFERENCES

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
APC	Antigen presenting cell
APR	Apremilast
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
β-hCG	Beta human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CMH	Cochran–Mantel–Haenszel
CRO	Contract Research Organization
CLcr	Creatinine clearance
CRF	Case report form
[redacted]	
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying antirheumatic drug
EC	Ethics Committee
eCRF	Electronic case report form
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EMA	European Medicines Agency
EOT	End of treatment
EQ-5D	European Quality of Life 5-Dimension Questionnaire
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimating equations
GGT	Gamma-Glutamyl Transferase
HDPE	High-density polyethylene
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent to treat
IUD	Intrauterine device
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligrams
MI	Multiple imputation
MMRM	Mixed-Effect Model Repeated Measure
Modified sPGA-G	Modified Static Physicians Global Assessment of Genitalia
NAPSI	Nail Psoriasis Severity Index
NRS	Numeric Rating Scale

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PASI	Psoriasis Area Severity Index
PBI	Patient Benefit Index
PBQ	Patient Benefit Questionnaire
PDE	Phosphodiesterase
PDE4	Phosphodiesterase type 4
PNQ	Patient Needs Questionnaire
PP	Per protocol
PPPGA	Palmoplantar Psoriasis Physicians Global Assessment
PC	Product Complaint
PUVA	Psoralens and long-wave ultraviolet radiation
QOL	Quality of life
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
ScPGA	Scalp Physician Global Assessment
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
sPGA	static Physicians Global Assessment
sPGA-G	static Physicians Global Assessment of Genitalia
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
UVB	Ultraviolet light B
VAS	Visual Analog Scale
WBC	White blood cell
WHO	World Health Organization
WPAI: PSO	Work Productivity and Activity Impairment Questionnaire: Psoriasis

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

Appendix B: The Dermatology Life Quality Index (DLQI) (Continued)

Please check one box for each question.

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

Source: Finlay, 1994.

Appendix C: Static Physicians Global Assessment (sPGA) Of Visible Locations

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. In this study, sPGA is used to evaluate psoriasis **only** in **visible locations**, defined as **dorsal hand, face, neck and hairline.**

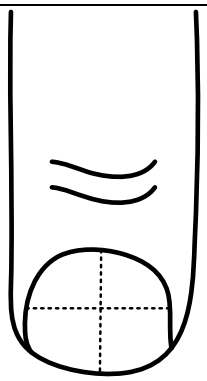
Score	Category	Description
0	Clear	**Plaque elevation** = 0 (no elevation over normal skin) **Scaling** = 0 (no evidence of scaling) **Erythema** = 0 (except for residual hyperpigmentation/ hypopigmentation)
1	Almost Clear	**Plaque elevation** = ± (possible but difficult to ascertain whether there is 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)

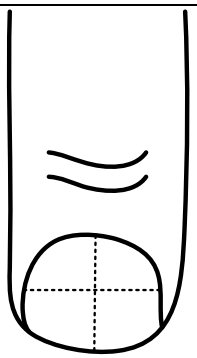
Source: Walsh, 2013.

Appendix D: Scalp Physician Global Assessment (ScPGA)

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

Appendix E: Nail Psoriasis Severity Index (NAPSI)

<table>
<tr><td colspan="2">The target thumb or finger nail which represents the worst nail psoriasis is graded for nail matrix psoriasis and nail bed psoriasis. The sum of these two scores is the total score for that nail.</td></tr>
<tr><td>Evaluation 1: <u>Nail matrix</u>. In each quadrant of the nail, nail matrix psoriasis is evaluated by presence of any of the nail matrix features (pitting, leukonychia red spots in the lunula, crumbling):</td><td rowspan="2">  </td></tr>
<tr><td>Score for nail matrix psoriasis _____

0 = none
1 = present in 1/4 nail
2 = present in 2/4 nail
3 = present in 3/4 nail
4 = present in 4/4 nail</td></tr>
<tr><td>Evaluation 2: <u>Nail bed</u>. Nail bed psoriasis is evaluated by the presence of any of the nail bed features (onycholysis, splinter hemorrhages, subungual hyperkeratosis, “oil drop” (salmon patch dyschroma):</td><td rowspan="2">  </td></tr>
<tr><td>Score for nail bed psoriasis _____

0 = none
1 = present in 1/4 nail
2 = present in 2/4 nail
3 = present in 3/4 nail
4 = present in 4/4 nail</td></tr>
<tr><td colspan="2">TOTAL FOR NAIL_____ (0-8)</td></tr>
</table>

Source: Rich, 2003.

Appendix F: Modified Static Physicians Global Assessment of Genitalia (Modified sPGA-G)

The Modified Static Physician Global Assessment of Genitalia		
Score[1]	**Category**	**Category Description[2]**
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 or deep red erythema **Plaque elevation:** substantial elevation, hard and sharp edges **Scaling:** coarse, non-adherent scale on most to all lesions

Adapted from source: Merola, 2017.

Appendix G: Palmoplantar Psoriasis Physicians Global Assessment (PPPGA)

Scores and Descriptions	
0 Clear	**No signs of plaque psoriasis on hands and/or feet**
1 Almost Clear	**Just perceptible erythema and just perceptible scaling on the hands and/or feet**
2 Mild	**Light pink erythema with minimal scaling and with or without pustules on hands and/or feet**
3 Moderate	**Dull red, clearly distinguishable erythema with diffuse scaling, and thickening of the skin, with or without fissures, and with or without pustule formation on the hands and/or feet**
4 Severe	**Deep/dark red erythema with clearly obvious and diffuse scaling and thickening, and numerous fissures with or without pustule formation on the hands and/or feet**

Source: Leonardi, 2007.

Appendix H: Itch Numeric Rating Scale (NRS)

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

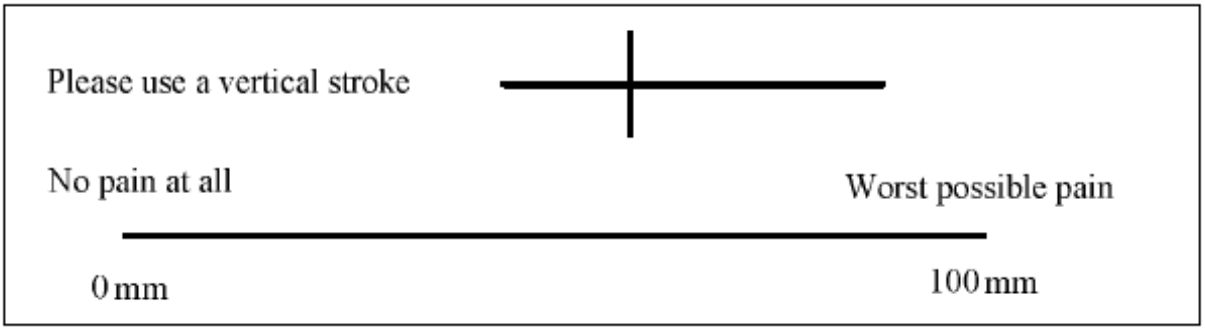
0 1 2 3 4 5 6 7 8 9 10

0 = No itching 10 = Worst itch imaginable

Source: Naegeli, 2015.

Appendix I: Skin Discomfort/Pain Visual Analog Scale (VAS)

On average, how much skin discomfort/pain have you had because of your condition in the past week?



Please note: VAS above is not drawn to scale and is for illustrative purposes only.

Appendix J: Psoriasis Area Severity Index (PASI)

* Round all calculations to 1 decimal place.

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

Source: Fredriksson, 1978.

Appendix K: Patient Needs Questionnaire (PNQ)

With the help of the following questions, we'd like to know how important the below mentioned goals are to you personally in the **current treatment** of your skin disease.

For each of the following statements, please mark **how important** this treatment goal is to you. If a statement does not apply to you, e.g. because you do not have pain, please mark "*does not apply to me"*.

	As a result of therapy, how important is it for you to...	not at all	somewhat	moderately	quite	very	*does not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on your skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...be able to sleep better	O	O	O	O	O	O
6	...feel less depressed	O	O	O	O	O	O
7	...experience a greater enjoyment of life	O	O	O	O	O	O
8	...have no fear that the disease will become worse	O	O	O	O	O	O
9	...be able to lead a normal everyday life	O	O	O	O	O	O
10	...be more productive in everyday life	O	O	O	O	O	O
11	...be less of a burden to relatives and friends	O	O	O	O	O	O
12	...be able to engage in normal leisure activities	O	O	O	O	O	O
13	...be able to lead a normal working life	O	O	O	O	O	O
14	...be able to have more contact with other people	O	O	O	O	O	O
15	...be comfortable showing yourself more in public	O	O	O	O	O	O
16	...be less burdened in your partnership	O	O	O	O	O	O
17	...be able to have a normal sex life	O	O	O	O	O	O
18	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
19	...need less time for daily treatment	O	O	O	O	O	O
20	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
21	...have fewer side effects	O	O	O	O	O	O
22	...find a clear diagnosis and therapy	O	O	O	O	O	O
23	...have confidence in the therapy	O	O	O	O	O	O
24	...get better skin quickly	O	O	O	O	O	O
25	...regain control of the disease	O	O	O	O	O	O

Appendix L: Patient Benefit Questionnaire (PBQ)

At the start of the treatment, you indicated in a questionnaire how important various goals were in the treatment of your skin disease.

Please mark each of the following statements according to the extent that these treatment goals **were achieved**, thereby indicating if the treatment has benefitted you. If a statement did not apply to you, e.g. because you had no pain, please mark "*did not apply to me"*.

	The current treatment has helped me to...	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*did not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on my skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...be able to sleep better	O	O	O	O	O	O
6	...feel less depressed	O	O	O	O	O	O
7	...experience a greater enjoyment of life	O	O	O	O	O	O
8	...have no fear that the disease will become worse	O	O	O	O	O	O
9	...be able to lead a normal everyday life	O	O	O	O	O	O
10	...be more productive in everyday life	O	O	O	O	O	O
11	...be less of a burden to relatives and friends	O	O	O	O	O	O
12	...be able to engage in normal leisure activities	O	O	O	O	O	O
13	...be able to lead a normal working life	O	O	O	O	O	O
14	...be able to have more contact with other people	O	O	O	O	O	O
15	...be comfortable showing myself more in public	O	O	O	O	O	O
16	...be less burdened in my partnership	O	O	O	O	O	O
17	...be able to have a normal sex life	O	O	O	O	O	O
18	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
19	...need less time for daily treatment	O	O	O	O	O	O
20	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
21	...have fewer side effects	O	O	O	O	O	O
22	...find a clear diagnosis and therapy	O	O	O	O	O	O
23	...have confidence in the therapy	O	O	O	O	O	O
24	...get better skin quickly	O	O	O	O	O	O
25	...regain control of the disease	O	O	O	O	O	O

Appendix M: European Quality of Life 5-Dimension Questionnaire (EQ-5D)

Health Questionnaire

(English version for the US)

Appendix M: European Quality of Life 5-Dimension Questionnaire (EQ-5D) (Continued)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

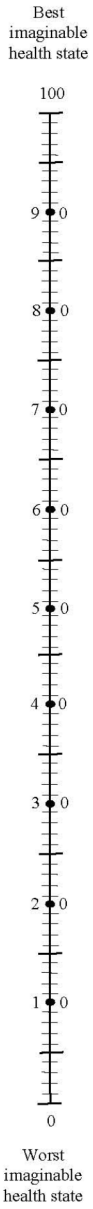
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix M: European Quality of Life 5-Dimension Questionnaire (EQ-5D) (Continued)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

Source: The EuroQol Group, 1990.

Appendix N: Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: PSORIASIS (WPAI:PSO)

The following questions ask about the effect of your psoriasis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? ____NO ___YES
If NO, check "NO" and skip to question 6

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of problems associated with your psoriasis? *Include hours you missed on sick days, times you went in late, left early, etc. because of psoriasis. Do not include time you missed to participate in this study.*
_____HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
_____HOURS

4) During the past seven days, how many hours did you actually work?
_____HOURS *(If "0", skip to question 6)*

5) During the past seven days, how much did psoriasis affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriasis affected your work only a little, choose a low number. Choose a high number if psoriasis affected your work a great deal.*

Psoriasis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from working

CIRCLE A NUMBER

6) During the past seven days, how much did psoriasis affect your ability to do your regular daily activities, other than work at a job? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If psoriasis affected your activities only a little, choose a low number. Choose a high number if psoriasis affected your activities a great deal.*

Psoriasis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from doing my daily activities

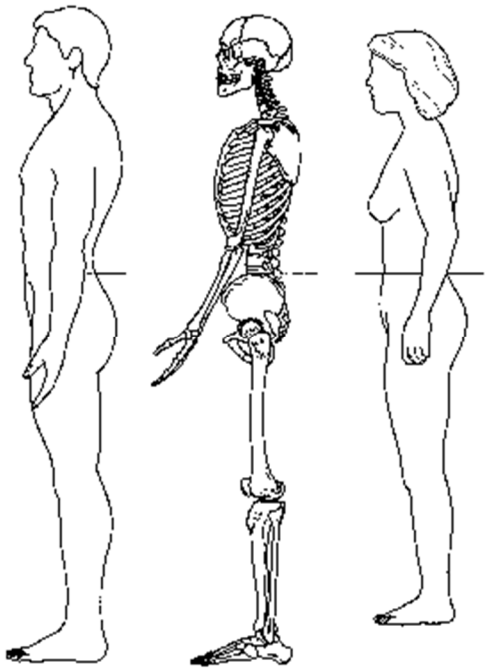
CIRCLE A NUMBER

WPAI:PSO (US English)

Source: Reilly, 2012.

Appendix O: Waist Circumference Measurement & Body Mass Index

Measuring Tape Position for Waist (Abdominal) Circumference



How to Measure Waist Circumference

1. Place a tape measure around subject's waist above the tip of hipbone.
2. Ask the subject to exhale.
3. Measure the waist after exhaling.

How to Measure Body Mass Index (BMI)

Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters. To estimate BMI, multiply the individual's weight (in pounds) by 703, then divide by the height (in inches) squared. This approximates BMI in kilograms per meter squared (kg/m2).

BMI calculator can be found at:
https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html

Source: NHLBI Obesity Education Initiative.

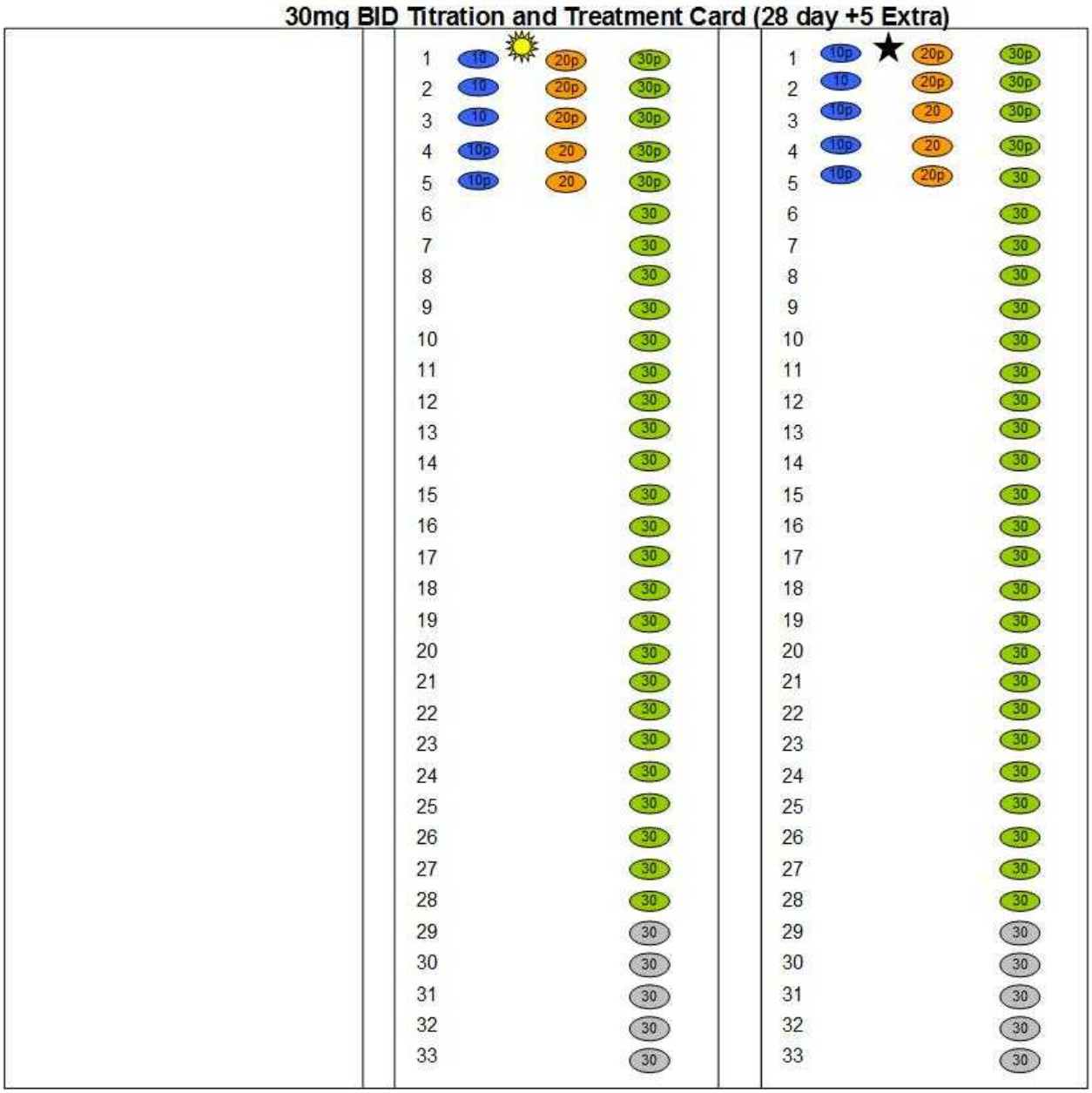
Appendix P: Treatment Schema for Dose Titration at Baseline

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

Appendix Q: Treatment Schema for Dose Titration at Week 16

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

Appendix R: Titration Blister Card



Appendix S: Sample Serious Adverse Event Form

AMGEN CC-10004-PSOR-020 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-current 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; 06 Persistent or significant disability /incapacity; 08 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			Action Taken with Product U1 Still being Administered U2 Permanently discontinued U3 Withheld	Lot # and Serial #
		Date of Dose Day Month Year	Dose	Route	Frequency	
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

Appendix S: Sample Serious Adverse Event Form (Continued)

AMGEN CC-10004-PSOR-020 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

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 02-April-2020*
Page 2 of 3

Appendix S: Sample Serious Adverse Event Form (Continued)

AMGEN CC-10004-PSOR-020 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

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 T: Pregnancy Notification Form

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: CC-10004-PSOR-020 (Apremilast/Ofezia)

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 U: 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-020 (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

Celgene Signing Page

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

UserName: [redacted]
Title: Vice President and Head of Immunology & Fibrosis Clinical Develo
Date: Tuesday, 05 May 2020, 08:23 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

Approved

– SUMMARY OF CHANGES –

A PHASE 4, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE IMPACT OF APREMILAST (CC-10004) ON QUALITY OF LIFE, EFFICACY, AND SAFETY IN SUBJECTS WITH MANIFESTATIONS OF PLAQUE PSORIASIS AND IMPAIRED QUALITY OF LIFE

AMENDMENT NO. 3

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSOR-020**
ORIGINAL DATE:	**26 SEP 2018**
AMENDMENT No. 1 DATE:	**17 JAN 2019**
AMENDMENT No. 2 DATE:	**01 NOV 2019**
AMENDMENT No. 3 DATE:	**01 MAY 2020**
EudraCT NUMBER:	**2018-002850-58**
IND NUMBER:	**070270**
NTC NUMBER:	**NCT03774875**

Contact Information:

Name:	[redacted], MD
Title:	Senior Director, Global Development
Address:	Amgen Inc, Amgen Center Dr, Thousand Oaks, CA 91320 USA
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], Vice President and Head of Immunology &Fibrosis Clinical Development
Printed Name of Celgene Therapeutic Area Head and Title By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable. NOTE: Signed by Celgene based on Approval from Amgen Therapeutic Head [redacted]

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 Monitoring and Reporting of Adverse Events was updated to align with Amgen Global Drug Safety processes.
- Section 10.4 Pregnancy was modified according to the Amgen Global Drug Safety process:
    - Collection of Pregnancy Information and Infant Health Information
    - Collection of information: Male Subjects with Partners Who Become Pregnant
    - Collection of Lactation Information
- Section 10.5 Reporting of Serious Adverse Events was updated to include instructions for paper reporting of SAEs
- Section 12.1 Emergency Contact was updated with Amgen emergency contact information.
- Section 15.3 Product Complaint Section was modified according to the Amgen product complaint reporting process

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

- Section 7.5 Investigational Product Accountability
- Section 15.2 Audits and Inspections
- Section 16 Publications
- Appendix S Sample Serious Adverse Event Form was added
- Appendix T Pregnancy Notification Form was added
- Appendix U Lactation Notification Form was added

– SUMMARY OF CHANGES –

AMENDMENT NO. 2

A PHASE 4, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE IMPACT OF APREMILAST (CC-10004) ON QUALITY OF LIFE, EFFICACY, AND SAFETY IN SUBJECTS WITH MANIFESTATIONS OF PLAQUE PSORIASIS AND IMPAIRED QUALITY OF LIFE

INVESTIGATIONAL PRODUCT (IP):	**Apremilast (CC-10004)**
PROTOCOL NUMBER:	**CC-10004-PSOR-020**
ORIGINAL DATE:	**26-SEP-2018**
AMENDMENT No. 1 DATE:	**17-JAN-2019**
AMENDMENT No. 2 DATE:	**01 NOV 2019**
EudraCT NUMBER:	**2018-002850-58**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], **MD**
Title:	Senior Medical Director, Global Medical Affairs, Dermatology
Address:	Celgene Corporation 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], PhD, Vice President, Medical Affairs Inflammation and Immunology, Rheumatology and Dermatology By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Randomization to each of the 5 manifestations of plaque psoriasis

The primary purpose of this protocol amendment is to remove the requirement for *equal* block-randomization to each of the 5 manifestations of plaque psoriasis. The basis for this change stems from the different enrollment rates in the 5 manifestation groups with a corresponding risk of missing the sample size required for the primary endpoint. This change does not impact the study endpoints.

Revised sections: Protocol Summary, 3.1 Study Design, 4.3 Exclusion Criteria, 7.3 Method of Treatment Assignment.

- Updated modalities for reporting of serious adverse events (SAEs) and pregnancy

Reporting modalities were updated to reflect the use of an electronic case report form (eCRF)-based system for reporting of SAEs and clarified expectations for pregnancy reporting.

Revised sections: 6.5.8 Adverse Events, 10.4.1 Females of Childbearing Potential, 10.5 Reporting of Serious Adverse Events (with 10.5.1 deleted) and 10.6 Expedited Reporting of Adverse Events

The Amendment also includes several other minor clarifications and corrections:

- Medical Monitor and Celgene Therapeutic Area Head information was updated.
- In Section 2, Table 2 Safety endpoints were combined with Secondary endpoints; Exploratory endpoint on [redacted]
- In Section 4.3, Exclusion Criteria # 3 clarified to refer specifically to arthritis requiring disease-modifying antirheumatic drug.
- In Section 5, Table 3, Screening visit window: clarified to be -35 to 0 days.
- In Section 6.5.4, Psychiatric Evaluation, language aligned with Risk Benefit Assessment and Investigator Brochure for patients with identified attempted suicide.
- Where appropriate, references to CRF have been revised to eCRF.

– SUMMARY OF CHANGES –

AMENDMENT NO 1.

A PHASE 4, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE IMPACT OF APREMILAST (CC-10004) ON QUALITY OF LIFE, EFFICACY, AND SAFETY IN SUBJECTS WITH MANIFESTATIONS OF PLAQUE PSORIASIS AND IMPAIRED QUALITY OF LIFE

INVESTIGATIONAL PRODUCT (IP):	**Apremilast (CC-10004)**
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EudraCT NUMBER:	**2018-002850-58**
IND NUMBER:	**070270**

Contact Information:

Name:	[redacted], MD
Title:	Medical Director
Address:	Celgene Corporation 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, Corporate Vice President, Global Medical Affairs Inflammation and Immunology By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- In the Protocol Summary; Overview of Key Safety Assessments, Physical examinations was changed to Body weight and waist circumference as body weight and waist circumference is done throughout the study and Physical examination is done at Screening.
- In Section 2, Table 1; removed text, "data from the exploratory objectives may not be included in the clinical study report", as the clinical study report will include data from exploratory analyses.
- In Section 2, Table 2; added Safety Endpoints, based on Health Authority recommendations.
- In Section 4.2; clarified Inclusion Criteria 4, 9 and 11, to align to approved label indication for psoriasis and address Health Authority recommendations.
- In Section 4.3; deleted Exclusion Criteria 1, clarified Exclusion Criteria 6 and added Exclusion Criteria 7, 8, 16 and 17 to align to approved label and address Health Authority recommendations. Exclusion Criteria # 18 was added to address exclusions for completion of randomization blocks for the disease manifestations noted in Inclusion Criteria #7.
- Modified Section 5 Table of Events to include additional Vital signs and body weight measures, based on Health Authority recommendations.
- Modified Section 6.1, to clarify demography data collection and clinical laboratory evaluation, based on Health Authority recommendations.
- Provided clarification in Section 6.2 for Efficacy assessment, as investigators may asses efficacy and safety at any unscheduled visit, following country guidelines.
- Modified Sections 6.4.14 and 6.4.15 to clarify that data from [redacted] and photography will be included in the clinical study report.
- Added Section 6.5 specifying safety assessments and address Health Authority recommendations.
- Modified Section 8.1 to clarify data collection of permitted concomitant medication.
- Added Section 8.2, "Concomitant Medications Not Recommended", based on Health Authority recommendations.
- Modified Sections 9.6.3 and 9.6.4 to include data from exploratory objectives in study report, based on Health Authority recommendations.
- Provided clarification in Section 9.7 Safety Analysis, based on Health Authority recommendations.
- Modified Sections 10.1 and 10.5 to clarify AE and SAE reporting will be done electronically through database.
- Clarified Section 11.1, Treatment Discontinuation, based on Health Authority recommendations.