Title Page

Protocol Title:		A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP)
Short Protocol Title:		Phase 3, Randomized Study of Apremilast in Japanese Subjects with Palmoplantar Pustulosis
Protocol Number:		20200195
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Trade Name:		Otezla
Sponsor	**Name of Sponsor:**	Amgen Inc.
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (International Council for Harmonisation [ICH] E6).

NCT Number: NCT05174065
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Investigator's Agreement:

I have read the attached protocol entitled A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP), dated **15 April 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

_____
Title and Role of Investigator

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Institution Name

_____
Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP)

Short Protocol Title: Phase 3, Randomized Study of Apremilast in Japanese Subjects with Palmoplantar Pustulosis

Study Phase: 3

Indication: Treatment of palmoplantar pustulosis

Study Rationale

The characteristic histopathological features of palmoplantar pustulosis (PPP) exhibit intraepidermal infiltration of polymorphonuclear neutrophils forming pustules. Although the mechanisms of neutrophil chemotaxis towards the epidermis are unknown, there are several publications that support a role for interleukin (IL)-17 as a promoter of neutrophil accumulation and activation (Yamamoto, 2009; Hagforsen et al, 2010). Patients with PPP have both elevated serum tumor necrosis factor (TNF)-α, IL-17, IL-22, and IL8 levels and elevated neutrophil and Th17 gene expression in the pustular skin (IL-8, IL-17A, IL-36G, IL-12A [p40], IL-17F, IL-22, IL-23B [p19], DEFB4A, and TNF-α) (Murakami, 2011). Eccrine ducts, keratinocyte, and more inflammatory cell involvement is also suggested in PPP pathogenesis (Hagforsen et al, 2010; Murakami et al, 2014; Murakami et al, 2017).

Although corticosteroids, active vitamin D3 ointments, and phototherapy (ultraviolet [UV] radiation therapy) are common PPP treatments, evidence showing their efficacy in moderate to severe PPP cases is quite limited, highlighting the need for optimal, convenient, and targeted therapeutic options for the disease (Kobayashi et al 2010). By inhibiting phosphodiesterase-4 (PDE4), an enzyme prevalent in immune cells, apremilast is expected to inhibit the production of IL-17, IL-8, and several other inflammatory cytokines related to PPP pathogenesis.

The efficacy of apremilast has also been reported in patients with synovitis, acne, pustulosis, hyperostosis osteitis (SAPHO) syndrome (Adamo, 2018). One form of SAPHO syndrome, pustulotic arthro-osteitis (PAO), is a known complication of PPP, suggesting that apremilast may be an effective treatment in PPP patients with or without PAO (Sonozaki et al, 1981; Okubo, 2012; Okuno et al, 2018).

Apremilast studies, CC-10004-PSOR-005, CC-10004-PSOR-008 (hereafter referred to as ESTEEM-1), and CC-10004-PSOR-009 (hereafter referred to as ESTEEM-2), showed improvement of palmoplantar disease status in subjects with palmoplantar psoriasis, a closely related dermatological condition (Bissonnette et al, 2016). Efficacy was also demonstrated in Study CC-10004-BCT-002 for oral ulcers in subjects with Bechet's Disease (BD) in which IL-17 and neutrophils play important roles (Hatemi et al, 2019).

In a randomized, double-blind, placebo-controlled phase 2 study in Japan (Study CC-10004-PPP-001 [20200055]), apremilast showed efficacy in PPP treatment and safety and tolerability data was consistent with the known safety profile of apremilast. The phase 3 study is intended to confirm the risk-benefit balance of apremilast in the treatment of PPP in Japanese patients.

Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the efficacy of apremilast 30 mg twice daily (BID) compared with placebo in subjects with PPP	• Achieving at least 50% reduction from baseline in Palmoplantar Pustulosis Area and Severity Index (PPPASI) total score (PPPASI-50) at week 16
Secondary	
• To evaluate the efficacy of apremilast 30 mg BID compared with placebo in subjects with PPP	• Change from baseline in PPPASI total score at week 16 • Change from baseline in Palmoplantar Pustulosis Severity Index (PPSI) total score at week 16 • Change from baseline in subject's Visual Analogue Scale (VAS) assessment for PPP symptoms (pruritis and pain**/discomfort**) at week 16 • Change from Baseline in Dermatology Life Quality Index (DLQI) total score at week 16
• To evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo in subjects with PPP	• Treatment-emergent adverse events, serious treatment-emergent adverse

	events, and adverse events of interest • Clinically significant changes in body weight, vital signs, and laboratory abnormalities

Primary Estimand

The primary efficacy endpoint is the achievement of PPPASI-50 at week 16 and the main estimand is the difference between apremilast 30 mg BID and placebo in the proportion of PPPASI-50 responders at week 16 based on the intent-to-treat (ITT) population including all randomized subjects, where subjects who discontinue investigational product (IP) due to lack of efficacy, adverse event, or use of protocol-prohibited medication are considered treatment failures.

- The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria.
- The primary endpoint is the achievement of PPPASI-50 at week 16.
- Intercurrent events (IEs) are IP discontinuation due to lack of efficacy, adverse event, or protocol-prohibited medication use. A subject will be considered a non-responder after any of the IEs.
- The summary measure is the difference in proportion of responders.

Missing values of the data in which the treatment failures are considered as non-responders will be imputed using multiple imputation (MI) method.

Secondary Estimand(s)

The main estimand for the secondary efficacy endpoints is the difference in change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score based on the ITT population in which subjects who discontinue the IP due to lack of efficacy, adverse event, or use of protocol prohibited medication are considered as treatment failures.

- The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria.
- The secondary endpoints are the change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score.

- The IEs are IP discontinuation due to lack of efficacy, adverse event, or use of protocol prohibited medication. The baseline value will be assigned to the data after any of the IEs through week 16 regardless of the observed data.

- The summary measure is the mean difference in change from baseline.

The data where the baseline value is assigned for the treatment failures will be used for the analysis model based on the assumption of missing at random (MAR) (eg, mixed-effect model for repeated measures (MMRM).

Overall Design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of apremilast 30 mg BID versus placebo in Japanese subjects with PPP. During the double-blind placebo-controlled study period, subjects will be randomized 1:1 to apremilast 30 mg BID or placebo for 16 weeks. During the active treatment period, all subjects will receive apremilast 30 mg BID from week 16 through week 52. Following the last treatment dose, subjects will enter a **30-day** observational safety follow-up period. The total study duration per subject is **approximately** 60 weeks. Randomization will be stratified by a subject's rounded PPPASI total score (≤ 20 / 21-30/ ≥31) at baseline and baseline focal infection status (yes/no).

Number of Subjects

Approximately 170 subjects will be randomized in this study.

Summary of Subject Eligibility Criteria

Eligible Japanese subjects must be ≥ **18** years of age with PPP diagnosed at least **24 weeks** prior to screening, have a PPPASI total score ≥ 12, a PPPASI severity score ≥ 2 for pustules/vesicles on palms or soles at screening and baseline, and an inadequate response to topical treatment therapy.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

During the double-blind placebo-controlled period of the study, all IP will be provided in blister cards. Apremilast will be provided as 10, 20, and 30 mg tablets in the titration cards. Placebo will be provided by the Sponsor as identically appearing 10, 20, and 30 mg tablets.

During the active treatment period, apremilast will be provided as 10, 20, and 30 mg tablets in titration cards and 30 mg will be provided in bottles containing 80 tablets after titration. Apremilast will be taken orally BID without food or drink restrictions. To mitigate potential gastrointestinal side effects, dose titration will be implemented in a blinded manner during the first week of the study and during week 16 for subjects initially randomized to placebo who are switching to apremilast 30 mg BID treatment.

Dose modifications outside of the doses described above are not permitted in this study.

Statistical Considerations

Sample Size Considerations

The sample size estimation is based on the results of the phase 2 study (CC-10004-PPP-001 [20200055]). Assuming that a proportion of subjects achieve PPPASI-50 response of 40% and 65% at week 16 for the placebo group and the apremilast 30 mg BID group, respectively, a sample size of approximately 170 subjects in total (85 subjects per group) provides 90% power using a chi-square test with a 2-sided alpha of 0.05. A dropout rate of 5% is anticipated during the double-blind placebo-controlled period of the study.

Planned Analyses

The primary analysis will be performed after all subjects have completed the week 16 visit (visit 8) or have been discontinued from the study. An additional analysis will be conducted after all subjects have completed the week 24 visit (visit 10) or have been discontinued from the study. At the end of the study, after all subjects have either completed the study or been discontinued, the final analysis will be performed. The efficacy analyses will be performed on the ITT population.

The primary endpoint is the achievement of PPPASI-50 at week 16. Subjects who discontinued treatment prior to week 16 (due to lack of efficacy, an adverse event, or protocol deviation due to prohibited medication usage) will be considered as treatment failures and non-responders in the primary analysis. Missing values of the data in which the treatment failures are considered as non-responders will be imputed using multiple imputation (MI).

The treatment difference between the apremilast 30 mg BID group and the placebo group will be analyzed using the Cochran–Mantel–Haenszel (CMH) test, adjusting for the stratification factor at randomization. The 2-sided p-value from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment

differences across the strata, and the associated 2-sided 95% CI will be provided. The statistical test will be 2-sided at the significance level of alpha = 0.05.

Secondary efficacy endpoints, such as the PPPASI total score change from baseline at week 16, will be analyzed using the mixed-effect model for repeated measures (MMRM) with treatment group, visit time, treatment-by-time interaction, and stratification factors as fixed effects, and the baseline value as a covariate.

To control the overall Type I error rate at the 0.05 level (2-sided) for comparisons between the apremilast 30 mg BID group and the placebo group, a fixed-sequence testing procedure will be applied for efficacy endpoints. Secondary efficacy endpoints will be statistically tested in the following order (change from baseline at week 16) if the primary analysis result is statistically significant:

1. PPPASI total score
2. PPSI total score
3. Subject's VAS assessment for PPP symptoms (pruritus)
4. Subject's VAS assessment for PPP symptoms (pain**/discomfort**)
5. DLQI total score

Further sequence will be prespecified in the statistical analysis plan (SAP) prior to the week 16 database lock.

For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

Null Hypothesis

The treatment effect of apremilast 30 mg BID and placebo is equivalent.

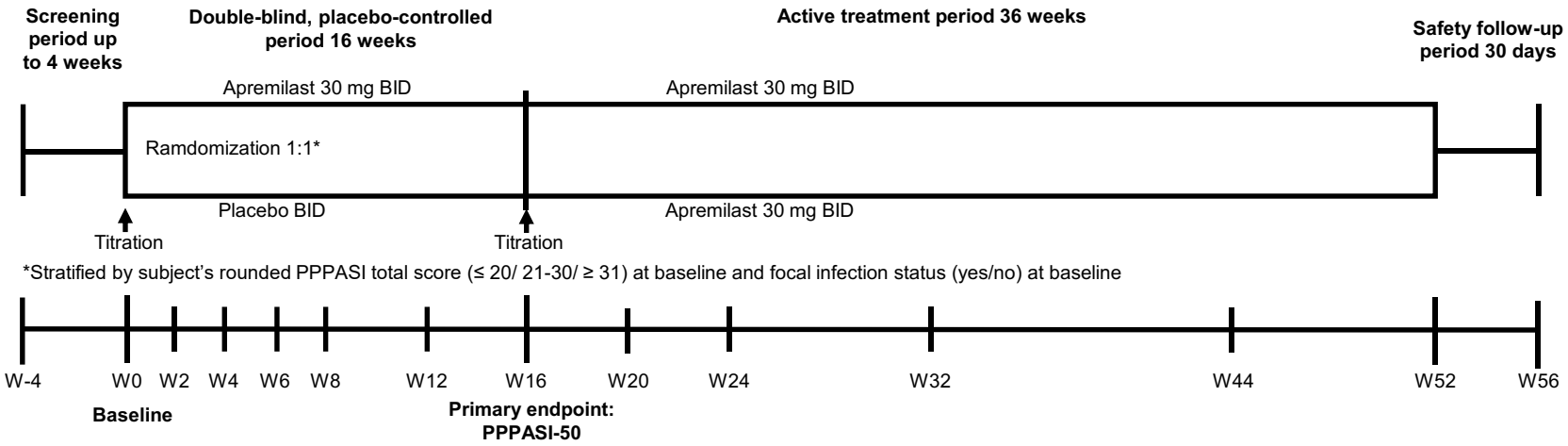
Alternative Hypothesis

There is a difference in treatment effect between apremilast 30 mg BID and placebo.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



BID = twice daily; PPPASI = Palmoplantar Pustulosis Area and Severity Index; W = week

1.3 Schedule of Activities

Table 1-1. Schedule of Activities

	Screening	Double-blind, placebo-controlled period							Active treatment period					Safety follow-up[a]
Visit Number	1	2[b] (Baseline)	3	4	5	6	7	8	9	10	11	12	13/ET	14
Week	- 4 to 0	0	2	4	6	8	12	16	20	24	32	44	52	**30 Days** after last dose
Allowance (days)	-	+ 2	± 2	± 2	± 2	± 2	± 2	± 2	± 4	± 4	± 4	± 4	± 4	+ 7
GENERAL AND SAFETY ASSESSMENTS														
Informed consent[c]	X													
Inclusion / Exclusion criteria	X													
Demographics	X													
Complete medical history[d]	X													
Disease history[e]	X													
Dental examination[f]	X													
Status of smoking[g]	X	X											X	
Prior / concomitant medications and procedures[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychiatric evaluation[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are defined on the last page of this table

Table 1-1. Schedule of Activities

	Screening	Double-blind, placebo-controlled period							Active treatment period					Safety follow-up[a]
Visit Number	1	2[b]	3	4	5	6	7	8	9	10	11	12	13/ET	14
		(Baseline)												
Week	- 4 to 0	0	2	4	6	8	12	16	20	24	32	44	52	**30 Days** after last dose
Allowance (days)	-	+ 2	± 2	± 2	± 2	± 2	± 2	± 2	± 4	± 4	± 4	± 4	± 4	+ 7
GENERAL AND SAFETY ASSESSMENTS														
Pregnancy test and contraception education for females of childbearing potential[j]	X	X						X					X	
Vital signs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[l]	X													
Weight[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination[m]	X							X					X	
Limited physical examination[n]		X[o]	X	X	X	X	X		X	X	X	X		X
LABORATORY ASSESSMENTS														
Hepatitis B and C[p]	X													
Clinical laboratory evaluations (Hematology/ Chemistry/Urinalysis)[p]	X	X				X		X		X	X		X	X
Urine Drug Screening[p]	X	X												
EFFICACY ASSESSMENTS														
PPPASI[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are defined on the last page of this table.

Table 1-1. Schedule of Activities

	Screening	Double-blind, placebo-controlled period							Active treatment period					Safety follow-up[a]
Visit Number	1	2[b]	3	4	5	6	7	8	9	10	11	12	13/ET	14
		(Baseline)												
Week	- 4 to 0	0	2	4	6	8	12	16	20	24	32	44	52	**30 Days** after last dose
Allowance (days)	-	+ 2	± 2	± 2	± 2	± 2	± 2	± 2	± 4	± 4	± 4	± 4	± 4	+ 7
EFFICACY ASSESSMENTS														
PPSI [r]		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
SUBJECT REPORTED OUTCOMES / QUALITY OF LIFE														
Subject's VAS assessment for PPP symptoms for palms and soles[t]		X	X	X	X	X	X	X		X	X		X	X
DLQI [u]		X				X		X		X	X		X	
[redacted]														
PHARMACOKINETIC ASSESSMENTS														
[redacted]														
BIOMARKER ASSESSMENTS														
[redacted]														
STUDY TREATMENT														
Randomization (IRT)		X												
Dispense IP		X		X		X	X	X	X	X	X	X		
Return and count IP tablets (IP accountability)				X		X	X	X	X	X	X	X	X	

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BID = twice daily; ET = End of Treatment; IP = investigational product; PAO = pustulotic arthro-osteitis; [redacted] PK = pharmacokinetic; PPP = Palmoplantar Pustulosis; PPPASI = Palmoplantar Pustulosis Area and Severity Index; PPSI = Palmoplantar Pustulosis Severity Index

a. Subjects who discontinue treatment with IP or withdraw during the active or placebo-controlled treatment period will be asked to enter the **30-day safety** follow-up period after the ET visit. **Once the study has ended, the investigator will report to Amgen any serious adverse event(s) suspected to be related to the investigational product that he becomes aware of. Refer to Section 8.4.4 for additional details.**
b. Visit 2 is Day 1 (Week 0) and the baseline for all efficacy assessments. All assessments should be conducted prior to the first administration of IP.
c. Written informed consent will be obtained by the Principal Investigator or designee prior to performing any study assessments.
d. A complete medical history starting within 5 years prior to screening must be taken.
e. Disease history will capture the following information: specific information regarding diagnosis, presence or absence of focal infection (eg, periapical pathosis, periodontitis, angina, and sinusitis), presence or absence of PAO, and presence or absence of PPP with nail.
f. Dental examination must be conducted by a dentist during screening period, with data obtained if there is any or no dental focal infection (eg, chronic periapical periodontitis, chronic marginal periodontitis), to evaluate the necessity of treatment (any endodontic treatment for periapical pathosis [eg, infected root canal treatment, tooth extraction], and periodontal surgery for moderate to severe periodontitis). Investigators should evaluate whether a treatment for dental focal infections is preferred to study enrollment. Focal infection status will be confirmed at baseline.
g. Smoking history (years/ amount) and current status (yes/no and average number of packs/day).
h. Inadequate response to any topical treatment should be confirmed.
i. At any time when suicidal thoughts or suicide attempt is identified, evaluate the need for referral to psychiatrist and other actions, including discontinuations, as required in Section 8.4.3.
j. See Section 11.5.
k. See Section 8.4.1.
l. See Section 8.2.5.
m. See Section 8.2.4.
n. A limited physical exam may be performed to evaluate an adverse event or for any reason at the discretion of the Investigator
o. Presence of PAO and focal infection status will be assessed during the limited physical examination at baseline.
[redacted]
q. See Section 11.8.
r. See Section 11.9.
[redacted]
t. Worst status between visit in which an assessment is scheduled and the previous visit should be recorded. Indicated assessments should be performed for any tests, procedures, or consultations (PPPASI, PPSI, and [redacted] for palms and soles) for that visit. See Section 11.11.

[redacted]

2. Introduction

2.1 Study Rationale

The characteristic histopathological features of palmoplantar pustulosis (PPP) exhibit intraepidermal infiltration of polymorphonuclear neutrophils forming pustules. Although the mechanisms of neutrophil chemotaxis towards the epidermis are unknown, there are several publications that support a role for interleukin (IL)-17 as a promoter of neutrophil accumulation and activation (Yamamoto, 2009; Hagforsen et al, 2010). Patients with PPP have both elevated serum tumor necrosis factor (TNF)-α, IL-17, IL-22, and IL8 levels and elevated neutrophil and Th17 gene expression in the pustular skin (IL-8, IL-17A, IL-36G, IL-12A [p40], IL-17F, IL-22, IL-23B [p19], DEFB4A, and TNF-α) (Murakami, 2011). Eccrine ducts, keratinocyte, and more inflammatory cell involvement is also suggested in PPP pathogenesis (Hagforsen et al, 2010; Murakami et al, 2014; Murakami et al, 2017).

Although corticosteroids, active vitamin D3 ointments, and phototherapy (ultraviolet [UV] radiation therapy) are common PPP treatments, evidence showing their efficacy in moderate to severe PPP cases is quite limited, highlighting the need for optimal, convenient, and targeted therapeutic options for the disease (Kobayashi et al 2010). By inhibiting phosphodiesterase-4 (PDE4), an enzyme prevalent in immune cells, apremilast is expected to inhibit the production of IL-17, IL-8, and several other inflammatory cytokines related to PPP pathogenesis.

The efficacy of apremilast has also been reported in patients with synovitis, acne, pustulosis, hyperostosis osteitis (SAPHO) syndrome (Adamo, 2018). One form of SAPHO syndrome, pustulotic arthro-osteitis (PAO), is a known complication of PPP, suggesting that apremilast may be an effective treatment in PPP patients with or without PAO (Sonozaki et al, 1981; Okubo, 2012; Okuno et al, 2018).

Apremilast studies, CC-10004-PSOR-005, CC-10004-PSOR-008 (hereafter referred to as ESTEEM-1), and CC-10004-PSOR-009 (hereafter referred to as ESTEEM-2), showed improvement of palmoplantar disease status in subjects with palmoplantar psoriasis, a closely related dermatological condition (Bissonnette et al, 2016). Efficacy was also demonstrated in Study CC-10004-BCT-002 for oral ulcers in subjects with Bechet's Disease (BD) in which IL-17 and neutrophils play important roles (Hatemi et al, 2019).

In a randomized, double-blind, placebo-controlled phase 2 study in Japan (Study CC-10004-PPP-001 [20200055]), apremilast showed efficacy in PPP treatment and safety and tolerability data was consistent with the known safety profile of apremilast. The phase 3 study is intended to confirm the risk-benefit balance of apremilast in the treatment of PPP in Japanese patients.

2.2 Background

2.2.1 Disease

Palmoplantar pustulosis is a chronic, inflammatory, and recurrent skin disease characterized by erythema, scaling, and pustule eruptions on the palm and sole (Misiak-Galazka et al, 2017; Misiak-Galazka et al, 2020; Murakami and Terui, 2020). An inflammatory hyperkeratosis, PPP appears most commonly in middle-aged men and women, particularly those who are smokers (Kobayashi, 2010). In 2010, the national prevalence of PPP was reported as 0.12% with 136 224 Japanese patients living with the disease (Kubota et al, 2015).

Following the early appearance of erythema with pruritus, fluid-filled vesicles begin to form. The blisters then gradually enlarge, becoming pustules enclosed by neutrophils that crust around the lesions before desquamating. In some cases, exanthem on the exterior of palm, sole, and nail lesions are also observed (Tsuruta and Terui, 2016).

The etiology of PPP remains unknown. Palmoplantar pustulosis usually presents in patients without a personal or family history of pustular psoriasis (PsO). There is still controversy surrounding whether PPP and localized PsO are distinct entities. The absence of immunogenetic associations of PPP with PsO suggests that PPP may represent a separate entity (Murakami et al, 2010; Murakami and Terui, 2020). Palmoplantar pustulosis was also reclassified as an independent disease by the International Psoriasis Council in 2007 (Griffiths and Barker, 2007).

2.2.2 Current Treatment Options

Topical treatments such as corticosteroids, active vitamin D3 ointments or phototherapy (UV radiation therapy) are listed as common treatments of PPP (Kobayashi, 2010; Okubo, 2016). Topical therapy is the basic treatment for exanthem on palm and sole. Combination therapy of topical steroid and topical active Vitamin D3 is applied for blisters and pustules. Monotherapy of topical active Vitamin D3 is applied for mild events after remission. However, the efficacy is limited because thicker stratum corneum of the palms and soles represents a barrier, and systemic treatments including phototherapy and some experimental therapies have shown limited efficacy in

comparison with the results seen in chronic plaque-type PsO (Terui et al, 2018; Ohtsuki et al, 2018).

In patients with limited response to topical treatment, ultraviolet B (UVB) therapy (Narrowband UVB or Excimer), etretinate and guselkumab are often used. Nonsteroidal anti-inflammatory drugs (NSAIDs), biotin, cyclosporine, bisphosphonate, methotrexate (MTX) or biologics are considered for the treatment of PAO. In cases with clear pathogenesis and complicating factors, patients should be treated for focal infection. Tonsillectomy with hospitalization or dental treatment for infection will be applied for treatment of focal infection.

Guselkumab was approved in 2018 for moderate to severe PPP patients as systemic therapy in Japan. However, guselkumab is a biologic which is administered subcutaneously and can be used in limited Japanese hospitals. Therefore, there is a high unmet medical need for an effective, convenient (eg, oral), and well tolerated treatment for moderate to severe PPP.

2.2.3 Amgen Investigational Product Background: Apremilast

Apremilast (AMG 407) is an oral, small-molecule PDE4 inhibitor that, through cyclic adenosine monophosphate elevation, intracellularly regulates a network of pro- and anti-inflammatory mediators, many of which have been implicated in PsO, psoriatic arthritis (PsA), inflammatory bowel disease, and PPP (Schett, 2010; Schafer, 2012). Not only has apremilast reduced **Th**17 gene expression in the lesioned skin and peripheral blood of patients with PsO, the treatment has also directly inhibited IL-8 production, migration, and adherence to endothelium (Schafer, 2010; Schafer, 2012; Gottlieb, 2013; Schafer, 2015). Clinical studies in North American, European, and Japanese subjects with PsO demonstrated that apremilast 30 mg BID similarly reduced peripheral IL-17 and IL-22 cytokine levels (Garcet, 2018).

Apremilast is approved in 56 countries for the treatment of inflammatory conditions, including PsO, PsA, and oral ulcers associated with BD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of apremilast is provided in the Investigator's Brochure/package insert.

2.3 Benefit/Risk Assessment

Pivotal phase 3 studies demonstrated statistically significant and clinically meaningful improvement in the signs and symptoms of PsA, PsO, and BD in subjects given apremilast 30 mg BID. The most commonly observed treatment-emergent adverse

events (reported in ≥ 5% of subjects) included diarrhea, nausea, headache, upper respiratory tract infections, and nasopharyngitis, most of which occurred within the first 2 weeks of treatment and resolved within 4 weeks. Most treatment-emergent adverse events were mild or moderate in severity and resolved during continued apremilast treatment. The incidence of serious adverse events was low and comparable between apremilast and placebo treatment groups in placebo-controlled periods and was not driven by any single preferred term or specific individual organ toxicity. The safety profile of apremilast is comparable across its approved indications of PsA, PsO, and BD.

A phase 2 study (CC-10004-PPP-001 [20200055]) evaluated the risk and benefit of apremilast 30 mg BID in Japanese subjects with PPP. The results from this phase 2 study supported the efficacy of apremilast across multiple endpoints with safety and tolerability data consistent with the known safety profile of apremilast. Based on these results this phase 3 confirmatory trial is being implemented.

As of 20 March 2021, over 9000 subjects have received apremilast doses ranging from 10 to 105 mg/day in various completed and ongoing clinical studies and more than 736 035 unique patients worldwide have been treated with apremilast. Frequently reported adverse events have included gastrointestinal disorders (diarrhea, nausea, vomiting, abdominal discomfort) and nervous system disorders (headache). The benefit-risk balance of apremilast continues to remain favorable for approved indications.

Amgen closely monitors the COVID-19 pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

Patients who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study activities.

Amgen considers that it is important to continue the proposed development of apremilast in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Subjects enrolled in this study are permitted to receive vaccinations for COVID-19.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure and Prescribing Information for further data on apremilast.

3. Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the efficacy of apremilast 30 mg twice daily (BID) compared with placebo in subjects with PPP	• Achieving at least 50% reduction from baseline in Palmoplantar Pustulosis Area and Severity Index (PPPASI) total score (PPPASI-50) at week 16
Secondary	
• To evaluate the efficacy of apremilast 30 mg BID compared with placebo in subjects with PPP	• Change from baseline in PPPASI total score at week 16 • Change from baseline in Palmoplantar Pustulosis Severity Index (PPSI) total score at week 16 • Change from baseline in subject's Visual Analogue Scale (VAS) assessment for PPP symptoms (pruritis and pain**/discomfort**) at week 16 • Change from Baseline in Dermatology Life Quality Index (DLQI) total score at week 16
• To evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo in subjects with PPP	• Treatment-emergent adverse events, serious treatment-emergent adverse events, and adverse events of interest • Clinically significant changes in body weight, vital signs, and laboratory abnormalities

Estimand for the Primary Endpoint

The primary efficacy endpoint is the achievement of PPPASI-50 at week 16 and the main estimand is the difference between apremilast 30 mg BID and placebo in the proportion of PPPASI-50 responders at week 16 based on the intent-to-treat (ITT) population including all randomized subjects, where subjects who discontinue

investigational product (IP) due to lack of efficacy, adverse event, or use of protocol-prohibited medication are considered treatment failures.

- The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria.
- The primary endpoint is the achievement of PPPASI-50 at week 16.
- Intercurrent events (IEs) are IP discontinuation due to lack of efficacy, adverse event, or protocol-prohibited medication use. A subject will be considered a non-responder after any of the IEs.
- The summary measure is the difference in proportion of responders.

- Missing values of the data in which the treatment failures are considered as non-responders will be imputed using multiple imputation (MI) method.

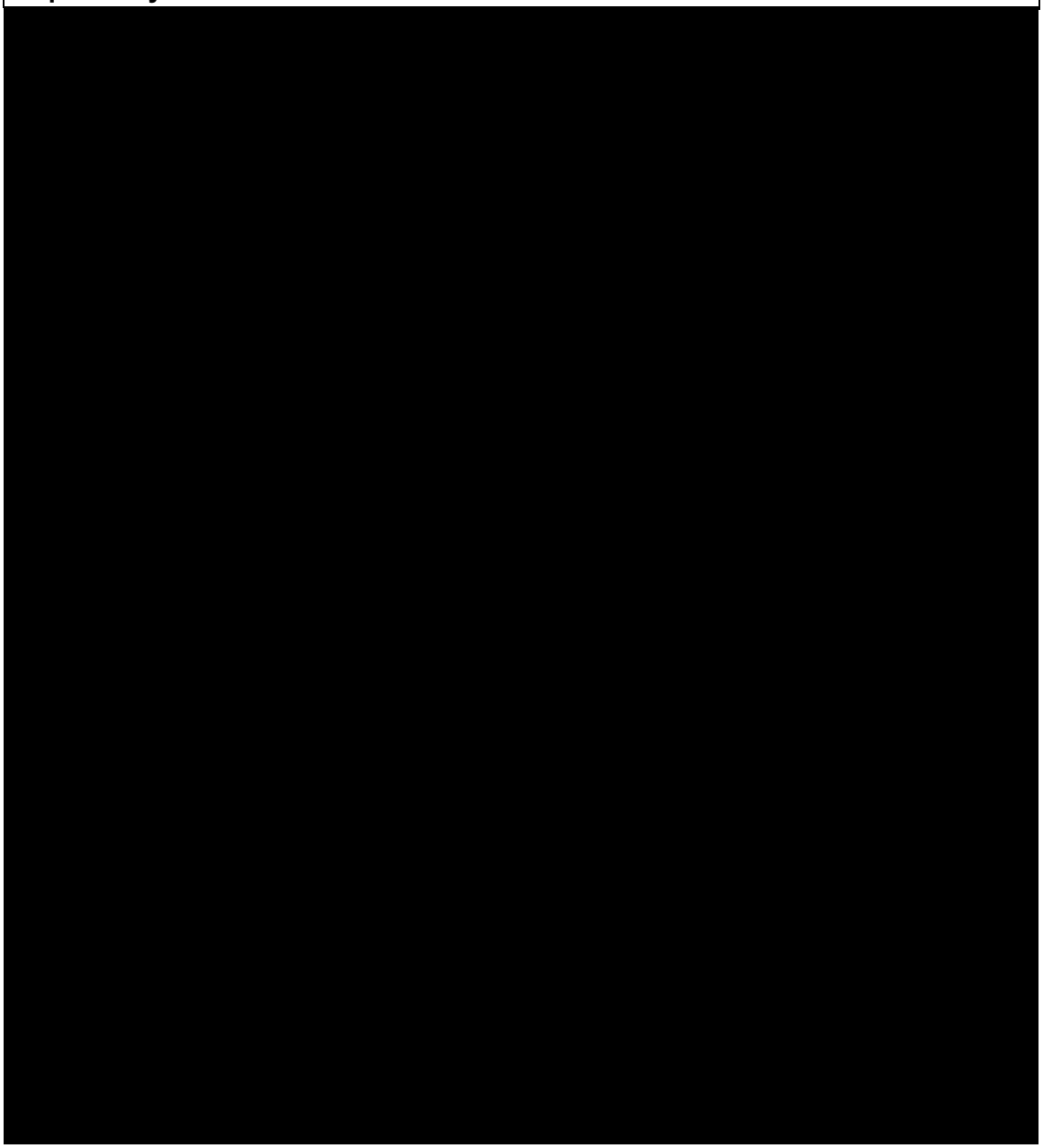
Estimand(s) for Secondary Endpoint(s)

The main estimand for the secondary efficacy endpoints is the difference in change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score based on the ITT population in which subjects who discontinue the IP due to lack of efficacy, adverse event, or use of protocol prohibited medication are considered as treatment failures.

- The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria.
- The secondary endpoints are the change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score.
- The IEs are IP discontinuation due to lack of efficacy, adverse event, or use of protocol prohibited medication. The baseline value will be assigned to the data after any of the IEs through week 16 regardless of the observed data.
- The summary measure is the mean difference in change from baseline.

The data where the baseline value is assigned for the treatment failures will be used for the analysis model based on the assumption of missing at random (MAR) (eg, mixed-effect model for repeated measures (MMRM).

Exploratory



4. Study Design

4.1 Overall Design

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

Approximately 170 subjects will be enrolled in the study, with subjects being randomized in a 1:1 ratio to 1 of 2 treatment arms: apremilast 30 mg BID or placebo. Subject

randomization will be stratified by a subject's rounded PPPASI total score (≤ 20/ 21 - 30/≥ 31) at baseline and baseline focal infection status (yes/no).

Randomized subjects will receive either apremilast 30 mg BID or placebo for 16 weeks, the duration of the double-blind placebo-controlled treatment period. During the active treatment period (week 16 to week 52), all subjects will receive apremilast 30 mg BID. The dose titration procedure (in line with the label) will be implemented for all subjects over a 5-day period at week 0 (the beginning of the double-blind placebo-controlled treatment period) and at week 16 (the beginning of the active treatment period) to mitigate potential gastrointestinal side effects and to maintain blinding.

After the final dose treatment, subjects will enter a **30-day** safety follow-up period. The total study duration per subject is **approximately** 60 weeks.

The primary analysis will be performed after the last subject has completed the week 16 visit (visit 8) or study discontinuation. An additional analysis will be conducted after all subjects have completed the week 24 visit (visit 10) or have been discontinued from the study. The final analysis will be conducted after all subjects have either completed or discontinued the study.

Approximately 45 sites in Japan are planned to participate in the study. Sites that do not enroll a subject within 6 months of site initiation may be closed.

Participants in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 9.2.

4.2 Patient Input into the Study Design

Patient input was not obtained in the design of this study.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

In this study, apremilast 30 mg BID, after a 5-day dose titration, will be evaluated. This dose was approved in Japan for PsA, PsO, and BD-associated oral ulcer treatment. Compared with placebo, apremilast 30 mg demonstrated significant efficacy and safety in clinical study subjects with PsO (CC-10004-PSOR-005 [Papp et al, 2012], ESTEEM-1 [Papp et al, 2015], ESTEEM-2 [Paul et al, 2015], CC-10004-PSOR-011 [Ohtsuki et al, 2017]), PsA (CC-10004-PSA-002 [PALACE-1] [Kavanaugh et al, 2015], CC-10004-PSA-003 [PALACE-2] [Cutolo et al, 2016], CC-10004-PSA-004 [PALACE-3] [Edwards et al, 2016]), BD (CC-10004-BCT-001 [Hatemi et al, 2015], CC-10004-BCT-002 [Hatemi et al, 2018]. A phase 2 PPP study (CC-10004-PPP-001

[20200055]) evaluated the risk and benefit of apremilast 30 mg BID in Japanese subjects. The results from this study supported the efficacy and safety of apremilast 30 mg BID in Japanese subjects. Apremilast can be administered whether in a fasting or fed state.

Apremilast PK, safety, and tolerability has been evaluated in a phase 1 study (CP-018) in healthy Japanese, Chinese (living in the United States), and white (Western) subjects after a single-dose administration of apremilast 20 or 40 mg. Results from this phase 1 study demonstrated that dose-normalized apremilast exposures in healthy Japanese and Chinese subjects were similar to dose-normalized exposures in healthy white subjects, thus suggesting that apremilast PK is not expected to be different between Japanese and white subjects.

In addition, apremilast population PK analyses in white subjects with PsO (CC-10004-PSOR-005) and Japanese subjects with PsO (CC-10004-PSOR-011) demonstrated that the steady-state (ss) exposures (AUC_{tau} [ss] and C_{max} [ss]) in Japanese subjects at doses of 20 mg BID and 30 mg BID were comparable to the values observed in non-Japanese (white subjects), demonstrating that ethnic factors do not significantly affect the PK of apremilast. The PK of apremilast was similar in Japanese and non-Japanese subjects following the same dosing regimen in subjects with BD-associated oral ulcers (CC-10004-BCT-002).

In summary, based on the available PK, efficacy, and safety data from several clinical studies in healthy Japanese and white subjects (CC-10004-CP-018), Japanese and non-Japanese subjects with moderate-to-severe PsO (CC-10004-PSOR-011, ESTEEM-1, and ESTEEM-2), BD (BCT-002), as well as Japanese subjects with PPP (PPP-001 [20200055]) suggests that exposures associated with a 30 mg BID dose of apremilast is expected to provide maximal efficacy in Japanese subjects with PPP, with a manageable safety profile.

4.4 End of Study

An individual subject is considered to have completed the study if he/she has completed the last visit or the last scheduled procedure shown in the Schedule of Activities. The total study duration for an individual subject is up to 60 weeks.

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

102 Japanese subjects ≥ **18** years of age upon entry into initial screening

103 Palmoplantar pustulosis diagnosis with or without PAO for no less than 24 weeks before screening. All 3 of the following diagnosis criteria must be fulfilled:

- Sterile pustules located on palms and/or soles,
- change from blister to pustule via pustule-vesicles with progression of disease, and
- repeat recurrence at the same skin location showing the chronic course profile (for at least 6 months).

104 PPPASI total score of ≥12 at screening

105 PPPASI total score of ≥ 12 at baseline

106 Moderate or severe pustules/vesicles on palms or soles (PPPASI severity score ≥ 2) at screening

107 Moderate or severe pustules/vesicles on palms or soles (PPPASI severity score ≥ 2) at baseline

108 Inadequate response (defined as repeated relapsing-remitting in the same location for a 24-week period) to topical treatments prior to or at screening.

109 Meet the following lab criteria at screening:

- White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9 /L) and ≤ 14,000/mm^3 (≤ 14 x 10^9 /L),
- Platelet count ≥ 100,000/µL (≥ 100 x 10^9 /L),
- Serum creatine ≤ 1.5 mg/dL (≤ 132.6 µmol/L),

- Aspartate aminotransferase (AST) / serum glutamic-oxaloacetic transaminase (SGOT), and alanine aminotransferase (ALT) / serum glutamic pyruvic transaminase (SGPT) ≤ 2.0 x upper limit of normal (ULN),
- Total bilirubin ≤ 2.0 mg/dL, and
- Hemoglobin > 9 g/dL

110 Agree to avoid prolonged sun exposure and avoid the use of tanning booths or other ultraviolet light sources to the palms and/or soles during the study

111 Agree to not make extreme changes to lifestyle habits (eg, exercise, diet, and smoking) during the study

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Changes in disease severity during screening (PPPASI total score change ≥ 5 improvement, from screening to baseline)

202 Periodontitis requiring treatment such as any endodontic treatment for periapical pathosis (chronic periapical periodontitis), infected root canal treatment, tooth extraction, and periodontal surgery for moderate to severe periodontitis (chronic marginal periodontitis)

203 Chronic or recurrent tonsillitis or sinusitis requiring any continuous treatment for ≥ 4 weeks or repeated and acute tonsillitis or sinusitis requiring treatment for ≥ 4 weeks; subject who received a continuous treatment less than one month prior to screening is excluded if the subject is assumed to continue the treatment more than one month. Subject who has repeated and acute tonsillitis or sinusitis and receive any treatment for a month or more is also excluded.

204 Has a diagnosis of plaque-type psoriasis at baseline

205 Has the presence of pustular psoriasis on any part of the body other than the palms and soles (excluding those derived from PPP) at baseline

206 Has evidence of skin conditions of hand and feet at baseline that would interfere with evaluations of the effect of Investigational Product

Other Medical Conditions

207 Positive for hepatitis B virus surface antigen (HBsAg) or positive for anti-hepatitis B core antibody (HBcAb) and anti-HBeAg antibody (HBeAb) with Hepatitis B virus DNA detected (indicative of chronic or acute hepatitis B)

208 Positive for hepatitis C antibody (HCVAb) and hepatitis C virus RNA is detected

209 Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, atrial fibrillation) or a cardiac hospitalization within 12 weeks prior to screening

210 Malignancy or history of malignancy, except for treated (eg, cured) basal cell or squamous cell in situ skin carcinomas or cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence within 5 years prior to screening

211 Has significant viral or fungal infections or bacterial infections requiring treatment with oral or injectable antibiotics within 4 weeks of baseline. Any treatment for such infections must have been completed at least 4 weeks prior to baseline

212 Has active tuberculosis (TB) or a history of incompletely treated TB at baseline

213 Has a history of positive human immunodeficiency virus (HIV) or has congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease) at baseline

Prior/Concomitant Therapy

214 Subject's current or planned use of excluded treatments. For excluded treatments, see Section 6.1.4

215 Subject has received any procedures for focal infection (eg, tonsillectomy and dental therapy) within 24 weeks of baseline. Examples of dental therapy: treatment for periodontitis include any endodontic treatment for periapical pathosis (chronic periapical periodontitis) (eg, infected root canal treatment, tooth extraction), and periodontal surgery for moderate to severe periodontitis (chronic marginal periodontitis).

Prior/Concurrent Clinical Study Experience

216 Currently receiving treatment in another investigational device or drug study, or less than 5 pharmacokinetic/pharmacodynamic half-lives of investigational study drug since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

217 Female subjects of childbearing potential unwilling to use protocol specified method of contraception see Appendix 5 (Section 11.5) during treatment and for an additional 30 days after the last dose of Investigational Product

218 Female subjects who are breastfeeding or who plan to breastfeed while on study through 30 days after the last dose of Investigational Product

219 Female subjects planning to become pregnant while on study through 30 days after the last dose of Investigational Product

220 Female subjects of childbearing potential with a positive pregnancy test assessed by a highly sensitive urine or serum pregnancy test

221 Had prior treatment with apremilast

222 Has scheduled surgery or other interventions that would interrupt the subject's participation in the study

223 Has active alcohol abuse, substance abuse, and/or recreational illicit drug use or has a history of alcohol abuse, substance abuse, and/or recreational illicit drug use within 12 months prior to screening based on medical records, patient self-report, or positive urine drug test performed during screening

224 Has a history of allergy to any of the products or components to be administered during dosing

225 Has a prior medical history of suicide attempt at any time in the subject's lifetime prior to signing of informed consent or randomization, or major psychiatric illness

requiring hospitalization within the last 3 years prior to signing of informed consent

226 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge

227 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's legally authorized representative must personally sign and date the IRB/IEC informed consent before commencement of study-specific procedures.

Each subject who enters into the screening period for the study (screening period begins after the subject signs and dates the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by interactive response technology (IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and has been randomized into the study. The investigator is to document this decision and date, in the subject's medical record and in/on the Subject Enrollment Case Report Form (CRF).

The sponsor may monitor enrollment into the prespecified strata. Enrollment into any particular stratum may be paused to ensure the adequate representation of other strata in the study population, in line with study objectives.

Sites that do not enroll subjects within 6 months of site initiation may be closed.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), non-investigational product(s), placebo, combination product(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

	Amgen Investigational Product:[a] Apremilast	**Placebo**
Dosage Formulation	film-coated tablet; 10, 20, and 30 mg tablets in blister cards for double-blind, placebo-controlled period; 30 mg tablets provided in bottles for the active treatment period	Placebo will be presented in identical packaging, and stored/packaged the same as apremilast
Unit Dose Strength(s)	30 mg	Placebo
Dosage Level(s)	BID	BID
Route of Administration	Oral	Oral
Accountability	The amount dispensed, amount returned, date dispensed, date returned, and lot number of Investigational Product(s) is to be recorded on each subject's CRF(s).	
Dosing Instructions	Dosing will occur as follows: Day 1 AM: 10 mg Day 2 AM: 10 mg Day 2 PM: 10 mg Day 3 AM: 10 mg Day 3 PM: 20 mg Day 4 AM: 20 mg Day 4 PM: 20 mg Day 5 AM: 20 mg Day 5 PM: 30 mg Day 6 and thereafter AM: 30 mg Day 6 and thereafter PM: 30 mg	
Dosage Preparation	N/A	

BID = twice daily; N/A = not applicable
[a] Apremilast will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Other Protocol-required Therapies

There are no other protocol-required therapies.

6.1.3 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational/non-investigational product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen:

Any product complaint(s) associated with an investigational product(s), non-investigational products(s), devices(s), or combination product(s) supplied by Amgen are to be reported.

6.1.4 Excluded Treatments and/or Procedures During Study Period

Table 6-2. Excluded Treatments and/or Procedures During Study Period

Prohibited Treatment	Time Period for Exclusion
Strong cytochrome P450 3A4 (CYP3A4) enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin and St. John's Wort)	2 weeks or 5 times the half-life, whichever duration is longer, prior to randomization and until the end of active treatment
Granulocyte and monocyte adsorption apheresis	2 weeks prior to randomization until the end of active treatment
Topical therapies that could affect PPP or the efficacy evaluation (including, but not limited to, corticosteroids, retinoid, vitamin D3 derivatives, tacrolimus, antihistamine, antibiotics or traditional Chinese/Japanese herbal preparations).	2 weeks prior to randomization and during double-blind, placebo-controlled period; allowed after week 16 Note: Only use of topical antibiotics for the treatment after skin biopsy is permitted. Unmedicated skin moisturizer (eg, Vaseline) will be permitted as needed.
Conventional systemic therapies that could affect PPP or the efficacy evaluation (including, but not limited to corticosteroids, antihistamine, antibiotics, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, dimethyl fumarate, biotin, or colchicine)	4 weeks prior to randomization until end of active treatment Note: Systemic antihistamines are allowed after week 16
Systemic therapy for PAO including, but not limited to bisphosphonates,	4 weeks prior to randomization and until end of active drug treatment period

immunosuppressants [eg, MTX, azathioprine, cyclosporine or 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus]) and other biologics (eg, anti-IL1 antibody)	Note: Background stable doses of NSAIDs for treatment of PAO are permitted.

Table 6-2. Excluded Treatments and/or Procedures During Study Period

Prohibited Treatment	Time Period of Exclusion
Prolonged sun exposure or used tanning booths or other ultraviolet light sources	4 weeks prior to randomization and until the end of active treatment period
Biologic therapy such as: TNFα or IL17 blockers (eg, adalimumab, brodalumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, or biosimilars for each) Anti-IL12 or anti-IL23 monoclonal antibodies such as guselkumab, ustekinumab or tildrakizumab and other biologics	12 weeks or 5 times the half-life, whichever duration is longer, prior to randomization and until end of active treatment period. 24 weeks OR 5 times the half-life, whichever duration is longer, prior to randomization and until end of active treatment period.
Phototherapy (ultraviolet B radiation [UVB] or psoralen ultraviolet A radiation [UVA])	4 weeks prior to randomization; allowed after week 16 during drug treatment period
The following focal infection treatments for PPP (but not limited to): • Tonsillectomy for tonsils • Endodontic treatment for periapical pathosis • Periodontal surgery for moderate to severe periodontitis	24 weeks prior to baseline until the end of active treatment period Note: Dental therapy (non-invasive dental care [eg, scaling and root planning for periodontal disease]) is permitted throughout the study
Systemic retinoids (eg, etretinate)	2 years prior to randomization for females of childbearing potential, 4 weeks prior to randomization for females of non-childbearing potential, and 6 months prior to randomization for males until end of active treatment period.

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6.2 Preparation/Handling/Storage/Accountability

Guidance and information on drug accountability for the investigational product will be provided to the site.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Subjects will be randomized in 1:1 allocation ratio to apremilast or placebo in a double-blind manner after meeting all randomization requirements.

Subject randomization for treatment assignments will be stratified according to a subject's rounded PPPASI total score (≤ 20/21 to 30/≥ 31) at baseline and whether a subject has any focal infection at baseline (yes/no).

The randomization will be performed by and the randomization number will be provided by IRT.

The randomization date is to be documented in the subject's medical record and on the Subject Enrollment CRF.

6.3.2 Blinding

This is a double-blind study. Unblinding information consists of subject treatment assignments, including contents of investigational product boxes (eg, manufacturing lot number), and potentially unblinding data (PUBD) which has the potential to indicate treatment assignment for an individual subject. Unblinding information will be blinded to all subjects, site personnel, and Amgen as described below (Section 6.3.2.1 and Section 6.3.2.2).

The following assessments will be considered unblinding information:

- Apremilast pharmacokinetic assessments (Section 8.5)
- Apremilast biomarker assessments (Section 8.6)

6.3.2.1 Site Personnel Access to Unblinding Information

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

Unblinding information will not be accessible by investigative sites or subjects prior to the completion of the final analysis except for an emergency unblinding.

6.3.2.2 Access to Unblinding Information by Amgen or Designees

Preidentified members of the clinical study team will be unblinded in order to conduct the primary analysis (Section 9.4.1.2). Other members of the clinical study team will not have access to unblinding information until the completion of the final analysis.

6.4 Treatment Compliance

When subjects self-administer apremilast at home, compliance with the treatment will be assessed at scheduled visits and documented in the source documents and CRF.

6.5 Treatment of Overdose

For this study, any dose **4 times** greater than the treatment-specified dose within a 24-hour time will be considered an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Amgen medical monitor immediately.
2. Evaluate adverse events associated with overdose and document them in the CRF.
3. Action will be taken for overdose associated adverse events if requested by the investigator or the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

Prior therapies that were being taken/used for PPP (eg, topicals, systemics, phototherapy, etc.) within the last 5 years prior to randomization, will be collected. For prior therapies that were being taken for PPP, collect therapy name, dose, unit, frequency, route, start date and stop date, and reason for discontinuation. **Prior focal infection and PAO therapies will be collected within the last 6 months (24 weeks) prior to randomization. For prior therapies that were being taken for focal infection and PAO, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.** All other prior therapies that were being taken/used from 4 weeks prior to screening through the first dose of IP, will be collected. For all other prior therapies, collect therapy name, **indication, dose, unit, frequency, route,** start date**,** and stop date**.**

6.6.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.4.

Concomitant therapies are to be collected from day 1 through the **30**-day post-treatment safety follow-up. For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- decision by Sponsor
- lost to follow-up
- death
- adverse event
- subject request
- lack of efficacy
- protocol deviation
- pregnancy

7.2 Subject Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- For subjects who are lost to follow-up, the investigator should search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

If the subject has missed more than 1 visit, and the actions above have been taken to contact the subject, then the subject will be considered lost to follow up.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-1).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 4 weeks.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 4-week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). On-study visits may be completed as specified in the Schedule of Activities. The date of the first dose of apremilast is defined as day 1. All subsequent doses and study visits will be scheduled

based on the day 1 date. Apremilast is to be administered during each visit that it is required.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately **30 days** (+ **7** days) after the end of the last dose of apremilast.

8.1.4 End of Study

A subject is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure / last follow up shown in the Schedule of Activities (Table 1-1).

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and pharmacokinetics of the protocol-required therapies.

8.2.3 Medical History

The Investigator or designee will collect a complete medical history that started within 5 years prior to enrollment through screening. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, PPP history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

8.2.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.5 Physical Measurements

Height [in centimeters] should be measured without shoes. Weight [in kilograms] should be measured without shoes. Body Mass Index should be calculated using the following formula: BMI (kg/m^2) = weight (kg)/[height (cm)/100] ^{2}.

8.2.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

8.3 Efficacy Assessments

8.3.1 Subject and Physician-reported Outcomes/ Quality of Life Measurements

8.3.1.1 Palmoplantar Pustulosis Area and Severity Index (PPPASI)

PPPASI is a disease-specific efficacy assessment tool used by Investigators established to detect a change of disease status on palms or soles (Section 11.8). As sub-scores right/left palm and right/left sole are evaluated for 3 signs of the disease (erythema, pustules/vesicle and desquamation/scale).

PPPASI produces numeric scores that can range from 0 to 72. A higher score indicates more severe disease.

8.3.1.2 Palmoplantar Pustulosis Severity Index (PPSI)

PPSI is a disease-specific efficacy assessment tools by Investigators (Section 11.9). This is established to detect a change of disease status on a specified palm or sole. Evaluated skin lesion is identified by either palms or soles, which has the most severe skin lesion at baseline.

PPSI produces numeric scores that can range from 0 to 12. A higher score indicates more severe disease.

[redacted]

8.3.1.4 Pruritis and Pain/Discomfort Assessment with Subject Visual Analogue Scale (VAS) for PPP Symptoms

Subjects will use VAS (with scores ranging from 0 to 100, with 100 being most severe) to assess the degree of PPP pain**/discomfort** and pruritus on the hands and feet (Section 11.11).

8.3.1.5 Dermatology Life Quality Index (DLQI)

DLQI is a skin disease-specific Quality of Life (QoL) questionnaire comprised of 10 items assessing the subject's status over the previous week (Section 11.12). DLQI can be used to assess 6 different aspects that may affect QoL: symptoms and feelings, daily activities, leisure, work, or school performance, personal relationships, and treatment. A numeric score ranging from 0 to 30 is produced with higher scores indicating increased disease severity.

8.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1).

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. If abnormalities are found and they are considered to be an adverse event, record on the event CRF.

8.4.2 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value

changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1).

8.4.3 Suicidal Risk Monitoring

Apremilast treatment is associated with increased depression adverse reactions. Prior to apremilast use in subjects with a history of depression and/or suicidal thought or behavior, the Investigator should carefully weigh apremilast treatment risks and benefits. Evaluation of suicidal ideation and treatment-emergent suicidal ideation, new or worsening psychiatric symptoms will be assessed at scheduled visits during the study. Subjects should be advised to be alert for the emergence and/or worsening of depression, suicidal thoughts, or mood changes. Should any changes occur, the Investigator should be contacted.

If a subject suffers from new and/or worsening psychiatric symptoms, suicidal ideation, or attempt suicide, subject treatment discontinuation is recommended. Any time suicidal thoughts or suicide attempts are identified, the need for psychiatrist referral and any other pertinent actions (including treatment discontinuation) should be evaluated. Psychiatric evaluation results should be recorded in the CRF.

8.4.4 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.4.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.4.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Amgen Standard Grading Scale and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of study are reported using the Events CRF.

8.4.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through **30 (+ 7) days** after the last day of the dosing interval of investigational product(s)/end of study/safety follow-up visit, whichever occurs later are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

8.4.4.1.3 Serious Adverse Events After the Protocol Required Reporting Period

There is no requirement to monitor study subjects for serious adverse events after the protocol-required reporting period **(as defined in Section 8.4.4.1.2) or after end of study. However**, these serious adverse events **should** be reported to Amgen (regardless of causality) **if the investigator becomes aware of them**. The investigator will report serious adverse events to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.4.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to inquire introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to about adverse event occurrence.

8.4.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is

otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.4.4.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

8.4.4.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.4.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 30 days.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and baseline for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.5 Pharmacokinetic Assessments

Subjects randomized to apremilast will have pharmacokinetic samples assessed. Drug concentration values will unblind the individual treatment assignment and will not be reported to investigative sites or accessible by blinded study team personnel until the completion of the final analysis.

[redacted]

8.6 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

8.6.1 Biomarker Discovery

Samples will also be collected for biomarker analysis, eg, to evaluate potential biomarkers that may correlate with treatment response.

[redacted]

8.6.1.1 Biomarker Development/Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

[redacted]

Amgen or another third party may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to apremilast to investigate and further understand PPP.

9. Statistical Considerations

9.1 Statistical Hypotheses

Null Hypothesis

The treatment effect of apremilast 30 mg BID and placebo is equivalent.

Alternative Hypothesis

There is a difference in treatment effect between apremilast 30 mg BID and placebo.

9.2 Sample Size Determination

The primary endpoint is the achievement of PPPASI-50 response at week 16. The sample size estimation is based on the results of the phase 2 (CC-10004-PPP-001 [20200055]) study. Assuming a proportion of subjects achieving PPPASI-50 response at week 16 of 40% and 65% for the placebo group and the apremilast 30 mg BID group,

respectively, a sample size of approximately 170 subjects in total (85 subjects per group) provides 90% power using a chi-square test with a 2-sided alpha of 0.05. A dropout rate of 5% during double-blind placebo-controlled treatment period is anticipated.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Intent-to-treat (ITT)	The ITT population will include all randomized subjects. Subjects will be included in the treatment group to which they are randomized.
Safety	The safety population will include all randomized subjects who received at least 1 dose of IP. Subjects will be included in the treatment group corresponding to the IP they received.
Pharmacokinetic	The PK analysis population will include all randomized subjects who received at least 1 dose of apremilast and have an evaluable PK concentration.

9.3.1 Covariates

Baseline value will be the covariate in the analysis model (eg, Mixed-effect Model for Repeated Measures [MMRM]) to derive within-group means and standard errors (SEs), treatment differences (from placebo) in means and SEs, and 95% CI.

9.3.2 Subgroups

Subgroup analyses based upon baseline demographic and baseline disease characteristics including the stratification factors at randomization will be provided to determine the robustness of the treatment effect. Details of the subgroup analyses will be specified in the statistical analysis plan (SAP).

9.4 Statistical Analyses

The SAP will be developed and finalized before the week 16 database lock for the primary analysis. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

No interim analysis will be conducted prior to the primary analysis. After all subjects have either completed week 24 (visit 10) or discontinued the study, an additional supplemental analysis will be conducted.

9.4.1.2 Primary Analysis

The primary analysis will be performed after all subjects have either completed week 16 or discontinued the study.

9.4.1.3 Final Analysis

Final analysis will be conducted based on all study data collected after all subjects have either completed or discontinued the study.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Efficacy analyses will be performed on the ITT population by randomized treatment group and safety analyses will be performed on the safety population by actual treatment group, unless otherwise specified.

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

Summary statistics for continuous variables including the number of subjects (n), mean, SD, median, the 25^{th} (Q1) and 75^{th} (Q3) percentiles, minimum, and maximum. All mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. Frequency summary for categorical variables includes number of percentages. All percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).

9.4.2.2 Efficacy Analyses

Endpoint/ Estimand	Statistical Analysis Methods
Primary	The primary efficacy endpoint is the achievement of PPPASI-50 at week 16 and the main estimand is the difference between apremilast 30 mg BID and placebo in proportion of PPPASI-50 responders at week 16 based on the ITT population in which subjects who discontinue IP due to lack of efficacy, adverse event, or use of protocol prohibited medication are considered as treatment failures. • The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria. • The primary endpoint is the achievement of PPPASI-50 at week 16. • The IEs are IP discontinuation due to lack of efficacy, adverse event, or protocol-prohibited medication use. A subject will be considered as a non-responder after any of the IEs. • The summary measure is the difference in proportion of the responders. Missing values of the data in which the treatment failures are considered as non-responders will be imputed using multiple imputation (MI) method based on similar subjects who remained in the study. The treatment difference between apremilast 30 mg BID and placebo will be analyzed using the Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factor at randomization. The testing will be conducted at the 2-sided 0.05 significance level and the adjusted treatment difference of the proportion of subjects achieving PPPASI-50 response, using the weighted average of the treatment differences across the strata, along with the associated 2-sided 95 % CIs will be provided.
Secondary	The main estimand for the secondary efficacy endpoints is the difference in change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score based on the ITT

	population in which subjects who discontinue the IP due to lack of efficacy, adverse event, or use of protocol prohibited medication are considered as treatment failures. • The target population of interest is Japanese subjects with PPP defined through the inclusion/exclusion criteria. • The secondary endpoints are the change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score. • The IEs are IP discontinuation due to lack of efficacy, adverse event, or use of protocol prohibited medication. The baseline value will be assigned to the data after any of the IEs through week 16 regardless of the observed data. • The summary measure is the mean difference in change from baseline. For the continuous efficacy secondary endpoints including change from baseline at week 16 in PPPASI total score, PPSI total score, subject's VAS assessment for PPP symptoms (pruritus and pain**/discomfort**), and DLQI total score, the MMRM with treatment group, visit time, treatment-by-time interaction, and stratification factors as fixed effects, and the baseline value as a covariate will be applied. The data where the baseline value is assigned for the treatment failures will be used for the MMRM analyses based on the assumption of MAR. The least square (LS) means and standard errors (SEs) within-group and treatment differences (from placebo) in LS means, and SEs along with 95%CI and p-values will be derived from the MMRM. To control the overall Type I error rate at the 0.05 level (2-sided) for comparisons between the apremilast 30 mg BID group and the placebo group, a fixed-sequence testing procedure will be applied for efficacy endpoints. Secondary efficacy endpoints will be statistically tested in the order following order (change from baseline at week 16) if the primary analysis result is statistically significant: 1. PPPASI total score 2. PPSI total score 3. Subject's VAS assessment for PPP symptoms (pruritus)

	4. Subject's VAS assessment for PPP symptoms (pain/**discomfort**) 5. DLQI total score Further sequence will be prespecified in the SAP prior to the week 16 database lock.
Exploratory	Will be described in the SAP finalized before the database lock for the primary endpoint.

Additional estimand(s) providing additional treatment efficacy insight will be included in the SAP.

9.4.2.3 Safety Analyses

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product or other protocol-required therapies, and treatment-emergent adverse events will also be provided. Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

9.4.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time. Shift tables of these safety laboratory parameters between baseline and worst on-study value will be provided.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics over time. Shifts in vital sign values of these safety vital sign parameters between baseline and worst on-study value will be provided.

9.4.2.3.4 Physical Measurements

The analyses of physical measurements will include summary statistics over time.

9.4.2.3.5 Exposure to Investigational Product

Exposure to and compliance with investigational product will be summarized using descriptive statistics.

9.4.2.3.6 Exposure to Prior/Concomitant Medications and Procedures

Number and proportion of subjects receiving prior/concomitant medications and procedures will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary.

[redacted]

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{tau}	area under plasma concentration-time curve for a dosing interval
BD	Bechet's disease
BID	twice daily
BMI	Body Mass Index
BUN	blood urea nitrogen
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report forms
CYP3A4	cytochrome P450 3A4
DLQI	Dermatology Life Quality Index
EMR	electronic medical record
ET	end of treatment
[redacted]	
GCP	good clinical practice
HBcAB	hepatitis B core antibody
HCVAb	hepatitis C antibody
Hep	hepatitis
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IE	intercurrent event
IEC	international ethics committee
IL	interleukin
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
LS	least square
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MI	multiple imputation

Abbreviation	Explanation
MMRM	mixed-effect model for repeated measures
MTX	methotrexate
N/A	not applicable
NSAIDS	nonsteroidal anti-inflammatory drugs
PAO	pustulotic arthro-osteitis
PDE4	phosphodiesterase-4
[redacted]	
PK	pharmacokinetic
PPP	palmoplantar pustulosis
PPPASI	Palmoplantar Pustulosis Area and Severity Index
PPSI	Palmoplantar Pustulosis Severity Index
PsA	psoriatic arthritis
PsO	psoriasis
QoL	quality of life
QTL	quality tolerance limit
RBC	red blood cell count
rSDR/V	remote Source Data Review and Verification
SAP	statistical analysis plan
SAPHO	synovitis, acne, pustulosis, hyperostosis osteitis syndrome
SE	standard error
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ss	steady-state
TB	tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VAS	Visual Analogue Scale
WBC	white blood cell count

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by central and local laboratory. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Other Lab Analytes
Sodium	Specific gravity	RBC	Central Laboratory
Potassium	pH	Nucleated RBC	Hep B surface antigen
Chloride	Blood	Hemoglobin	Hep B core antibody
Total protein	Protein	Hematocrit	Hep B envelope antigen
Albumin	Glucose	MCV	Hep B envelope antibody
Calcium	Bilirubin	MCH	Hep B DNA
Magnesium	WBC	MCHC	Hep C antibody
Phosphorus	RBC	RDW	Hep C RNA
Glucose	Epithelial cells	Reticulocytes	Serum pregnancy[b]
BUN or Urea	Bacteria	Platelets	
Creatinine	Casts	WBC	Local Laboratory
Uric acid	Crystals	Differential	Urine drug screening
Total bilirubin		• Bands/stabs	HIV[a]
Direct bilirubin		• Eosinophils	Urine pregnancy[b]
ALP		• Basophils	
LDH		• Lymphocytes	
AST (SGOT)		• Monocytes	
ALT (SGPT)		• Myeloblasts	
Cholesterol		• **Neutrophils**	
HDL		• Promyelocytes	
LDL		• Myelocytes	
Triglycerides		• Metamyelocytes	
		• Atypical lymphocytes	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count
[a] HIV assessment is recommended
[b] Female of child-bearing potential only.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Fasting is not required.

11.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at **their** site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or **their** delegated representative will explain to the subject, or **their** legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have **their** primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of **their** notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the

subject or a legally authorized representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

If important new information becomes available that may be relevant to the subject's consent during their participation in the study, subjects **will** be re-consented.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

Subjects who are rescreened are required to sign a new informed consent form.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

The subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to **their** study-related records, including personal information.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the Sponsor's systems. The Sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The Sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the Sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or

adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Quality tolerance limit parameters (QTLs) will be predefined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability of the study results. These predefined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case Report Forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including [Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of

the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event Case Report Form (CRF). • The investigator must assign the following mandatory adverse event attributes: – Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – Dates of onset and resolution (if resolved); – Did the event start prior to first dose of investigational product – Assessment of seriousness; – Severity (or toxicity defined below); – Assessment of relatedness to apremilast, other protocol-required therapies and/or study-mandated activity and/or procedures; – Action taken; and – Outcome of event. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Events CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity	
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: **The Amgen Standard Grading Scale as show below:**	
Grade	Definition

MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

a An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s) protocol-required therapies, and/or study-mandated activity and/or procedure(s) and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in **their** assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change **their** opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide [Amgen] with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed Events CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event (eSAE) Contingency Report Form) (see Figure 11-1) within 24 hours of the investigator's awareness of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1). • Once the study has ended, serious adverse event(s) **should** be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

A Study # 20200195 AMG 407	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *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	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <Device> No ✓ / Yes ✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

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

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

		Prior to, or at time of Event					Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IP/Amgen Device:		Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency		
<<IP\Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP\Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 Version 7.0 Effective Date: 1 February 2016

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A Study # 20200195 AMG 407	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any 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

A Study # 20200195 AMG 407	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. 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

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for females of childbearing potential are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Female subjects of childbearing potential puberty should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant during treatment and for 30 days after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30 days.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness 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 protocol-required therapies through 30 days of the study drug. 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 pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the

investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.

- Any female subject who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 30 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 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 protocol-required therapies through 30 days.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 217.
- 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 protocol-required therapies 30 days after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

AMGEN Pregnancy Notification Form

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (___)_____ Email _____

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

AMGEN® Lactation Notification Form

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 1-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of biomarker discovery or biomarker development are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as an United States Food and Drug Administration (FDA) Investigational New Drug (IND) safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 8.4.4 and Appendix 11.4.

Anticipated Serious Adverse Events for Study 20200195

MedDRA Preferred Term[a]
Diarrhea
Abdominal Pain

[a] Exact Preferred Term according to MedDRA Version 24.0

11.8 Appendix 8. Palmoplantar Pustulosis Area and Severity Index (PPPASI)

The PPPASI is a system used for assessing and grading the severity and area of palmoplantar pustulosis lesions and their response to therapy. The PPPASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PPPASI system, the palms and soles are divided into 4 regions: the right palm, left palm, right sole, and left sole, which account for 20%, 20%, 30%, and 30% of the total body surface area (BSA) of the palms and soles, respectively. Each of these areas is assessed separately for erythema, pustules and desquamation, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, pustules/vesicle and desquamation /scale) is:

0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for pustular lesions is outlined below.

0 = no involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

The PPPASI formula is:

PPPASI = (E + P + D) Area×0.2 (right palm) + (E + P + D) Area×0.2 (left palm) + (E + P + D) Area×0.3 (right sole) + (E + P + D) Area×0.3 (left sole)

E = erythema; P = pustul**es**/vesicle; D = desquamation/scale

References: Bhushan, 2001.

11.9 Appendix 9. Palmoplantar Pustulosis Severity Index (PPSI)

The PPSI is a system used for assessing and grading the severity of palmoplantar pustulosis lesions and their response to therapy. The PPSI produces a numeric score that can range from 0 to 12.

In the PPSI system, evaluation skin lesion sites are identified by either palms or soles, which has the most severe skin lesion at baseline. Any identified skin lesion site will be assessed at all subsequent visits.

Evaluation of skin lesion site are assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4.

The severity of the disease is calculated as follows.

The scoring system for the signs of the disease (erythema, pustules/vesicle and desquamation/scale) is:

0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The PPSI formula is:

PPSI total score= (E + P + D)

Where E = erythema, P = pustul**es**/vesicle and D = desquamation/scale

The total score ranges from 0 to 12.

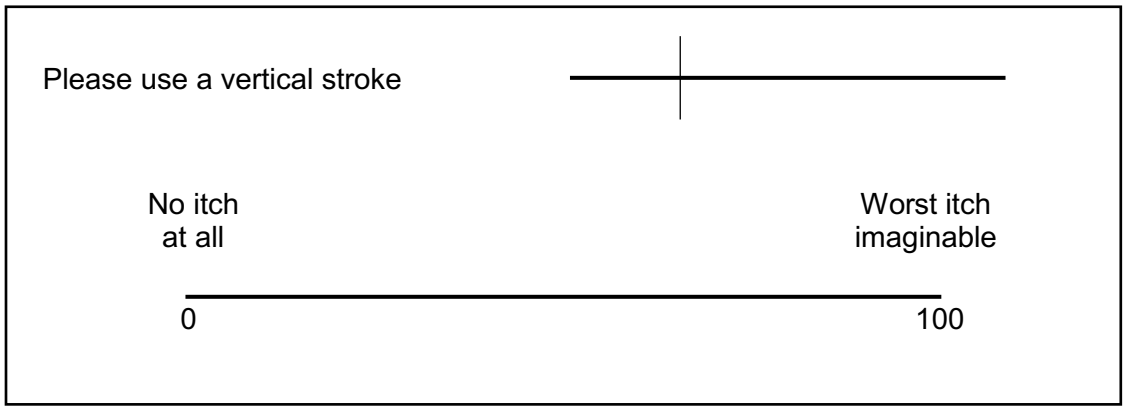
Modified from: Terui, 2018.

[redacted]

11.11 Appendix 11. Visual Analogue Scale (VAS) —PPP Symptoms for Palms and Soles

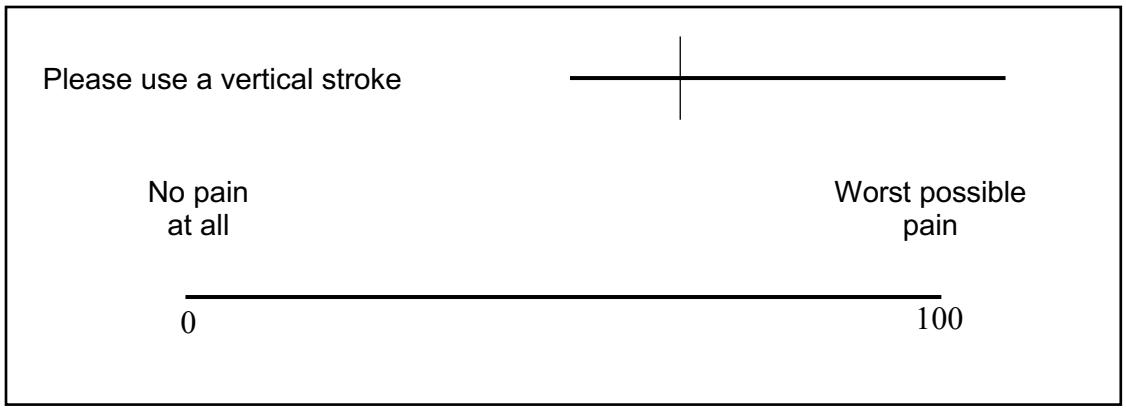
Subject's assessment for pruritus of palms and soles:

At its worst, how much itch (on palms and soles) have you had because of your condition between the last visit and this visit?



Subject's assessment for pain of palms and soles:

At its worst, how much skin discomfort/pain (on hands and feet) have you had because of your condition between the last visit and this visit?



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

Reference: Sobell, 2016.

11.12 Appendix 12. Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

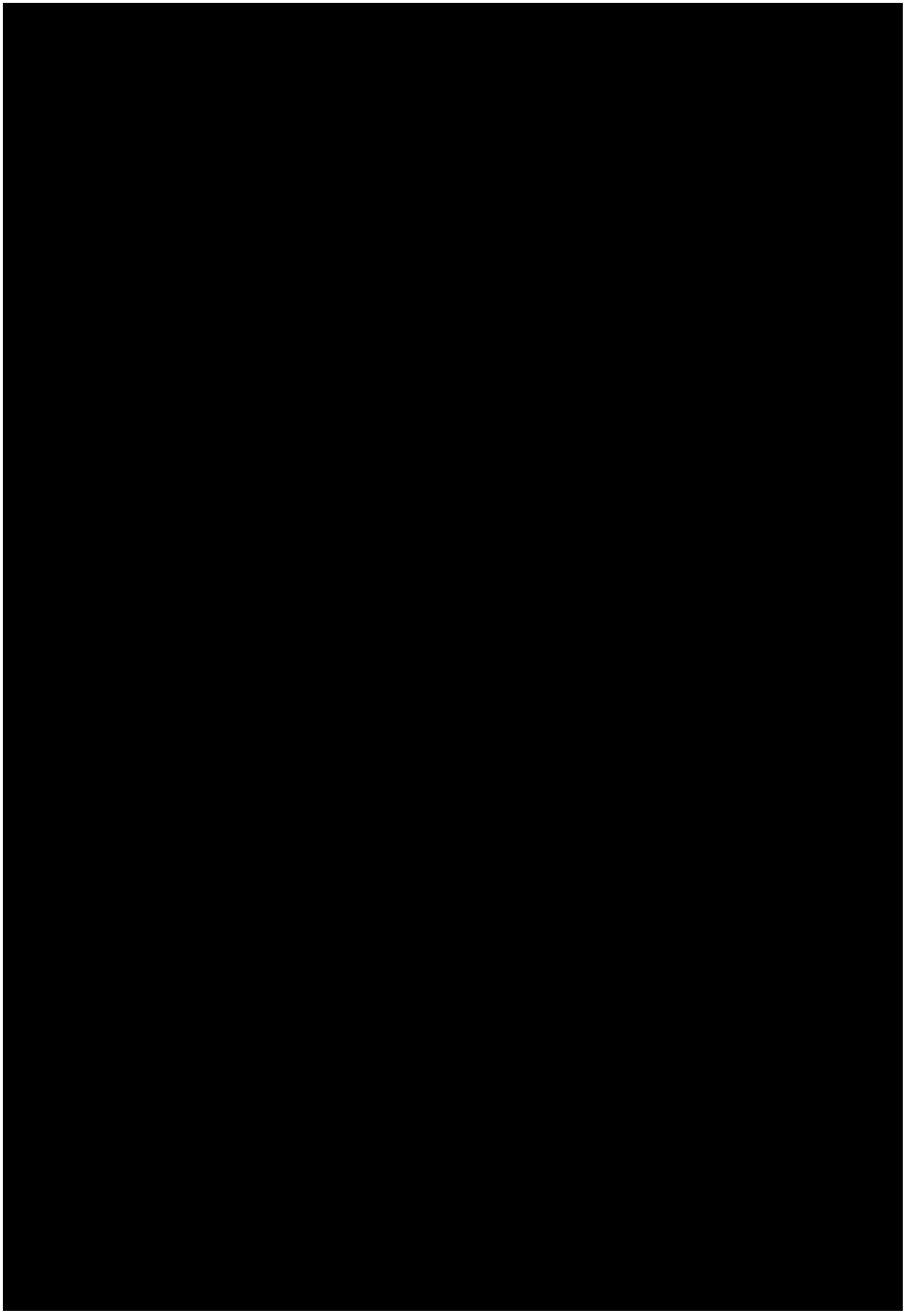
DLQI

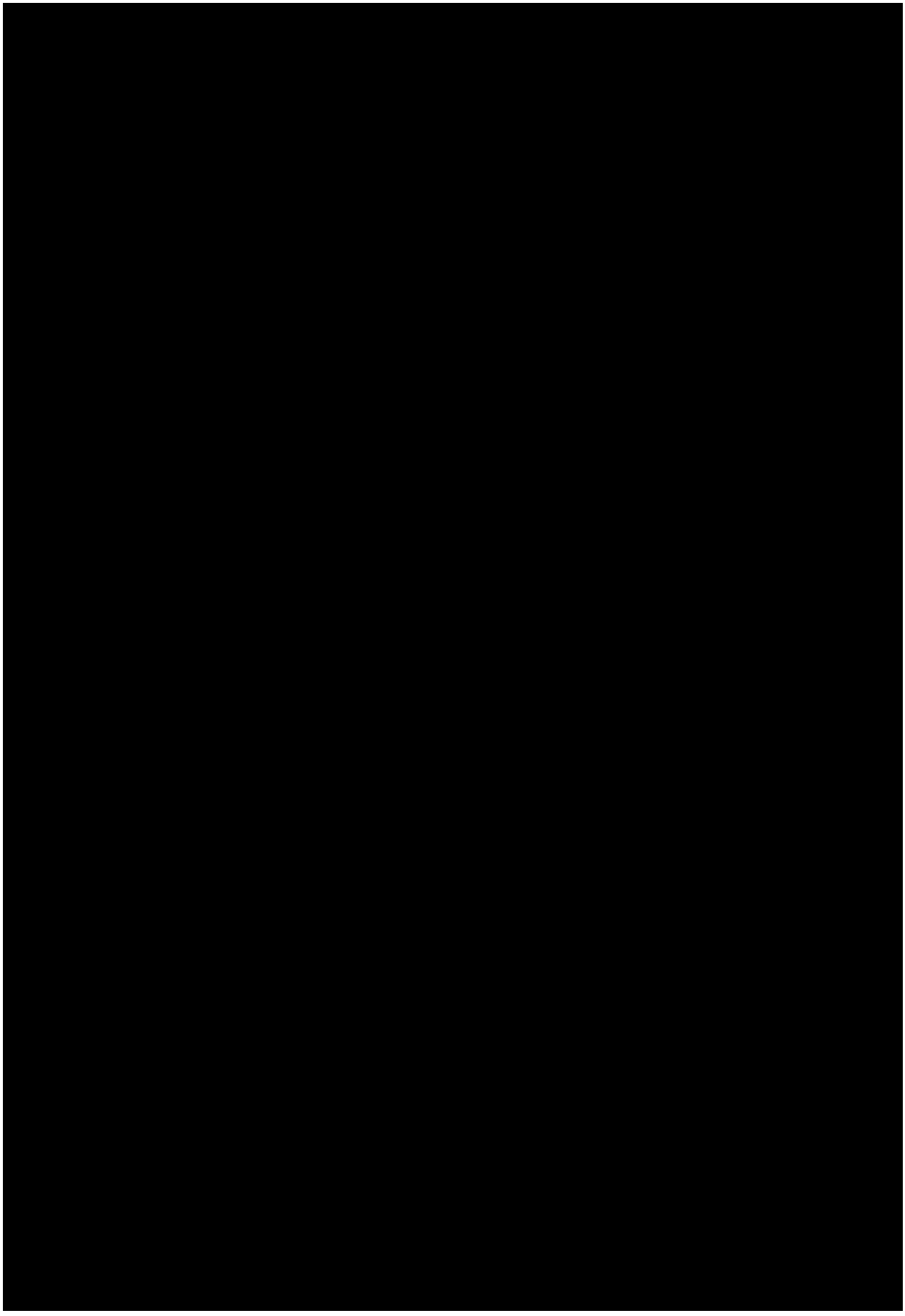
Hospital No: Date:
Name: Score: ☐
Address: Diagnosis:

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

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	 Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check you have answered EVERY question. Thank you.





[redacted]

Superseding Amendment 2

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP)

Amgen Protocol Number 20200195

Amendment Date: 15 April 2022

Rationale:

This protocol is being amended to make changes including, but not limited to, the following:

- Update the age of inclusion to ≥ 18 years of age to follow the updated Japan Civil Code.
- [redacted]
- Change "observational follow-up period" to "safety follow-up period" throughout the protocol to align with current Amgen standard language.
- Update the protocol to correct "IL-17" to "Th17" in Section 2.2.3 Amgen Investigational Product Background: Apremilast.
- Update the protocol to clarify that "pain" is intended to capture "pain/discomfort."
- Update the safety follow-up (SFU) period to 30 (+ 7) days throughout the protocol to align with Amgen requirements.
- Update Section 6.5 Treatment of Overdose to clarify that any dose of apremilast greater than 4 times the treatment-specified dose within 24 hours will be considered an overdose to align with the overdose definition in the apremilast program.
- Update Section 6.6.1 Prior Treatment to change "procedures" to "therapies" to ensure both procedures and medications are captured. Added the collection of pustulotic arthro-osteitis (PAO) therapies within the last 6 months (24 weeks) prior to randomization. Updated "baseline" to "randomization" for consistency throughout the protocol and clarified prior treatment collection within the section.
- [redacted]
- Update Appendix 2: Clinical Laboratory Tests (Section 11.2) to include neutrophils.
- Update reconsent language in Appendix 3: Study Governance Considerations, Informed Consent Process (Section 11.3) to state that subjects will be reconsented if important new information becomes available that may be relevant to the subject's consent during their participation in the study.

- Update adverse event and serious adverse event reporting language throughout protocol to align with current Amgen protocol template.
- Update sample pregnancy and lactation notification forms.
- Make typographical, formatting, and editorial changes throughout the protocol.

Amendment 2

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP)

Amgen Protocol Number 20200195

Amendment Date: 30 March 2022

Rationale:

This protocol is being amended to make changes including, but not limited to, the following:

- Update the age of inclusion to ≥ 18 years of age to follow the updated Japan Civil Code.
- [redacted]
- Change "observational follow-up period" to "safety follow-up period" throughout the protocol to align with current Amgen standard language.
- Update the protocol to correct "IL-17" to "Th17" in Section 2.2.3 Amgen Investigational Product Background: Apremilast.
- Update the protocol to clarify that "pain" is intended to capture "pain/discomfort."
- Update the safety follow-up (SFU) period to 30 (+ 7) days throughout the protocol to align with Amgen requirements.
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- [redacted]
- Update Appendix 2: Clinical Laboratory Tests (Section 11.2) to include neutrophils.
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- Update adverse event and serious adverse event reporting language throughout protocol to align with current Amgen protocol template.
- Make typographical, formatting, and editorial changes throughout the protocol.

Amendment 1

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Apremilast (AMG 407) in Japanese Subjects with Palmoplantar Pustulosis (PPP)

Amgen Protocol Number 20200195

Amendment Date: 30 July 2021

Rationale:

The purpose for this amendment is to reflect changes requested by the Japan Pharmaceuticals and Medical Devices Agency. The following changes were made to the protocol, dated 29 June 2021:

- An analysis at week 24 was added to fulfill the requirement for at least 6 months of efficacy and safety data for all patients being evaluated (Sections 4.1, 9.4, 9.4.1.1, and 9.4.2.2)
- This amendment also includes the following minor updates:
  - Change the order of exclusion criteria (Section 5.2)
  - Clarification to subject enrollment and randomization (Section 5.3)
  - Change the information collected from screen failures (Section 5.4)
  - Clarification of timeframe prior treatments are collected (Section 6.6.1)
  - Clarifications on the biomarkers (Sections 8.6.1.1 and Appendix 6)
  - Correct the list of abbreviations (Appendix 1)
  - Modify the laboratory analyte listing (Table 11-1)
- Grammatical and typographical changes were made throughout the protocol.