Study Identifier: CC-10004-PSOR-023
NCT number: NCT03930186

Official Title on page 1 of the Protocol: OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

Official Title on page 5 of the Protocol: A PHASE 3B, OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

Official Title in the Statistical Analysis Plan (SAP): A PHASE 3B MULTI-CENTER, OPENLABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

Note: The official title in the Protocol (page 1 and 5) and Statistical Analysis Plan (SAP) are slightly different but these documents pertain to the same study CC-10004-PSOR-023.

This cover page has been appended to the document for purpose of posting on Clinicaltrials.gov.

OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

PROTOCOL NUMBER:	CC-10004-PSOR-023
DATE FINAL:	30 Jan 2019
AMENDMENT DATE FINAL	28 Apr 2020
EudraCT NUMBER:	Not Applicable
IND NUMBER:	N/A
SPONSOR NAME/ ADDRESS:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320, US

NCT Number: NCT03930186
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information:	**Amgen K.K. Clinical Research Physician/Medical Monitor**
Name:	[redacted] MD
Title:	Associate Medical Director, Inflammation and Immunology, Amgen K.K.
Address:	9-7-1 Akasaka Minato-ku Tokyo 107-6239
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: +1-800-772-6436

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted] Vice President
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.

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 Conference on Harmonisation Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title

A Phase 3B, open-label, single-arm study of the efficacy and safety of apremilast, in subjects with plaque psoriasis that is not adequately controlled by topical therapy

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).

Psoriasis is a disease that requires long-term treatment, ideally with effective agents that offer convenient dosing and a low incidence of adverse events. The American Academy of Dermatology recommends use of topical treatments for patients with localized disease; however, their effectiveness is limited by the inconvenience associated with application and low adherence rates (Menter, 2008). Moderate psoriasis is often inadequately treated and there remains an unmet medical need for an effective convenient agent that is well tolerated and less immunosuppressive than the currently available treatment options (Armstrong, 2013).

While the Japanese Phase 2b study (PSOR-011) with apremilast in psoriasis was conducted in subjects with moderate to severe disease, the mean Psoriasis Area Severity Index (PASI) was 22 and the mean body surface area (BSA) was 30%. Over 30% of subjects had a static Physician's Global Assessment (sPGA) of ≥ 4 or a PASI > 20 in PSOR-011, with 60% or more of the subjects having a BSA involvement of $> 20\%$. In addition, 32.3% of subjects were treated with previous conventional systemic therapy and 3.5% were treated with prior biologics. This would suggest that there was a high proportion of subjects with severe disease in this study (Ohtsuki, 2017). This Phase 3B study is designed to focus on the efficacy and safety of apremilast added to topicals in subjects with plaque psoriasis who have not responded adequately to topical therapies.

A significant proportion of patients with mild or moderate plaque psoriasis still have active disease despite treatment with topical therapies. Topical treatments, although safe and effective, are limited by inconvenience and poor adherence. This study would generate data to help understand the impact of apremilast when added to background topical therapy, which is an important scientific data gap in Japan. In addition, the usage of topical therapies would also be collected to help understand if the addition of apremilast to the therapeutic regimen for plaque psoriasis could reduce the usage of topical therapies.

Objectives

Primary Objective
• The primary objective of the study is to assess the efficacy and safety of the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.
Secondary Objective(s)
The secondary objectives of the study are: • To assess the efficacy of the combination of apremilast plus topical therapies for the treatment of subjects with scalp psoriasis who have not achieved an adequate response with topicals alone. • To assess the impact on quality of life for the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.

Study Design

This is a Phase 3B, multi-center, open-label, single arm study of the efficacy and safety of the combination of apremilast and topical therapy in subjects with plaque psoriasis that have not responded adequately to topical treatments alone.

Approximately 150 subjects will be enrolled at approximately 30 sites in Japan. After a 5-day titration, subjects will receive apremilast 30 mg tablets orally twice daily (BID) for 32 weeks in addition to their existing topical therapy. Beginning at Week 16, subjects will be permitted to decrease the use of topical therapy at their discretion.

The study will consist of four phases:

- Screening Phase – Week -4 ± 1 week
- Open-label Combination Therapy Phase – Weeks 0 to 16

  Subjects will receive treatment with
  - apremilast 30 mg tablets orally BID, AND
  - existing topical therapy
- Open-label Combination Therapy Phase with Optional Topical Reduction – Weeks 16 to 32
  - All subjects will continue to receive apremilast 30 mg tablets orally BID AND existing topical therapy
  - Subjects will be permitted to decrease the use of topical therapy at their own discretion
- Post-treatment Observational Follow-up Phase – Week 36

- Four-week post-treatment observational follow-up phase for all subjects who complete the study or discontinue from the study early. Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit.

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

Study Population

Approximately 150 subjects with plaque psoriasis who have not achieved an adequate response from topical treatment alone (according to Investigator's discretion) will be enrolled in the study across multiple centers in Japan.

Length of Study

The study is designed as a 32-week study. Visits will be scheduled at Screening (Week -4 ± 1), Week 0 (Baseline), Weeks 2, 4, 8, 16, 24, and 32.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, 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

During Week 0 (Days 1 to 7), subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets for the dose titration. The treatment schema for dose titration at Baseline is shown in Table 4.

All subjects will maintain this dosing through Week 32.

Apremilast tablets will be taken orally twice daily (BID), 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 that achieve static Physicians Global Assessment score of 0 (clear) or 1 (almost clear) at week 16.

Secondary Efficacy Endpoints

- Scalp Physicians Global Assessment (ScPGA)
- Dermatology Life Quality Index (DLQI)
- Treatment Satisfaction Questionnaire for Medication (TSQM) Version II

Exploratory Endpoints

Overview of Key Safety Assessments

Safety assessments will include:

- Adverse Events (AEs)
- Pregnancy tests for females of childbearing potential (FCBP)
- Vital signs
- Clinical laboratory tests
- Body weight

Statistical Methods

This study will enroll 150 subjects to apremilast 30 mg BID combined with topical therapy. It will support a 95% confidence interval with at least 80% probability that the length of the interval is within 13%, assuming the expected response rate of 15% [8.5% -21.5%] at Week 16 and allows for a 10% discontinuation rate prior to week 16. The sample size calculation is based on nQuery software version 7.0, and the 80% probability supporting the margin of error is based on simulation results.

The primary analysis for the primary endpoint will be analyzed using descriptive statistics which involve the sample size, the number of responders, point estimate of proportion of responders along with the associated two-sided 95% confidence intervals.

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, 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 can be made.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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 subjects 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).

Psoriasis is a chronic disease that requires long-term treatment, ideally with effective agents that offer convenient dosing and a low incidence of adverse events. The American Academy of Dermatology recommends use of topical treatments for subjects with localized disease and recognizes that the systemic options for subjects with more severe psoriasis are limited by potential risks of organ toxicities and immunosuppression (Menter, 2008).

Mild or moderate psoriasis is often treated with topical therapy only. However, a significant proportion of subjects with mild or moderate plaque psoriasis still have active disease despite treatment with topical therapies. Topical treatments, although safe and effective, are limited by inconvenience and poor adherence. Therefore, there remains an unmet medical need for an effective convenient agent that is well tolerated and less immunosuppressive than the currently available treatment options (Armstrong, 2013).

1.2. Study Drug

Apremilast (CC-10004) is a specific phosphodiesterase type 4 (PDE4) inhibitor (Schafer, 2010) 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 levels in immune cells, which in turn down-regulates the inflammatory response by reducing the expression of pro-inflammatory mediators such as TNF-α, IL-23, IL-17, and other inflammatory cytokines, and increasing the production of anti-inflammatory mediators.

In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies, apremilast (OTEZLA) is approved in the US, Canada, Europe, Japan, and Latin America for both moderate to severe plaque psoriasis and active psoriatic arthritis. A Phase 2B study (PSOR-011) was conducted in Japan in subjects with moderate to severe plaque psoriasis, and also included subjects with active psoriatic arthritis, which supported the approval of apremilast for plaque psoriasis and psoriatic arthritis in Japan.

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

Please refer to the Investigator's Brochure 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

While the Japanese Phase 2b study (PSOR-011) with apremilast in psoriasis was conducted in subjects with moderate to severe disease, the mean Psoriasis Area Severity Index (PASI) was 22 and the mean BSA was 30%. Over 30% of subjects had a static Physician Global Assessment (sPGA) of ≥ 4 or a PASI > 20 in PSOR-011, with 60% or more of the subjects having a BSA involvement of > 20%. In addition, 32.3% of subjects were treated with previous conventional systemic therapy and 3.5% were treated with prior biologics. This would suggest that there was a high proportion of subjects with severe disease in this study. This Phase 3B study is designed with a specific focus on the efficacy and safety of apremilast added to topicals in subjects with plaque psoriasis who have not responded adequately to topical therapies.

A significant proportion of subjects with mild or moderate plaque psoriasis still have active disease despite treatment with topical therapies. Topical treatments, although safe and effective, are limited by inconvenience and poor adherence. This study would generate data to help understand the impact of apremilast when added to background topical therapy, which is an important scientific data gap in Japan. In addition, the usage of topical therapies would also be collected to help understand if the addition of apremilast to the therapeutic regimen for plaque psoriasis could reduce the usage of topical therapies.

1.3.2. Rationale for the Study Design

This will be a multi-center, open-label, single-arm study of the efficacy and safety of apremilast in combination with existing topical therapy in subjects who have not achieved an adequate response to topical therapy alone. A placebo control is not necessary because apremilast will be added to a therapy which is not adequately controlling the disease. In addition, the proportion of subjects that achieve sPGA 0 or 1 with placebo is historically low (~5%), reducing the need for a placebo control. Finally, a 32 week study is sufficient to assess the efficacy and safety of apremilast in combination with topical therapy and the impact of apremilast on the use of topical therapy.

1.3.3. Rationale for Choice of Combination Compounds

Subjects will be required to remain on their existing topical therapy through the Open-label Combination Therapy Phase (Weeks 0 to 16). After Week 16, subjects may decrease or discontinue the use of topical therapies at their discretion.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to assess the efficacy and safety of the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.
Secondary Objective(s)
The secondary objectives of the study are: • To assess the efficacy of the combination of apremilast plus topical therapies for the treatment of subjects with scalp psoriasis who have not achieved an adequate response with topicals alone. • To assess the impact on quality of life for the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.
Exploratory Objective(s)
The exploratory objectives of the study are: [redacted] Data from the exploratory objectives may not be included in the clinical study report.

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	static Physicians Global Assessment (sPGA)	Proportion of subjects who achieve sPGA 0 or 1	Week 16

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary	static Physicians Global Assessment (sPGA)	Proportion of subjects who achieve sPGA 0 or 1	Week 32
	Scalp Physicians Global Assessment (ScPGA)	Proportion of subjects who achieve ScPGA score of 0 or 1	Weeks 16, 32
	Body Surface Area (BSA)	Mean percent change from baseline in psoriasis-affected BSA	Weeks 16, 32
	Pruritus Visual Analog Scale (VAS)	Mean percent change from baseline	Weeks 2, 16, 32
	Shiratori's Pruritus Severity Score	Mean change in severity score from baseline	Weeks 2, 16, 32
	Nail Psoriasis Severity Index (NAPSI)	Proportion of subjects that achieve a ≥ 50% reduction from baseline in NAPSI score (NAPSI-50) at Week 32 among subjects with NAPSI ≥ 1 at baseline	Weeks 16, 32
	Dermatology Life Quality Index (DLQI)	Mean change from baseline	Weeks 16, 32
	Psoriasis Area and Severity Index (PASI)	• Mean percentage change from baseline • Proportion of subjects who achieve ≥ 75% reduction from baseline (PASI-75) • Proportion of subjects who achieve ≥ 50% reduction from baseline (PASI-50)	Weeks 16, 32
	Treatment Satisfaction Questionnaire for Medication (TSQM)	Mean overall score and mean score in sub-domains	Weeks 0, 16, 32
	Patient Benefit Index (PBI)	Proportion of subjects who achieve PBI ≥ 1	Weeks 16, 32
Exploratory	[redacted]		
Safety	Adverse Events	Type, frequency, severity, and relationship of adverse events (AEs) to apremilast	Throughout study duration

Endpoint	Name	Description	Timeframe
	Discontinuation due to AEs	Number of subjects who discontinue apremilast due to any AE	Throughout study duration

BSA = body surface area; DLQI = The Dermatology Life Quality Index; [redacted]; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index; PBI = Patient Benefit Index; [redacted]; ScPGA = Scalp Physician Global Assessment; sPGA = Static Physician's Global Assessment; TSQM = Treatment Satisfaction Questionnaire for Medication; VAS = Visual Analog Scale.

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 3B multi-center, open-label, single-arm study of the efficacy and safety of apremilast, in subjects with plaque psoriasis that is not adequately controlled by topical therapy.

Approximately 150 subjects will be enrolled at approximately 30 sites in Japan. After a 5-day titration, subjects will receive apremilast 30 mg tablets orally twice daily (BID) for 32 weeks in addition to their existing topical therapy. Beginning at Week 16, subjects will be permitted to decrease the use of topical therapy at their discretion.

The study will consist of four phases:

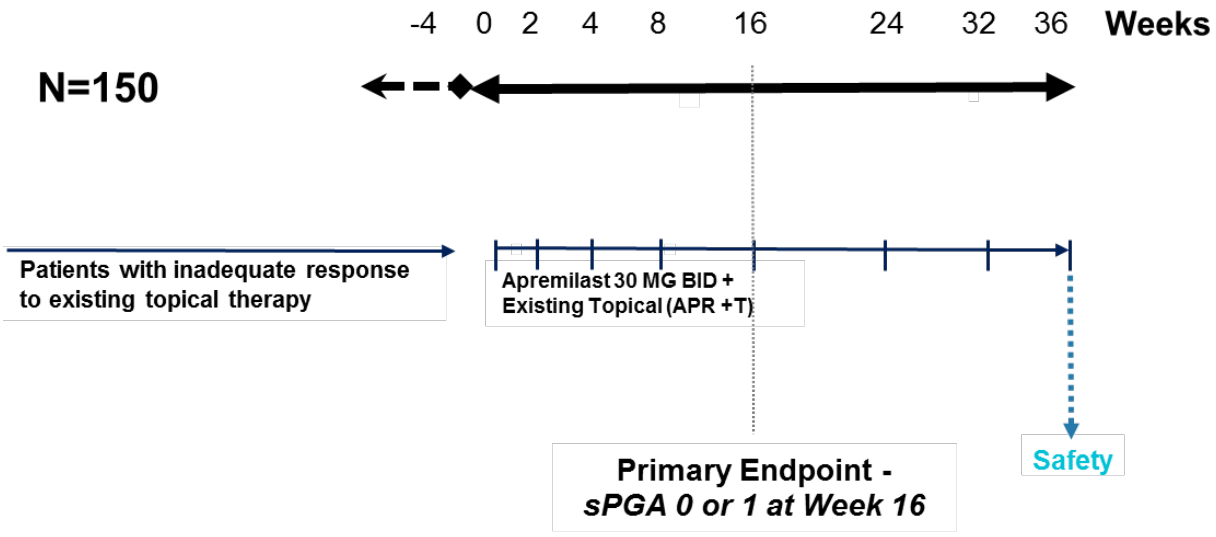
- Screening Phase – Week -4 ± 1 week
- Open-label Combination Therapy Phase – Weeks 0 to 16

  Subjects will receive treatment with:

  - apremilast 30 mg tablets orally BID, AND
  - existing topical therapy
- Open-label Combination Therapy Phase with Optional Topical Reduction – Weeks 16 to 32
  - All subjects will continue to receive apremilast 30 mg tablets orally BID AND existing topical therapy
  - Subjects will be permitted to decrease the use of topical therapy at their own discretion
- Post-treatment Observational Follow-up Phase
  - Four-week Post-treatment Observational Follow-up Phase for all subjects who complete the study or discontinue from the study early. Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit.

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

Figure 1: Overall Study Design



3.2. Study Duration for Subjects

The study is designed as a 32-week study with a 4-week Post-treatment Observational Follow-up Phase. Visits will be scheduled at Screening (Week -4 ± 1 week), Week 0 (Baseline), Weeks 2, 4, 8, 16, 24, and 32. A follow-up visit will be conducted at Week 36 or in the case of subjects withdrawing prior to Week 32, 4 weeks after investigational product (IP) discontinuation. Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit.

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 150 subjects with plaque psoriasis who have not achieved an adequate response from topical treatment (according to Investigator's discretion) will be enrolled in the study across multiple centers in Japan.

4.2. Inclusion Criteria

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

1. Subject is ≥ 20 years of age at the time of signing the informed consent form (ICF) with plaque psoriasis.
2. Subject has understood and voluntarily signed an informed consent document prior to any study related assessments/procedures being conducted.
3. Subject is able to adhere to the study visit schedule and other protocol requirements.
4. Subject has chronic plaque psoriasis based on a diagnosis for at least 6 months prior to Baseline.
5. Subject has psoriasis with sPGA = 2 or 3 at screening and baseline.
6. Subject is currently treated for psoriasis with topical therapies only for at least 4 weeks prior to Baseline.
7. Subject has inadequate response to current topical therapy as per Investigator's discretion.
8. Subject is naïve to all biologic therapies for psoriasis vulgaris.
9. 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).
10. Subjects that are 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; tubal ligation; or partner's vasectomy;

[†] 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 enrolled into the study (for example, hormonal contraception should be initiated at least 28 days before enrollment).

OR

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

4.3. Exclusion Criteria

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

1. Subject has any condition, including other inflammatory diseases or dermatologic conditions, which confounds the ability to interpret data from the study, including other types of psoriasis (ie, pustular, inverse, erythrodermic, or guttate), other than plaque psoriasis.
2. Subject has psoriatic arthritis that requires systemic therapy.
3. Subject has history of drug-induced psoriasis.
4. Subject has had prior treatment with biologic therapies for psoriasis.
5. Subject has used phototherapy or conventional systemic therapy for psoriasis within 8 weeks prior to baseline and during the study (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine).
6. Subject has worsening of psoriasis indicated by an increase in sPGA of ≥ 1 from Screening to Baseline.
7. Subject cannot avoid excessive sun exposure or use of tanning booths for at least 8 weeks prior to Baseline and during the study.
8. Subject is currently enrolled in any other clinical trial involving an investigational product.
9. Subject has other than psoriasis, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
10. Subject has 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.
11. Subject has received a live vaccine within 3 months of baseline or plans to do so during study.
12. Subject is pregnant or breastfeeding (lactating) women.
13. Subject has bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of Screening. Any treatment for such infections must have been completed and the infection cured, at least 4 weeks prior to Screening and no new or recurrent infections prior to the Baseline Visit.

14. Subject is hepatitis B surface antigen positive or hepatitis B core antibody positive at screening.
15. Subject is positive for antibodies to hepatitis C at screening.
16. Subject has any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study.
17. Subject has prior history of suicide attempt at any time in the subject's life time prior to signing the informed consent and enrollment, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent.
18. Subject has active substance abuse or a history of substance abuse within 6 months prior to signing the informed consent.
19. Subject has prior treatment with apremilast or participation in a clinical study involving apremilast.

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening	Open-label Combination Phase[a]					Open-label Combination with Optional Topical Reduction Phase[b]		Early Termination[c]	Post-Treatment Observational Follow-Up[k]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**		**9**
Week	**-4 (± 7 days)**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**16 (± 3 days)**	**24 (± 4 days)**	**32 (± 4 days)**		**36 (or 4 weeks after investigational product (IP) discontinuation)**
Informed consent[d]	X	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion criteria	X	X	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Prior / concomitant medications	X	X	X	X	X	X	X	X	X	-
Review Diaries	-	-	X	X	X	X	X	X	X	-
[redacted]										
Clinical and Laboratory Assessments										
Adverse events/Serious Adverse Events	X	X	X	X	X	X	X	X	X	X
Pregnancy test and contraception education[e]	X	X	-	-	-	-	-	X	X	X
Hepatitis B and C	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	X	-
Physical Examination	X	-	-	-	-	-	-	-	-	-

	Screening	Open-label Combination Phase[a]					Open-label Combination with Optional Topical Reduction Phase[b]		Early Termination[c]	Post-Treatment Observational Follow-Up[k]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**		**9**
Week	**-4 (± 7 days)**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**16 (± 3 days)**	**24 (± 4 days)**	**32 (± 4 days)**		**36 (or 4 weeks after investigational product (IP) discontinuation)**
Clinical laboratory evaluations[f]	X	X	-	-	-	X	-	X	X	-

Table 3: Table of Events (Continued)

	Screening	Open-label Combination Phase[a]					Open-label Combination with Optional Topical Reduction Phase[b]		Early Termination[c]	Post-Treatment Observational Follow-Up[k]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**		**9**
Week	**-4 (± 7 days)**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**16 (± 3 days)**	**24 (± 4 days)**	**32 (± 4 days)**		**36 (or 4 weeks after investigational product (IP) discontinuation)**
Efficacy Assessment(s)										
sPGA	X	X	X	X	X	X	X	X	X	-
BSA	-	X	X	X	X	X	X	X	X	-
Pruritus VAS	-	X	X	X	X	X	X	X	X	-
Shiratori's Pruritus Severity Score	-	X	X	X	X	X	X	X	X	-
PASI	-	X	X	X	X	X	X	X	X	-
ScPGA	-	X	-	X	X	X	X	X	X	-
NAPSI	-	X	-	-	X	X	X	X	X	-
TSQM	-	X	-	X	-	X	X	X	X	-
PNQ[j]	-	X	-	-	-	-	-	-	-	-
PBQ[j]	-	-	-	X	-	X	X	X	X	-

	Screening	Open-label Combination Phase[a]					Open-label Combination with Optional Topical Reduction Phase[b]		Early Termination[c]	Post-Treatment Observational Follow-Up[k]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**		**9**
Week	**-4 (± 7 days)**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**16 (± 3 days)**	**24 (± 4 days)**	**32 (± 4 days)**		**36 (or 4 weeks after investigational product (IP) discontinuation)**
Photographs[i]	-	X	-	-	-	X	-	X	X	-
Health-related Quality of Life Assessment(s)										
DLQI	-	X	X	X	X	X	X	X	X	-
[redacted]										

Table 3: Table of Events (Continued)

	Screening	Open-label Combination Phase[a]					Open-label Combination with Optional Topical Reduction Phase[b]		Early Termination[c]	Post-Treatment Observational Follow-Up[k]
Visit Number	**1**	**Baseline 2**	**3**	**4**	**5**	**6**	**7**	**8**		**9**
Week	**-4 (± 7 days)**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**16 (± 3 days)**	**24 (± 4 days)**	**32 (± 4 days)**		**36 (or 4 weeks after investigational product (IP) discontinuation)**
[redacted]										
Dosing										
Dispense IP	-	X	-	X	X	X	X	-	-	-
Return and count IP tablets	-	-	-[h]	X	X	X	X	X	X	-

Abbreviations: BSA = body surface area; DLQI = The Dermatology Life Quality Index; FCBP = female of childbearing potential; IP = investigational product; [redacted]; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index; PBQ = Patient Benefit Questionnaire; [redacted]; PNQ = Patient Needs Questionnaire; ScPGA = Scalp Physician Global Assessment; sPGA = Static Physician's Global Assessment; TSQM = Treatment Satisfaction Questionnaire for Medication ver II; VAS = Visual Analog Scale.

[a] Visits in the Open-label Combination Phase to be performed ± 3 days.

[b] Visits in the Open-label Combination with Optional Topical Reduction Phase to be performed ± 4 days.

[c] Subjects who discontinue before week 32 will be asked to attend an Early Termination Visit.

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

[e] Females of child bearing potential (FCBPs) only. Serum pregnancy tests are performed at Screening, Baseline, Early Termination Visit/Last Treatment Visit and 4 weeks thereafter (Observational Follow-up Visit). Urine pregnancy test kit will also be provided to the site and performed at baseline prior to enrollment. 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.

[f] Laboratory assessments will include routine/standard chemistry and hematology panel of tests, hs-CRP, and urinalysis. A lipid panel will be included in the standard chemistry panel.

[redacted]

[h] There will be no drug return at week 2.

[i] Photographs are optional and will only be collected in subjects who consent.

[j] The Patient Benefit Index represents the subject benefits (PBQ) realized as a function of most important subject needs (PNQ).

[k] Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit.

6. PROCEDURES

6.1. Screening Period

An Informed Consent Document must be signed by the subject before any study-related assessments are performed. Details of the informed consent process are found in Section 13.3.

Screening evaluations, including assessment of inclusion and exclusion criteria, will be performed for all subjects to determine study eligibility. These evaluations must be completed 3 to 5 weeks prior to enrollment. Subjects who do not meet eligibility criteria for the study may not be re-screened.

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 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 (Initials, date of birth, sex, race, and ethnicity-if allowed by local regulations, will be collected)
- Complete medical history
- Prior and concomitant medications
- Physical examination, height, weight, waist circumference (see Appendix L), body mass index
- Vital signs (including blood pressure and heart rate)
- Urinalysis
- Hepatitis testing will include hepatitis B surface antigen, anti-hepatitis B core antibody, and anti-hepatitis C antibody.
- Hematology panel including complete blood count with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC morphology, mean corpuscular volume, white blood cell count (with differential), and platelet count.
- Chemistry panel including sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, glucose, hemoglobin A1c, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, gamma-glutamyl transferase, lactate dehydrogenase. A lipid panel will be included in the standard chemistry panel. Fasting is not required. However, if significant elevation of serum lipid(s) is observed, a fasting re-test should be requested to determine whether or not the elevation was caused by food.

- High-sensitivity C-reactive protein (hs-CRP)
- 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/Serious Adverse event assessment begins when the subject signs the informed consent form
- Assessment of sPGA to determine study eligibility and Investigator's assessment of response to existing topical therapy

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment 3 to 5 weeks after signing the ICF. An administrative window of ± 3 days is permitted for Visits 3 through 6 and ± 4 days is permitted for Visits 7 and 8.

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 evaluation
- Vital signs
- Weight, waist circumference
- Adverse event/Serious Adverse Event evaluation (continuously and through 28 days after last dose of apremilast). Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit.
- Clinical laboratory evaluations [For subjects who are not of child bearing potential, 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 assessments (see Section 6.4)

- 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 8) 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 evaluation
- Adverse event/Serious Adverse Event evaluation (through 28 days after last dose of apremilast). Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit.
- Clinical laboratory evaluations
- Urine/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 any SAEs made known to the Investigator at any time thereafter, as described in Section 10.1. A 4-week post-treatment observational follow-up visit will be conducted for subjects who complete the 32-week study treatment. Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit and will not have a 28-day follow-up.

6.4. Efficacy Assessments

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

6.4.1. Static Physician Global Assessment (sPGA)

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. The National Psoriasis Foundation Psoriasis Score version of a static PGA is calculated by averaging the total body erythema, induration, and desquamation scores. Erythema (E), induration (I), and desquamation (D) are scored on a 5-point scale, ranging from 0 (clear) to 4 (severe). See Appendix B for grading criteria.

6.4.2. Body Surface Area (BSA)

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

6.4.3. Scalp Physicians Global Assessment

The ScPGA will assess scalp involvement, if present at Baseline. See Appendix C 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. Pruritus VAS

The Pruritus VAS assessment will be conducted as outlined in the Table of Events. The subject will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents no itch, and the right-hand boundary represents itch as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded. See Appendix D for grading criteria.

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

The number of fingers with psoriasis nail involvement will be counted, if present at Baseline.

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

6.4.6. Psoriasis Area Severity Index (PASI)

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

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

6.4.7. 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 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 G for grading criteria.

6.4.8. Shiratori's Pruritus Severity Score

Shiratori's Pruritus Severity Score is a pruritus severity assessment tool used in Japan. Symptom severity is assessed for daytime and nighttime symptoms, separately, on a 5-point scale (0, No Symptoms; 1, Minimal; 2, Mild; 3, Moderate; 4, Severe). See Appendix H for grading criteria.

6.4.9. Treatment Satisfaction Questionnaire for Medication Version II

The TSQM version II is an 11-question self-administrated instrument to understand a subject's satisfaction on the current therapy (Atkinson, 2005). See Appendix I for questionnaire.

6.4.10. 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 J). After a period of treatment, subjects are then asked to assess the benefits of treatment by completing the Patient Benefit Questionnaire (PBQ) (See Appendix K). 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).

6.4.11. Photographs

Photographs will be collected only in subjects who consent, and will be considered as supportive evidence of efficacy, but these will not be addressed in the statistical analysis plan (SAP) or included in the clinical study report.

Photographs will be taken of affected locations of plaque psoriasis at Weeks 0, 16, and 32. 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 in the main study will be asked to enrol at selected photography sites and will be asked to sign a separate consent form specific to photography at Visit 1 (Screening Visit), prior to being photographed.

6.4.12. Subject Diary

Subjects will be instructed to record their daily usage of topical medication in a standardized diary (Appendix M). Subjects will record the quantity of topical medication used compared to the previous day as "Decreased", "No change", or "Increased". The subject diary will be provided to subjects at the baseline visit and subjects will be instructed to bring the diary to visits 3 through 8 (or Early Termination visit).

[redacted]

6.5. Safety Assessments

In addition to daily 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 32 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 enrollment. 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, Height and Weight

Vital signs, including temperature, pulse, and seated blood pressure, will be taken during the visits indicated in Table 3, Table of Events. Height will be measured and recorded at Screening;

weight will also be measured and recorded at the Screening Visit and then as indicated in the Table of Events, Body mass index (BMI) will be calculated programmatically.

6.5.3. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as indicated in Table 3, Table of Events. These include complete blood count with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC morphology, mean corpuscular volume, white blood cell count (with differential), platelet count and serum chemistries including sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, gamma-glutamyl transferase, lactate dehydrogenase. A lipid panel will be included in the standard chemistry panel.

6.5.4. 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 findings, physical examination findings, 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) and in the subject's source documents. All SAEs must be reported immediately (ie, within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

Details of AE reporting can be found in Section 10 of the protocol. It should be noted that worsening of a subject's psoriasis should be considered as worsening of disease under study and should not be captured as an adverse event.

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 Corporation as 10, 20, or 30 mg tablets in blister cards for dose titration purposes. Apremilast will also be provided as 30 mg tablets in blister cards for the Maintenance Phase of the study.

7.2. Treatment Administration and Schedule

During Week 0 (Days 1 to 7), subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets for the dose titration. The treatment schema for dose titration at Baseline is shown in Table 4. All subjects will maintain this dosing through Week 32.

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

Table 4: Treatment Schema for Dose Titration At Baseline

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

7.3. Method of Treatment Assignment

After the informed consent is signed, subjects will be assigned a subject identification number using a centralized interactive web response system (IWRS).

Designated study personnel at the investigational sites will be assigned password protected, coded identification numbers, which give them authorization to call into the IWRS. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the IWRS will assign an enrollment number. Confirmation of the enrollment will be sent electronically to the investigational site, Amgen and/or its representative.

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 will be supplied by Amgen. Investigational product (IP) for dose titration at baseline and through Week 32 will be supplied in blister cards.

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 drug 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 investigational product 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. 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 Post-treatment 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 for this protocol, on a per dose basis, is defined as ingestion of 4 or more 30 mg apremilast 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 electronic case report form (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 must remain on their existing topical therapy from at least 4 weeks prior to baseline through week 16 of the study. Principal Investigator or Sub-investigator will instruct subjects to continue to apply their existing topical therapy without a change in quantity or frequency through week 16. After week 16, subjects are permitted to decrease the use of their existing topical therapy, in consultation with the principal Investigator or Sub-investigator.

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. The recording of any permitted topical medications taken for psoriasis should also include the area of the body to which they are applied.

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.

8.2. Prohibited Concomitant Medications and Procedures

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

- Systemic therapy
  - Systemic therapy including but not limited to cyclosporine, corticosteroids, methotrexate, retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters
- Phototherapy
  - Ultraviolet light B or psoralens and long-wave ultraviolet radiation
- Biologic agents, including:
  - Adalimumab, etanercept, infliximab, or certolizumab pegol
  - Ustekinumab
  - Secukinumab, ixekizumab, or brodalumab
  - Guselkumab, risankizumab, or tildrakizumab
- Use of any investigational drug or device

- Prolonged sun exposure or use of tanning booths, which may confound the ability to interpret data from the study

8.3. Required Concomitant Medications and Procedures

Existing topical therapy used for the treatment of plaque psoriasis is required from at least Week -4 to Week 16 of the treatment period. Beginning at Week 16, subjects will be permitted to decrease the use of topical therapy at their discretion.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

The objective of this study is to assess the efficacy and safety of the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.

9.2. Study Population Definitions

The safety population will consist of all subjects who received at least one dose of study medication (IP).

The Enrolled population will consist of all subjects who receive a IWRS identification number and are enrolled into the study. This will be the population for all efficacy analyses.

The per protocol (PP) population will consist of all subjects included in the enrolled population who have both baseline sPGA and at least one post-baseline sPGA evaluation and no important protocol deviations.

9.3. Sample Size and Power Considerations

The primary endpoint of this study is the proportion of subjects who achieve a static Physicians Global Assessment (sPGA) score of 0 or 1 at Week 16, in subjects on combined therapy of apremilast and topicals. Because there is no control arm for the study, if the lower bound of the 95% confidence interval (CI) of the observed response rate is above 8% (ie, the upper bound of 95% CI of the response rate from the placebo group in pooled Phase III studies, namely, PSOR-008 and PSOR-009), one can safely conclude that the treatment effect from the combined therapy is real. A sample size of 150 subjects will support a 95% confidence interval (CI) with at least 80% probability that the length of the interval is within 13%, assuming the expected response rate of 15% [8.5% to 21.5%] (conservatively estimated based on data of Phase III clinical trials). This sample size allows for a 10% discontinuation rate prior to week 16. The sample size calculation is based on nQuery software version 7.0, and the 80% probability supporting the margin of error is based on simulation results.

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, waist circumference, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations. The disease characteristics at baseline will also be summarized using appropriate descriptive statistics. Medical history data will be summarized using frequency tabulations by MedDRA system organ class and preferred term.

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 Open-label Combination Therapy Phase (Week 0 to 16) and for the Open-label Combination Therapy Phase with Optional Topical

Reduction Phase (Week 16 to 32). Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

No statistical comparisons will be made for this single-arm study.

9.6.1. Primary Endpoint

The primary endpoint is the proportion of subjects that achieve sPGA score of 0 (clear) or 1 (almost clear) at Week 16. It will be analyzed using the Enrolled population. In addition, a supplemental analysis will be performed using the PP population.

The primary endpoint will be analyzed using descriptive statistics which involve the sample size, the number of responders, point estimate of proportion of responders along with the associated two-sided 95% confidence intervals (CI).

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, multiple imputation 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 an unbiased estimation can be made.

Sensitivity analysis will be conducted to account for missing data using the last observation carried forward (LOCF) method and the non-responder imputation method.

9.6.2. Secondary and Exploratory Efficacy Endpoints

The secondary and exploratory efficacy endpoints will be analyzed based on the Enrolled population.

The continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM) as the primary method. The MMRM model will use the change from baseline as the response variable and include visit time as a fixed effect, and the baseline value as a covariate. Within-group least-squares means and the associated standard errors and two-sided 95% CIs will be derived from the MMRM model. A sensitivity analysis will be conducted using LOCF method to impute the missing data. For discrete endpoints, similar analysis conducted for the primary endpoint will be performed for the secondary and exploratory endpoints.

9.7. Safety Analysis

The safety analyses will be performed using the Safety populations as defined in Section 9.2.

Adverse events will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. Adverse events will be tabulated by study phase (Open-label Combination Therapy Phase [Week 0 to 16] and for the Open-label Combination Therapy Phase with Optional Topical Reduction Phase [Week 16 to 32]). All treatment-emergent 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 pre-treatment versus post-treatment will be provided.

9.8. Interim Analysis

No interim analysis is planned for this study.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the 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 an 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 AE CRF but should not be reported as an SAE itself.

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

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

All AEs (non-serious and serious) will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study. Subjects who transition to commercial supply of apremilast after the week 32 visit are not required to attend the post-treatment observational follow-up visit. All adverse events (serious/non-serious) will be recorded on the CRF 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 using the paper Serious Adverse Event Report Form (refer to Appendix O) by facsimile/email of the paper SAER Form directly to Amgen Global Patient Safety.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

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

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

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

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

If an AE is considered serious, both the AE page/screen of the CRF and the paper Serious Adverse Event Report Form in English language (refer to Appendix O) must be completed and

must be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event using the paper Serious Adverse Event Report Form by facsimile or email of this form 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.

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

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

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

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by 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, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

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

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

10.3. Abnormal Laboratory Values

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

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

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

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

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

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in 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 a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP 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 facsimile, or other appropriate method, using the Pregnancy Notification Form, or approved equivalent form in English language (refer to Appendix O). The Pregnancy Notification Form in English language 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 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 via the paper Serious Adverse Event Report Form in English language within 24 hours of the Investigator's knowledge of the event using the SAE Report Form in English language.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported to Amgen Global Patient safety

by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the paper SAE Report Form in English language.

Male Subjects With Partners Who Become Pregnant

In the event a male subject fathers a child during treatment, and for an additional **28 days** after discontinuing IP, the information will be recorded on the Pregnancy Notification Form in English language. The form must be submitted to Amgen Global Patient Safety with 24 hours of the 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,

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 in English language (refer to Appendix P) and submitted by facsimile or email to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study (refer to exclusion criterion # 12).
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking IP through 28 days after discontinuing IP.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of the AE/SAE page/screen of the eCRF and the completion of the paper Serious Adverse Event Report Form in English language (refer to Appendix N). All SAEs must be reported to Amgen Global Patient Safety by facsimile or email via the paper Serious Adverse Event Report form within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time following the protocol-required reporting

period or after end of study. Serious adverse events occurring prior to treatment (after signing the ICF) will be collected/recorded/reported.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Amgen Global Patient Safety as soon as these become available. Any follow-up data should be detailed in a subsequent paper SAE Report Form, or approved equivalent form, and sent to Amgen Global Patient Safety jn English language.

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

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

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

10.5.1. Safety Queries

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

10.6. Expedited Reporting of Adverse Events

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

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

In Japan, Amgen KK shall notify the Heads of the Institutes in addition to the Investigators:

- 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.

- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc., or annual SAE report according to the local regulations.

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

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

Amgen Global Patient Safety Contact Information:

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

11. DISCONTINUATIONS

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

- Adverse event
- Lack of efficacy
- Non-compliance with investigational product
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- 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.

The decision to discontinue a subject 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.

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- 800-772-6436. 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

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

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

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

13.2. Investigator Responsibilities

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

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Amgen information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail Screening must have the reason(s) recorded in the subject's source documents.

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

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

13.4. Confidentiality

Amgen affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Amgen requires the Investigator to permit Sponsor'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/IEC approval but will be submitted to the IRB/IEC for information purposes.

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

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

IP can only be supplied to an Investigator by Amgen or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

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

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

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

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

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

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

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

13.8. Termination of the Study

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of 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). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator 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, Celgene/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 eCRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

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

The Investigator must notify Amgen if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Amgen prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Amgen for permission to make alternative arrangements. Details of these arrangements should be documented.

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

15.1. Study Monitoring and Source Data Verification

Amgen ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, 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 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, PMDA, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Amgen immediately.

15.3. Product Complaint

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

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

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

How to Report a PC to Amgen. Please report in English language:

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 Phase2 and Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

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

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

17. REFERENCES

Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl, MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States. findings from the National Psoriasis Foundation surveys 2003-2011. JAMA Dermatol 2013;149(10):1180-5.

Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health 2005;8 Suppl 1:S9-S24.

Feuerhahn J, Blome C, Radtke M, Augustin M. Validation of the patient benefit index for the assessment of patient-relevant benefit in the treatment of psoriasis. Arch Dermatol Res. 2012;304(6):433–41.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.

Frederiksson T, Pettersson U. Severe psoriasis - oral therapy with a new retinoid. Dermatologica 1978;157:238-44.

Gottlieb AB, Psoriasis – Enhanced epidermal differentiation and reduced cell-mediated inflammation are unexpected outcomes. Dis Manag Clin Outcomes 1998;1(6):195-202.

Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007;445(7130):866-73.

Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58(5):826-50.

Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361(5):496-509.

Ohtsuki M, Okubo Y, Komine M, Imafuku S, Day RM, Chen P et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. J Dermatology 2017;44(8): 873-884.

Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol 2003;49(2):206-12.

Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Brit J Pharmacol 2010;159:842-55.

Shiratori A., Efficacy of Mequitazine (LM-209) on pruritus' skin disease. West Japan Dermatology 1983;45:470-473.

The Practical Guide, Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NHLBI Obesity Education Initiative, October 2000: https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf. Accessed on April 23, 2018.

Walsh JA, McFadden M, Woodcock J, Clegg DO, Helliwell P, Dommasch E, et al. Product of the Physician Global Assessment and body surface area: a simple static measure of psoriasis severity in a longitudinal cohort. J Am Acad Dermatol 2013;69(6):931-7.

18. APPENDICES

Appendix A: Table of Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
AE	Adverse event
ANC	Absolute neutrophil count
APC	Antigen presenting cell
β-hCG	β-subunit of human chorionic gonadotropin
BID	Twice daily
BSA	Body surface area
CI	Confidence interval
CRF	Case report form
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
eCRF	Electronic case report form
EDTA	Ethylenediaminetretraacetic acid
EOT	End of treatment
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
[redacted]	
NAPSI	Nail Psoriasis Severity Index of target nail

Abbreviation or Specialist Term	Explanation
PBI	Patient Benefit Index
PBQ	Patient Benefit Questionnaire
PDE4	Phosphodiesterase type 4
[redacted]	
PASI	Psoriasis Area Severity Index
PNQ	Patient Needs Questionnaire
PC	Product Complaint
RBC	Red blood cell count
SAE	Serious adverse event
ScPGA	Scalp Physician Global Assessment
sPGA	static Physician's Global Assessment
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TSQM	Treatment Satisfaction Questionnaire for Medication (TSQM) Version II
VAS	Pruritis Visual Analog Scale

Appendix B: Static Physician's Global Assessment (sPGA)

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation.

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.

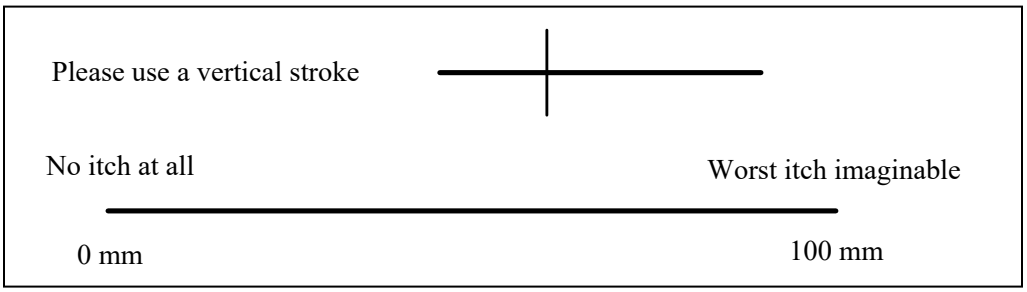
Appendix C: Scalp Physicians Global Assessment (ScPGA)

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 D: Pruritus Visual Analog Scale (VAS)

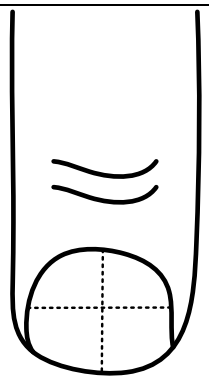
Subject's assessment of pruritus (Itch)

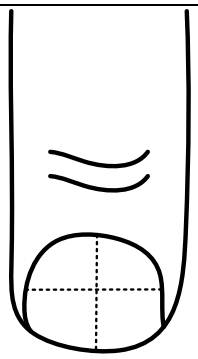
On average, how much itch have you had because of your condition in the past week?



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

Appendix 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: 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: Frederiksson, 1978.

Appendix G: The Dermatology Life Quality Index (DLQI)

Please check/tick (√) 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**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	_ Yes _ No _ A lot _ A little _ Not at all	_ Not relevant
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 H: Shiratori's Pruritus Severity Score

程度	日中の症状	夜間の症状
0 なし	ほとんど、あるいは全く痒みを感じない	ほとんど、あるいは全く痒みを感じない
1 軽微	時にムズムズするが、特に掻かなくても我慢できる	就寝時わずかに痒いが、特に意識して掻くほどでもない。よく眠れる。
2 軽度	時には手がいき、軽く掻く程度。一度おさまり、あまり気にならない。	多少、痒みはあるが、掻けばおさまる。痒みのために目が覚めることはない。
3 中等度	痒くなり、人前でも掻く。痒みのためにイライラし、たえず掻いている。	痒くて目が覚める。ひと描きすると一応は眠れるが、無意識のうちに眠りながら掻く
4 高度	いてもたってもいられない痒み。掻いてもおさまらずますます痒くなり仕事も勉強も手につかない。	痒くてほとんど眠れない。しょっちゅう掻いているが、掻くとますます痒みが強くなる。

Severity	Day Time Symptom	Night Time Symptom
0 Nothing	Little or not at all feel the itch.	Little or not at all feel the itch.
1 Minimal	Sometimes feel creepy, but able to endure it without scratching.	Feel slight itching at bedtime, but not particularly scratched by consciousness. Sleep well.
2 Mild	Sometimes hands go up, getting scratched slightly but it does not bother much.	There is somewhat itching, but after scratching, it will relent. Not to be awakened by itching.
3 Moderate	Feel pretty itchy and scratches even in public. Irritated due to itching, scratching constantly.	Awoke due to itching. Scratch for a while and fall in sleep, but scratch unconsciously while asleep.
4 Severe	Can't endure itching. Even if scratch, itchiness does not relent, it becomes more and neither work nor study can get it on my hands.	Hardly sleep due to itchiness. Often scratching, but it becomes itching more and more.

Source: Shiratori, 1983.

Appendix I: Treatment Satisfaction Questionnaire for Medication (TSQM) Version II

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐ 1 Yes
☐ 0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐ 1 A Great Deal
☐ 2 Quite a Bit
☐ 3 Somewhat
☐ 4 Minimally
☐ 5 Not at All

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐ 1 A Great Deal
☐ 2 Quite a Bit
☐ 3 Somewhat
☐ 4 Minimally
☐ 5 Not at All

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐ 1 A Great Deal
☐ 2 Quite a Bit
☐ 3 Somewhat
☐ 4 Minimally
☐ 5 Not at All

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

Source: Atkinson, 2005.

Appendix J: 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

Source: Feuerhahn, 2012.

Appendix K: 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.

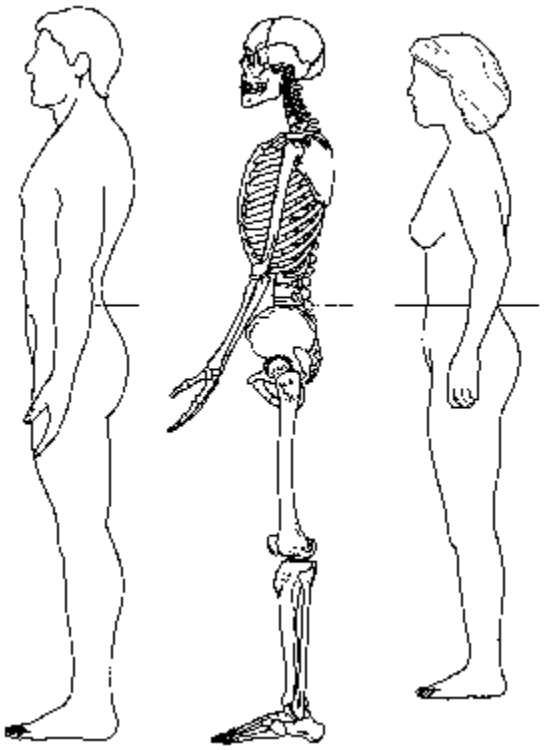
Please mark each of the following statements according to the extent that these treatment goals **were achieved**, thereby indicating if the treatment has benefitted you. If a statement did not apply to you, e.g. because you had no pain, please mark "*did not apply to me*".

	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

Source: Feuerhahn, 2012.

Appendix L: Waist Circumference Measurement

Measuring Tape Position for Waist (Abdominal) Circumference



How to Measure Waist Circumference

a. Place a tape measure around subject's waist above the tip of hipbone.

b. Ask the subject to exhale.

c. Measure the waist after exhaling.

Sources: NHLBIObesity.

Appendix M: Subject Diary

mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase
mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase
mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase
mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase
mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase
mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase
mm/dd (a day of the week)	Application quantity compared with the previous day		
	☐decrease	☐no change	☐increase

Appendix N: SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

AMGEN CC-10004-PSOR-023 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

Report to Amgen Japan Safety - Fax: +81120077507. If FAX is unavailable, email form to the following address: svc-ags-in-jp-cmic@amgen.com

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 occurred before first dose of IP	Enter Serious Criteria code: (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? If yes see section 10 Apremilast No Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

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

4. HOSPITALIZATION

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

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event				Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 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: 00-April-2020*
Page 1 of 3

AMGEN CC-10004-PSOR-023 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN CC-10004-PSOR-023 Apremilast (Otezla)	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

Appendix O: PREGNANCY NOTIFICATION FORM

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen Japan Safety at: Fax: +81120077507. If FAX is unavailable, email form to: svc-ags-in-jp-cmic@amgen.com

1. Case Administrative Information

Protocol/Study Number: CC-10004-PSOR-023 (Apremilast/Otezla)

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

If yes, provide date of delivery: mm_____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix P: LACTATION NOTIFICATION FORM

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

Report to Amgen Japan Safety at: Fax: + 81120077507. If FAX is unavailable, email form to: svc-ags-in-jp-cmic@amgen.com

1. Case Administrative Information

Protocol/Study Number: CC-10004-PSOR-023 (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, 28 April 2020, 10:04 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

– SUMMARY OF CHANGES –

AMENDMENT NO. 1

OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

INVESTIGATIONAL PRODUCT (IP):	**Apremilast (CC-10004)**
PROTOCOL NUMBER:	**CC-10004-PSOR-023**
ORIGINAL DATE:	**30 Jan 2019**
AMENDMENT No.1 DATE:	**28 Apr 2020**
EudraCT NUMBER:	**Not Applicable**
IND NUMBER:	**Not Applicable**

Contact Information:

Name:	[redacted], **M.D., Ph.D.**
Title:	**Associate Medical Director, Inflammation and Immunology**
Address:	**9-7-1 Akasaka Minato-ku Tokyo 107-6239, Japan**
Phone:	[redacted]
E-mail:	[redacted]

AMGEN THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

1. JUSTIFICATION FOR AMENDMENT

Those changes are not significant but administrative changes for sponsor name change , related sentences and other minor change.

1. **Change of sponsor name from 'Celgene' to 'Amgen' and related function name.**

Rationale: Because sponsor is changed from Celgene to Amgen

2. **Change of 'Confidential' Box in Page 1**

Rationale: Change to Amgen wordings from Celgene's

3. **Revise 'EMERGENCY CONTACT INFORMATION' in Page 2.**

Rationale: Change to Amgen wordings from Celgene's

4. **Change of CELGENE THERAPEUTIC AREA HEAD signer in Page 3**

Rationale: According to sponsor change, signer is changed

5. **Revise of description for SAE, AE and the reporting and pregnancy and lactation related sentence in Sections 5, 6, 10**

Rationale: Revised to adjust to global standard for Otezla study protocol in Amgen

6. **Revise of description for 'Section 9.1 and 9.2**

Rationale: To clear inappropriate description

7. **Revise 'Section 12.1 Emergency Contact'**

Rationale: Change to Amgen standard wordings from Celgene's

8. **Revise 'Section 15. Quality Control and Quality Assurance'**

Rationale: According to sponsor change, revised to Amgen policy

9. **Revise 'Section 16. Publications'**

Rationale: Change to Amgen standard wordings from Celgene's

10. Add Appendix N, O, P

Rationale: Add Amgen standard forms

Approval Signatures

Document Name: Protocol-Published Amendment apremilast 20200062 1

Document Description:

Document Number: CLIN-000275771

Approval Date: 26 Aug 2021

Type of Study Protocol: Amendment

Protocol Amendment No.: 1

Document Approvals	
Reason for Signing: Functional Area	Name: Hernan Picard Date of Signature: 26-Aug-2021 16:01:35 GMT+0000