Table 2: Study Endpoints (Continued)

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

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Table 3: Table of Events (Continued)

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

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Table 4: Abbreviations and Specialist Terms (Continued)

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

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

3.3. End of Trial

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

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

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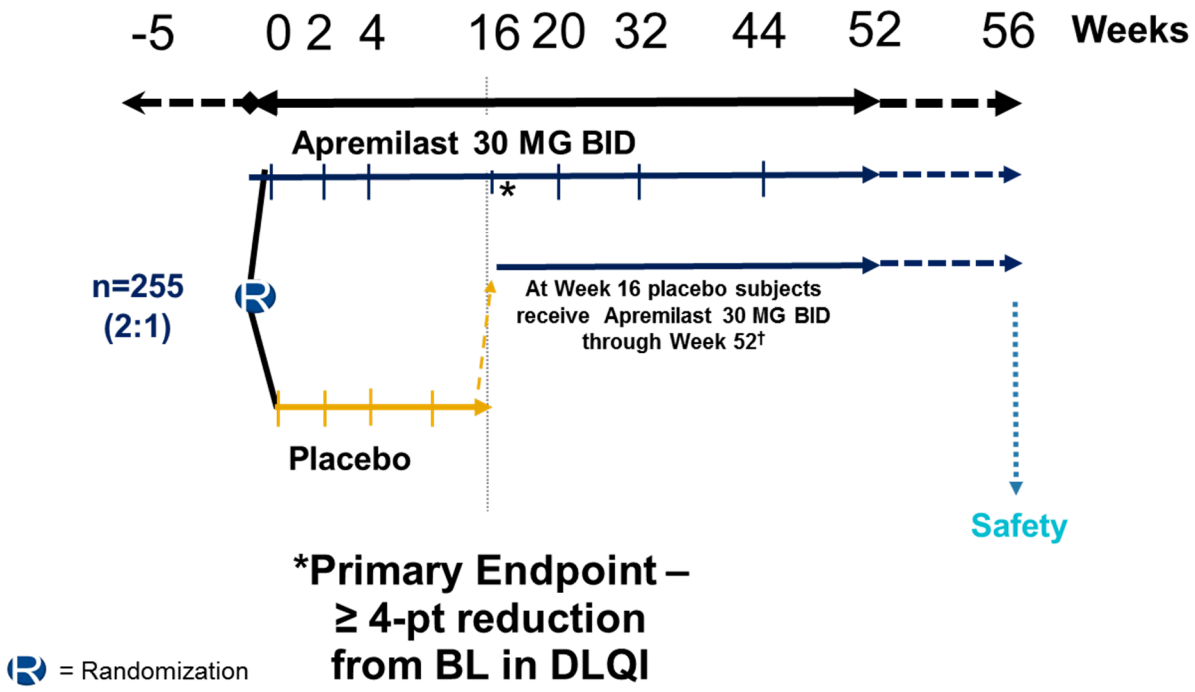
Director and the Statistician. The results from these analyses may be published prior to the end of the study.

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

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

Figure 1: Overall Study Design



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

3.2. Study Duration for Subjects

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

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

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been at work or study over the past week, with response alternatives being "A lot," "A little," or "Not at all."

The DLQI total score has a possible range from 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best score. The developers suggest that the DLQI can be grouped into six subscales: symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores correspond to poorer quality of life. See Appendix B.

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

The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. In this study, sPGA is used to evaluate psoriasis **only** in **visible locations**, defined as **dorsal hand, face, neck and hairline**. When making the assessment of overall severity, the investigator should factor in areas that have already been cleared (ie, have scores of 0) and not just evaluate remaining lesions for severity, ie, the severity of each sign is averaged across all areas of involvement, including cleared lesions. In the event of different severities across disease signs, the sign that is the predominant feature of the disease should be used to help determine the sPGA score. See Appendix C for grading criteria.

6.4.3. Scalp Physician Global Assessment (ScPGA)

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

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

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

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

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

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

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

6.4.6. Palmoplantar Psoriasis Physicians Global Assessment (PPPGA)

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

6.4.7. Itch Numeric Rating Scale (NRS)

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

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

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

6.4.9. Body Surface Area (BSA)

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

6.4.10. Psoriasis Area Severity Index (PASI)

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

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

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

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

The procedure for taking the photographs and processing and shipping photographs will be described in a separate procedure manual distributed to investigational sites performing photographic assessments.

Photographic assessments are an optional part of this study. Subjects enrolled at the selected photography sites will be asked to sign a separate consent form specific to photography at Visit 1 (Screening Visit), prior to being photographed.

6.5. Safety Assessments

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

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

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

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

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

6.5.2. Vital Signs, Weight and Waist Circumference

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

6.5.3. Physical Examination

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

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6.5.4. Psychiatric Evaluation

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

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

6.5.5. Severe Diarrhea, Nausea and Vomiting

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

6.5.6. Clinical Laboratory Evaluations

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

6.5.7. Tuberculosis

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

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6.5.8. Adverse Events

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP. Adverse events and serious adverse events (SAEs) will be recorded on the AE page of the electronic case report form (eCRF), the paper SAE reporting form (SAEs) and in the subject's source documents. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event by recording on the CRF and using the paper Serious Adverse Event Report Form by facsimile/email of the paper SAER Form directly to Amgen Global Patient Safety.

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

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7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

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

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

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

7.2. Treatment Administration and Schedule

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

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

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

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

Dose modifications are not permissible in this study.

7.3. Method of Treatment Assignment

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

Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which gives them authorization to enter the IRT to randomize subjects. The system will present a menu of questions by which the research center personnel will identify the subject and confirm subject eligibility. When all questions have been answered and the subject deemed eligible, the IRT will assign a randomization identification number. Confirmation of the randomization will be sent to the investigational site, Amgen, and/or its representative. The confirmation reports should be maintained as source documents. During the

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

7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

All IP tablets, including apremilast and identically-appearing placebo, will be supplied by Amgen. Investigational product for dose titration at Baseline and to Week 20 will be supplied in blister cards. Investigational product tablets at Week 20 and through Week 52 will be supplied in open label HDPE bottles with child-resistant caps.

7.5. Investigational Product Accountability and Disposal

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

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

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

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

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7.6. Investigational Product Compliance

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

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) should be discussed with Amgen. Compliance is defined as taking between 75% and 120% of dispensed IP.

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

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race, and other categorical variables will be provided using frequency tabulations. The disease characteristics at baseline will also be summarized using appropriate descriptive statistics. These descriptive statistics will be summarized by the randomized treatment group using the ITT population.

9.5. Subject Disposition

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

9.6. Efficacy Analysis

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

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

9.6.1. Primary Endpoint

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

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

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

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

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

9.6.2. Secondary and Exploratory Efficacy Endpoints

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

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

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9.6.3. Photography

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

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

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

[redacted]

9.6.5. Multiplicity Adjustment

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

9.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 9.2, defined as all subjects who are randomized and receive at least one dose of investigational product. Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, and vital signs; no inferential testing for statistical significance will be performed. Data from safety assessments will be summarized descriptively for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast Exposure Period when subjects receive apremilast treatment. For safety analyses in the Placebo-controlled Phase, baseline will be relative to the first dose date following randomization at Week 0. For safety analyses in Apremilast Exposure Period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the Apremilast Extension Phase (Weeks 16-52).

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

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

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

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

9.8. Interim Analysis

No interim analysis is planned for this study.

9.9. Other Topics

9.9.1. Investigational Product Compliance (Tablets)

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

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

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

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

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

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

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

10.4. Pregnancy

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

10.4.1. Females of Childbearing Potential – Collection of Pregnancy Information

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

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

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

The Investigator will monitor the progress of the pregnancy of a female subject, and must notify Amgen Global Patient Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Amgen Global Patient Safety by facsimile, email or other appropriate method, within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form.

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

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(from the time the subject signs informed consent until 28 days after the last dose of IP) and all SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study. . Serious adverse events occurring prior to treatment (after signing the ICF) are to be collected/recorded/reported.

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

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

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

10.5.1. Safety Queries

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

10.6. Expedited Reporting of Adverse Events

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

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

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

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

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

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

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

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Appendix L: Patient Benefit Questionnaire (PBQ)

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

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

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

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

Health Questionnaire

(English version for the US)

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

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

Mobility

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

Self-Care

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

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

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

Pain/Discomfort

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

Anxiety/Depression

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

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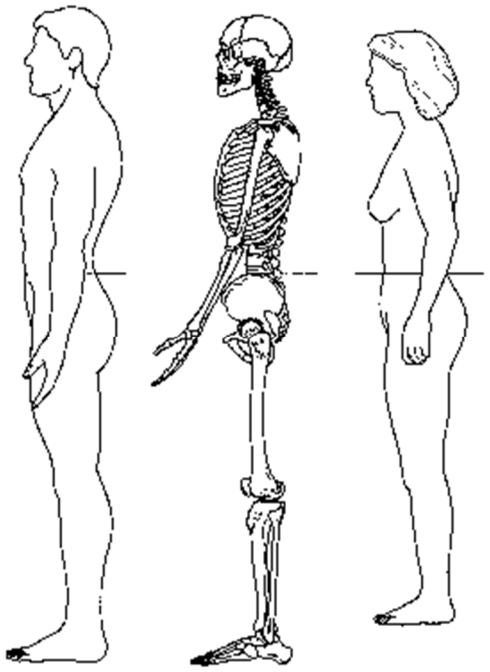
Appendix O: Waist Circumference Measurement & Body Mass Index

Measuring Tape Position for Waist (Abdominal) Circumference



How to Measure Waist Circumference

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

How to Measure Body Mass Index (BMI)

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

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

Source: NHLBI Obesity Education Initiative.

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Appendix P: Treatment Schema for Dose Titration at Baseline

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

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Appendix S: Sample Serious Adverse Event Form (Continued)

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

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

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Table 2: Study Endpoints (Continued)

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

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Table 3: Table of Events (Continued)

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

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

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

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

[c] Visit 9 will serve as the Early Termination Visit for any subject who prematurely discontinues from the study, prior to Week 52. All subjects who complete the study or discontinue the study early will be asked to enter the Four-week Post-treatment Observational Follow-up Phase.

[d] Post-treatment observational follow-up will be conducted by telephone.

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

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

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

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

[redacted]

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

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

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

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

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Table 4: Abbreviations and Specialist Terms (Continued)

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

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4. STUDY POPULATION

4.1. Number of Subjects

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

4.2. Inclusion Criteria

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

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has diagnosis of chronic plaque psoriasis for at least 6 months prior to baseline, that cannot be controlled by topical therapy.
5. Subject has a PASI score ranging from ≥3 to ≤ 10 at baseline.
6. Subject has a DLQI score > 10 at baseline.
7. Subject has presence of ≥ 1 clinical manifestations of plaque psoriasis, defined as at least one of the following:
    a. Moderate to severe scalp psoriasis, defined as Scalp Physician Global Assessment (ScPGA) ≥ 3
    b. Nail psoriasis, defined as onycholysis and onychodystrophy in at least 2 fingernails
    c. Moderate to severe genital plaque psoriasis, defined as modified static Physicians Global Assessment of Genitalia (sPGA-G) ≥ 3
    d. Moderate to severe palmoplantar psoriasis, defined as Palmoplantar Psoriasis Physicians Global Assessment (PPPGA) ≥ 3
    e. Moderate to severe plaque psoriasis in visible locations (dorsal hand, face, neck, and hairline) with static Physicians Global Assessment (sPGA) ≥ 3
8. Subject must be in general good health (except for psoriasis) as judged by the Investigator, based on medical history, physical examination, and clinical laboratories. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions.)
9. Subject must have failed to respond to, or be contraindicated to, or intolerant to other systemic therapy including, but not limited to, cyclosporine, methotrexate, acitretin, psoralen and ultraviolet-A-light (PUVA), fumaric acid esters or biologic therapies.
10. Subjects (**in Italy only**) must be non-responder to, contraindicated to, or intolerant to other systemic therapy (including cyclosporine, methotrexate, or PUVA) **AND** also be contraindicated to, or intolerant to biologics.

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2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

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

Table 2: Study Endpoints

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

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6.4.11. Patient Benefit Index (PBI)

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

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

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

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

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

[redacted]

6.4.15. Photography

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

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7.7. Overdose

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

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

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

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9.9.2. Concomitant Therapy

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

9.9.3. Steering Committee

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

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

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

10.2.2. Severity / Intensity

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

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

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Patient Safety, by facsimile, email, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form.

10.4.2. Male Subject With Partners Who Become Pregnant

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

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

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

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

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

10.4.3. Collection of Lactation Information

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

10.5. Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires the completion of the relevant eCRFs and the paper SAE report form. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event by sending the SAE data/information using the paper SAE report form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study

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11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

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

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

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

The decision to discontinue a subject can be taken at any time and remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor or designee and forward appropriate supporting documents for review and discussion, without identifying the subject.

11.2. Study Discontinuation

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

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

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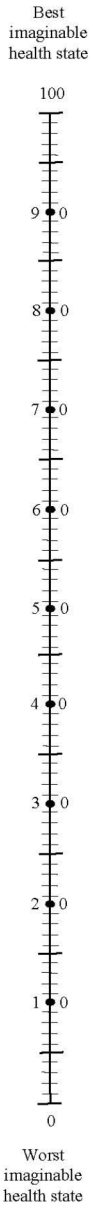
Appendix M: European Quality of Life 5-Dimension Questionnaire (EQ-5D) (Continued)

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

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

Your own health state today



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Source: The EuroQol Group, 1990.

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Appendix Q: Treatment Schema for Dose Titration at Week 16

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

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Appendix S: Sample Serious Adverse Event Form (Continued)

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

	Site Number	Subject ID Number	

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

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

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