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

	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	-

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).

2. STUDY OBJECTIVES AND ENDPOINTS

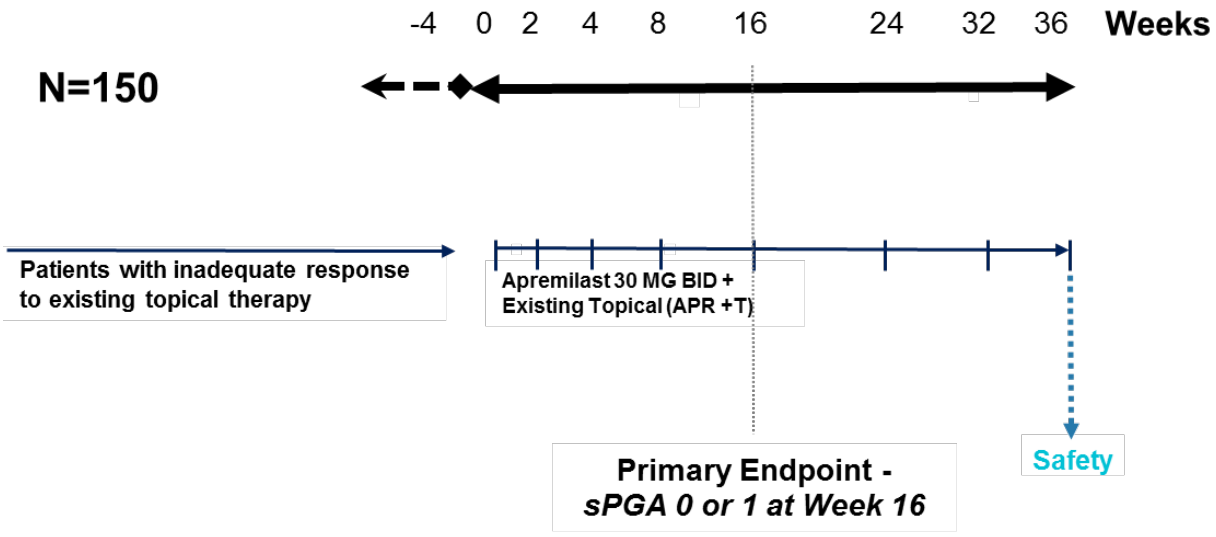
Table 1: Study Objectives

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

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.

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.

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.

- 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

- 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

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**).

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

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

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.

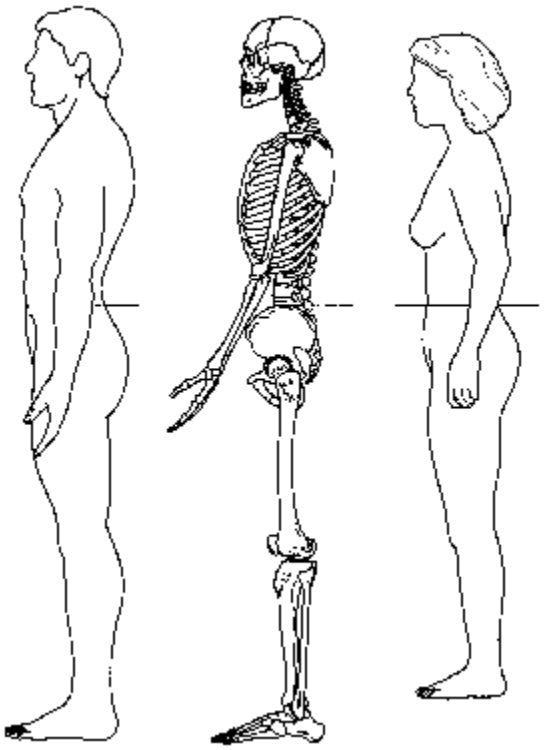
Please mark each of the following statements according to the extent that these treatment goals **were achieved**, thereby indicating if the treatment has benefitted you. If a statement did not apply to you, e.g. because you had no pain, please mark "*did not apply to me*".

	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

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

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.

	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	-

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.

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

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:

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.

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

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.

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.

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 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

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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