A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN JAPANESE SUBJECTS WITH PALMOPLANTAR PUSTULOSIS

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PROTOCOL SUMMARY

Study Title

A Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of apremilast (CC-10004) in Japanese subjects with Palmoplantar pustulosis

Indication

Palmoplantar pustulosis (PPP)

PPP is a chronic and intense inflammatory skin disease with pustules, erythema and scaling localized to the palms and soles. PPP is an inflammatory hyperkeratosis that appears most commonly in middle-aged men and women, particularly those who are smokers.

The etiology of PPP remains unknown, and it is still controversial whether PPP and localized pustular psoriasis are distinct entities. However, typical PPP usually presents in patients who do not have a personal or family history of psoriasis. Furthermore, the absence of immunogenetic associations of PPP with psoriasis suggests that PPP may represent a separate and distinct entity.

Objectives

The primary objective of the study is to evaluate the efficacy of apremilast 30 mg twice daily (BID) compared with placebo in Japanese subjects with PPP.

The secondary objective is to evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo in Japanese subjects with PPP.

The exploratory objectives are:

[redacted]

Study Design

CC-10004-PPP-001 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study of one dose of apremilast in Japanese subjects with PPP.

Approximately 86 subjects will be randomized in a 1:1 ratio to one of the two treatment groups. Subject randomization for treatment assignments will be stratified according to a subject's rounded Palmo-Plantar Pustulosis Area and Severity Index (PPPASI) score (≤20 / 21-30 / ≥31), and whether a subject has any focal infection (yes/no).

The study includes 4 phases:

1. Screening phase for up to 4 weeks (28 days)
2. Sixteen weeks, double-blind, placebo-controlled phase (apremilast 30 mg BID and placebo)
3. Sixteen weeks, active treatment phase (apremilast 30 mg BID)
    - Subjects randomized to apremilast continue apremilast treatment

- Subjects randomized to placebo treatment switch to apremilast treatment in a blind manner.

4. Four weeks post-treatment observational follow-up phase at any time the subject completes or discontinues the trial

During the treatment phase, all subjects will visit the clinical site every 2 weeks until Week 16 and every 4 weeks from Week 16 to Week 32.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed and the primary data analysis will be conducted. However, unblinded data will only be made available to selected Sponsor and contract research organization (CRO) team members involved with analysis of the data. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

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

Study Population

Study population is adult Japanese subjects (≥ 20 years of age) with PPP and inadequate response to the treatment with topical steroid and/or topical vitamin D3 derivative preparations.

Length of Study

This study consists of 4 phases: screening period of up to 4 weeks, 16 weeks for double-blind, placebo-controlled phase, 16 weeks for active treatment phase and 4 weeks for follow-up. Total study duration per subject is approximately 40 weeks at maximum.

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

Study Treatments

All Investigational Product (IP) will be provided in blister cards throughout the entire study. Apremilast will be provided as 10, 20, or 30 mg tablets. Placebo will be provided as identically appearing 10, 20, or 30 mg tablets by the Sponsor.

Apremilast will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To mitigate potential gastrointestinal (GI) side effects, dose titration will be implemented in the first week of this study and at Week 16 for subjects initially randomized to placebo when they switch to apremilast 30 mg BID treatment.

Any dose modifications outside of the dose described above are not permitted in this study.

Overview of Key Efficacy Assessments

1. Primary Efficacy Assessments

- PPPASI
  - The primary endpoint is the proportion of subjects who achieve ≥ 50% improvement in PPPASI total score from baseline (PPPASI-50) at Week 16.

2. Secondary/Exploratory Efficacy Assessments
    - PPPASI
        - Proportion of subjects who achieve a PPPASI-50 except for Week 16.
        - Proportion of subjects who achieve ≥ 75% improvement in PPPASI total score from baseline (PPPASI-75).
        - Area under the curve (AUC) of PPPASI total score
        - Percent change from baseline of PPPASI total score
        - Change from baseline of individual sub scores
    - Palmo-Plantar Pustulosis Severity Index (PPSI)
        - AUC of PPSI total score
        - Percent change from baseline of PPSI total score
    - Physician's Global Assessment (PGA) score for palms and soles
        - Change from baseline of PGA score for palms and soles
        - Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1)
        - Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) and have at least a 2-grade improvement
    - Modified PPPASI
        - Proportion of subjects who achieve a modified PPPASI-50.
        - Proportion of subjects who achieve a modified PPPASI-75.
        - AUC of modified PPPASI total score
        - Percent change from baseline of modified PPPASI total score
        - Change from baseline of individual sub scores
    - Subject's Reported Outcome (SRO)
        - Subject's Visual Analogue Scale (VAS) assessment for PPP symptoms
        - Subject's assessment for each sign/finding of PPP (using PPSI scale)
    - Health-Related Quality of Life (HRQoL) questionnaires
        - Dermatology Life Quality Index (DLQI)
        - EuroQol 5 Dimension (EQ-5D)

Overview of Key Safety Assessments

Safety and tolerability assessments will include;

1. Treatment-emergent adverse events (TEAEs)

- Frequency and incidence rate of any TEAEs by System Organ Class (SOC), Preferred Term (PT), severity, and relationship of adverse events (AEs) to IP.

2. Clinically significant changes in body weight, vital signs, and/or laboratory findings
   - Frequency of clinically significant changes in body weight, vital signs, and/or laboratory findings.

[redacted]

Statistical Methods

Efficacy

The primary analysis of the proportion of subjects who achieve a PPPASI-50 at Week 16 will be carried out using a chi-square test. A result will be expressed as number and percentages of subjects who achieve a PPPASI-50 and associated 90% confidence intervals (CIs) and p-values. The statistical test will be conducted at the $\alpha = 0.10$ (two-sided) level.

For the exploratory purpose, secondary and exploratory efficacy endpoints including but not limited to PPPASI, PPSI, PGA and SRO, will be tested without multiplicity adjustment, therefore p-values for those endpoints will be regarded as nominal.

Safety

All safety data will be listed and summarized by treatment group and/or study period as appropriate. All treatment-emergent AEs will be coded and tabulated by system organ class and preferred term. Incidence of treatment-emergent AEs, serious adverse events (SAEs), AEs leading to discontinuation, and AEs of special interest will be summarized and presented in descending order of frequency in the apremilast 30 mg BID group. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced. The change from baseline for the vital signs including weight will be summarized. Incidence of abnormal vital signs parameters will be tabulated.

Sample Size Justification

A total of approximately 86 subjects will be randomized 1:1 ratio to receive apremilast 30 mg BID or placebo. The study has 80% power (based on a chi-square test at a 2-sided significance level of 0.10) to demonstrate the superiority of apremilast 30 mg BID over placebo with respect to the primary endpoint of PPPASI-50 at Week 16, assuming the PPPASI-50 rates of 45% (apremilast 30 mg BID) and 20% (placebo), respectively. PPPASI-50 rate of 20% at Week 16 in placebo is based on the placebo rate of 21% at Week 16 in guselkumab Phase 2 study. Considering at least 20% difference as a clinically meaningful difference, apremilast 30 mg BID PPPASI rate of 45% is expected in this study.

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Palmoplantar Pustulosis

Palmoplantar pustulosis (PPP) is a chronic and intensely inflammatory skin disease with pustules, erythema and scaling localized to the palms and soles. PPP is an inflammatory hyperkeratosis that appears most commonly in middle-aged men and women, particularly those who are smokers (Kobayashi, 2010). PPP was first reported by Andrews in 1934, which described 15 patients with recalcitrant pustular eruptions of the extremities in whom there was no evidence of psoriasis (Andrews, 1934). Andrews called this disease "Pustular Bacterid of the hands and feet" (Andrews, 1935).

PPP is characterized by the mixture of blisters and pustules on the palms and soles. Pseudo-vesicle with pimple and pustule are observed in the center of the blister. Pimples can be observed by dermoscopic examination, even if it is difficult to be observed by the naked eye. Symptoms first develop as erythema with pruritus followed by vesicle formation. The blister gradually enlarges to form a pustule with neutrophils. Then, it becomes crusted and scaly around the lesion, and it desquamates. After that, erythematous desquamation plaque is observed in addition to the blister and the pustule. In some cases, exanthem on the outside of the palm, sole and nail lesion is also observed (Tsuruta, 2016).

The etiology of PPP remains unknown, and it is still controversial whether PPP and localized pustular psoriasis are distinct entities. However, typical PPP usually presents in patients who do not have a personal or family history of psoriasis. Furthermore, the absence of immunogenetic associations of PPP with psoriasis suggests that PPP may represent a separate and distinct entity (Murakami, 2010). Also, it was reclassified as an independent disease in 2007 by the International Psoriasis Council (Griffiths, 2007).

The number of Japanese PPP patients was reported as 136,224 in 2010 and the national prevalence of PPP was reported as 0.12% (Kubota, 2015).

1.1.2. Diagnosis of PPP

The diagnosis criteria of PPP are proposed as follows (Hayama, 2017):

- Sterile pustules located in palms and/or soles,
- Change from blister to pustule via pustulo-vesicles with progression of disease, and
- Repeat recurrence at the same skin lesion and shows the chronic course profile

Tinea pedis, dyshidrosis, pustular psoriasis, palmoplantar exanthem with eosinophilic pustular folliculitis, and acrodermatitis continua suppurativa hallopeau are excluded. Only the blister (dyshidrosis) or the pustule (pustular psoriasis, exanthem with eosinophilic pustular folliculitis on palm and sole, and acrodermatitis continua suppurativa hallopeau) is also excluded from palmoplantar pustulosis. If a tinea is suspected on an interdigit and nail and trichophyton is observed by KOH direct microscopy, it is excluded from palmoplantar pustulosis, even if mixed with the blister and the pustule is observed. However, palmoplantar pustulosis is rarely complicated with tinea pedis.

1.1.3. Evaluation of Complication

It is necessary to evaluate if patients have any focal infection such as tonsillitis, periodontal disease and sinusitis. Focal infection is the infected lesion localized somewhere in the body and the infection itself is asymptomatic and mild, or the symptoms are repeated only intermittently. Focal infection such as tonsillitis, sinusitis and dental lesion including periodontal disease are suggested as important players in PPP pathogenesis. (Kobayashi, 2016).

Pustulotic arthro-osteitis (PAO) associated with PPP are observed in 10~20% of Japanese PPP patients and PAO is frequently observed in the sternum, clavicles, upper ribs, body axis (including but not limited to spine and sacroiliac joints) and peripheral joints (including but not limited to acromioclavicular joint and finger joint). Sternum arthritis is most commonly observed (Sonozaki, 1981; Yamamoto, 2013). Bone scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI) should be employed to confirm inflammation at the joint, bone and its extent, in order to evaluate complication of arthralgia (sternocostal joint) with pain in chest, neck and lower back.

If necessary, a complication of thyroid disease, diabetes mellitus and Immunoglobulin A (IgA) nephropathy is evaluated.

1.1.4. Current Treatment Guidance

Topical treatments such as corticosteroids, active vitamin D3 ointments or phototherapy (ultraviolet [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 psoriasis (Terui, 2018; Ohtsuki, 2018).

In the case of patients with limited response to topical treatment, ultraviolet B (UVB) therapy (Narrowband UVB or Excimer) may be applied 1 to 3 times a week.

As oral / systemic treatment, etretinate (orally [po]) and guselkumab (subcutaneous [sc]) are listed.

Nonsteroidal anti-inflammatory drugs (NSAIDs), biotin, cyclosporine, bisphosphonate, methotrexate (MTX) or biologics are considered for the treatment for PAO.

In case pathogenesis and complicating factors are clear, 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 needs to be injected and can be used in limited Japanese hospitals. Therefore, high unmet medical needs for an effective, convenient (eg, oral), and well tolerated treatment for moderate to severe PPP still exist.

1.2. Compound Background

Apremilast (CC-10004) is an oral small-molecule inhibitor of Phosphodiesterase 4 (PDE4) that works intracellularly to modulate a network of pro- and anti-inflammatory mediators. PDE4 is a cAMP specific PDE and the dominant PDE in inflammatory cells (dendric cells, monocytes, neutrophils, T-cells, natural killer (NK) cells, keratinocytes and synoviocytes). Inhibition of PDE4 elevates intracellular cAMP levels, which in turn downregulates the inflammatory response by modulating the expression of TNFα, IL23, IL17, and other inflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines. These pro- and anti-inflammatory mediators have been implicated in psoriasis, psoriatic arthritis (PsA), Inflammatory Bowel Disease (IBD), and PPP (Schett, 2010; Schafer, 2012). Apremilast has been shown to reduce Th17 gene expression in lesioned skin and in the peripheral blood of psoriasis patients, and directly inhibits neutrophil responses in vitro such as IL8 production, migration, and adherence to the endothelium (Schafer, 2010; Schafer, 2012; Gottlieb, 2013; Schafer, 2015). In clinical studies for psoriasis, it is reported that apremilast 30 mg twice daily (BID) reduced peripheral Th17 and Th22 cytokine levels in subjects with psoriasis from North America/Europe and Japan in a similar manner (Garcet, 2018).

Apremilast was approved in 53 countries for the treatment of psoriasis and PsA and is under clinical development for the treatment of Behcet's disease (BD) as of 29 Nov 2018.

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

1.3. Rationale

1.3.1. Study Rationale and Purpose

This is the first study of apremilast administered in Japanese subjects with PPP. In completed clinical studies (See Section 1.3.3), apremilast demonstrated acceptable safety and pharmacokinetics in several populations, such as Psoriasis, PsA and BD in a similar manner.

As mentioned above, there remains an unmet medical need for an effective, convenient, and well tolerated treatment for moderate to severe PPP.

The characteristic histopathological features of 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 IL17 as a promoter of neutrophil accumulation and activation (Yamamoto, 2009; Hagforsen, 2010). PPP patients have elevated serum TNFα, IL17, IL22, and IL8, and elevated neutrophil and Th17 gene expression in the pustular skin (IL8, IL17A, IL36G, IL12A (p40), IL17F, IL22, IL23B (p19), DEFB4A, TNFα) (Murakami, 2011). Also, the involvement of eccrine ducts, keratinocytes and more inflammatory cells, such as lymphocytes T, dendritic cells, and Langerhans cells is suggested in PPP pathogenesis (Hagforsen, 2010; Murakami, 2014; Murakami, 2017).

By inhibiting PDE4, apremilast is expected to inhibit production of several inflammatory cytokines related to pathogenesis of PPP such as IL17 and IL8, followed by inhibition of development of pustules. Given apremilast's action in a wide spectrum of cytokines and its

efficacy reported in palmoplantar psoriasis (Bissonnette, 2018), apremilast may also be effective treatment in patients with PPP.

Also, there are a few reports about the clinical efficacy of apremilast in PPP subjects (Haebich, 2017; Eto, 2019) and additionally, on synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome (Adamo, 2018). PAO which is known as a complication of PPP, is considered as a part of SAPHO syndrome (Sonozaki, 1981; Okubo, 2012; Okuno, 2018), therefore, it is suggested that apremilast may also be effective treatment in patients with PAO in PPP patients.

As mentioned above, completed apremilast studies PSOR-005, ESTEEM-1 and ESTEEM-2 showed an improvement of palmoplantar disease status in subjects with palmoplantar psoriasis (Bissonnette, 2016), even if it is not palmoplantar pustulosis.

Moreover, efficacy is demonstrated in Study BCT-001 for oral ulcers in subjects with BD in which IL17 and neutrophils play important roles (Hatemi, 2015).

1.3.2. Rationale for the Study Design

This is the first study to evaluate directly the efficacy and safety of apremilast in Japanese PPP patients.

In several completed studies for moderate to severe plaque psoriasis of apremilast, efficacy and safety of apremilast have been demonstrated (PSOR-005 [Papp, 2012], PSOR-008 [ESTEEM-1] [Papp, 2015], PSOR-009 [ESTEEM-2] [Paul, 2015], PSOR-011 [Ohtsuki, 2017]). The overall design of this study was selected based on these psoriasis clinical studies of apremilast.

The clinical efficacy of apremilast was assessed by 16 weeks of observation in moderate to severe plaque psoriasis studies mentioned above. The time to maximal effect of apremilast in Japanese PPP patients is still unknown. However considering obtained observations in moderate to severe plaque psoriasis studies and the mode of action of apremilast, and furthermore a recent publication of guselkumab study in Japanese PPP patients (Terui, 2018; Terui, 2018), the primary endpoint evaluation is set at Week 16. Also, the use of placebo for the first 16 weeks would be medically acceptable for PPP considering patients will not be intolerably uncomfortable. Sixteen weeks without concomitant treatment has also been accepted in the study for systemic psoriasis. A total treatment duration of 32 weeks was selected in order to assess longer term effect of apremilast in the treatment of PPP.

Experience in clinical studies for PPP is very limited. Palmo-Plantar Pustulosis Area and Severity Index (PPPASI) is reported as a relatively objective endpoint and recently used to evaluate the efficacy in several studies for PPP, palmoplantar psoriasis and such kinds of localized dermatological diseases (Bhushan, 2001; Guenther, 2007; Bissonnette, 2014; Reich, 2016; Hayashi, 2017). Considering current published data of guselkumab in Japanese PPP subjects, PPPASI-50 (≥50% improvement in PPPASI total score from baseline) at Week 16 can be a primary endpoint to detect clinical meaningful efficacy compared with placebo because of poor response of PPP to current treatment and being refractory (Terui, 2018).

1.3.3. Rationale for Dose, Schedule and Regimen Selection

The efficacy and safety of apremilast 30 mg BID is demonstrated in several clinical studies of apremilast for psoriasis (CC-10004-PSOR-005 [Papp, 2012], PSOR-008 [ESTEEM-1] [Papp,

2015], PSOR-009 [ESTEEM-2] [Paul, 2015], PSOR-011 [Ohtsuki, 2017]), PsA (CC-10004-PSA-002 [PALACE-1] [Kavanaugh, 2015], PSA-003 [PALACE-2] [Cutolo, 2016], PSA-004 [PALACE-3] [Edwards, 2016]) and BD (CC-10004-BCT-001 [Hatemi, 2015], BCT-002 [Hatemi, 2018], and the risk and benefit of apremilast 30 mg BID is also established. Details of each study are described in the IB. Based on these findings, apremilast 30 mg BID was selected as the investigated dose in this study.

1.3.4. Rationale for Choice of Comparator Compounds

A placebo control in the double blind, placebo-controlled phase will be used to establish the frequency and magnitude of changes in clinical response that may occur in the absence of active treatment. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

1.3.5. Rationale for Pharmacodynamics and Predictive Biomarkers

Although several pathogeneses of PPP such as concomitant tonsillitis, periodontitis or metal allergy have been proposed, the etiology of PPP remains unknown.

Recently, pathophysiology of PPP at skin lesion (from vesicle formation to pustule development via pustulo-vesicle) is reported that shows serum IL17, IL22, TNFα, and IL8 are elevated in serum in PPP patients (Murakami, 2011) and IL-36 pathway and neutrophil gene expression (IL8, CXCL1, IL17A, IL36G, IL12A, IL17F, IL22, IL23B, DEFB4A, TNFα) in the pustular skin is also reported (Murakami, 2011; Liang, 2017).

Evidence of an anti-neutrophil effect in lesioned skin from psoriasis patients was observed after apremilast 20 mg BID treatment for 12 weeks resulted in a 44% decrease in IL8 messenger RNA (mRNA) levels (N=15, p=0.018) (Gottlieb, 2013).

Based on those results, the following hypotheses are expected.

1. Apremilast will significantly reduce the serum IL17A protein level as part of suppressed Th17 response
2. Apremilast will significantly reduce expression of IL8 mRNA as marker of neutrophils at the pustular skin

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy of apremilast 30 mg BID compared with placebo in Japanese subjects with PPP.
Secondary Objective(s)
The secondary objective is to evaluate the safety and tolerability of apremilast 30 mg BID compared with placebo in Japanese subjects with PPP.
Exploratory Objective(s)
The exploratory objectives are: [redacted]

Table 2: Study Efficacy Endpoints

Endpoint	Name	Description	Timeframe
Primary	PPPASI: PPPASI-50 See Appendix B about PPPASI total score.	Proportion of subjects who achieve a PPPASI- 50 at Week 16.	Week 16
Secondary	PPPASI: PPPASI-50	Proportion of subjects who achieve a PPPASI- 50 at each visit.	By visit in double blind, placebo-controlled phase (except for baseline and Week 16)
	PPPASI: PPPASI-75	Proportion of subjects who achieve a PPPASI- 75 at each visit.	By visit in double blind, placebo-controlled phase (except for baseline)
	PPPASI total score	AUC.	Week 0-16
		Percent change from baseline.	By visit in double blind, placebo-controlled phase (except for baseline)
	PPSI total score See Appendix C about PPSI total score.	AUC.	Week 0-16
		Percent change from baseline.	By visit in double blind, placebo-controlled phase (except for baseline)

Table 2: Study Efficacy Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary (cont.)	PGA score for palms and soles: See Appendix D about PGA for palms and soles score	Change from baseline.	By visit in double blind, placebo-controlled phase (except for baseline)
		Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1)	By visit in double blind, placebo-controlled phase (except for baseline)
		Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) and have at least a 2-grade improvement	By visit in double blind, placebo-controlled phase (except for baseline)
	SRO: Subject's VAS assessment for PPP symptoms Details are shown in Appendix E.	Change from baseline.	By visit until Week 8 and Week 12, 16 in double blind, placebo-controlled phase (except for baseline)
Exploratory	PPPASI: Three sub scores (Erythema, Pustules/Vesicle, Desquamation/Scale)	Change from baseline of individual sub scores.	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up (except for baseline)
	Modified PPPASI: modified PPPASI-50 See Appendix F about modified PPPASI total score.	Proportion of subjects who achieve a modified PPPASI-50.	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up (except for baseline)
	Modified PPPASI: modified PPPASI-75	Proportion of subjects who achieve a modified PPPASI-75.	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up (except for baseline)
	Modified PPPASI total score Modified PPPASI: Two sub scores (Pustules, Vesicle)	AUC.	Week 0-16
		Percent change from baseline.	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up (except for baseline)
		Change from baseline of individual sub scores.	By visit in double blind, placebo-controlled phase, active treatment phase and follow-up (except for baseline)

Table 2: Study Efficacy Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory (cont.)	SRO: Subject's assessment for each sign/finding of PPP (Erythema, Pustules/Vesicle and Desquamation/Scale) PPSI scale is used for assessment. Details are shown in Appendix G.	Change from baseline.	By visit in double blind, placebo-controlled phase, Week 24 and 32 in active treatment phase and follow-up (except for baseline)
	SRO: DLQI See Appendix H.	Change from baseline.	Week 8, 16, 24 and 32
	SRO: EQ-5D See Appendix I about EQ-5D	Change from baseline of the utility index and VAS score.	Week 8, 16, 24 and 32
	PPPASI: PPPASI-50	Proportion of subjects who achieve a PPPASI- 50 at each visit.	By visit in active treatment phase
	PPPASI: PPPASI-75	Proportion of subjects who achieve a PPPASI- 75 at each visit.	By visit in active treatment phase
	PPPASI total score	Percent change from baseline.	By visit in active treatment phase
	PPSI total score	Percent change from baseline.	By visit in active treatment phase
	PGA score for palms and soles	Change from baseline.	By visit in active treatment phase
		Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1)	By visit in active treatment phase
		Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) and have at least a 2-grade improvement	By visit in active treatment phase
Exploratory (cont.)	SRO: Subject's VAS assessment for PPP symptoms	Change from baseline.	Week 24 and 32 in active treatment phase

AUC = Area under the curve; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5 Dimension; modified PPPASI-50 = defined as ≥50% improvement of modified PPPASI total score from baseline; modified PPPASI-75 = defined as ≥75% improvement of modified PPPASI total score from baseline; PGA = Physician's Global Assessment; PPP = Palmoplantar pustulosis; PPPASI = Palmo-Plantar Pustulosis Area and Severity Index; PPPASI-

50 = defined as ≥ 50% improvement in PPPASI total score from baseline; PPPASI-75 = defined as ≥ 75% improvement in PPPASI total score from baseline; PPSI = Palmo-Plantar Severity Index; SRO: Subject's Reported Outcome; VAS = Visual Analogue Scale.

Table 3: Study Safety Endpoint

Endpoint	Name	Description	Timeframe
Safety	TEAEs	Frequency and incidence rate of any TEAE by SOC, PT, severity, and relationship of AEs to IP.	During double blind, placebo-controlled phase and active treatment phase
	Clinically significant changes in body weight, vital signs, and/or laboratory findings	Frequency of clinically significant changes in body weight, vital signs, and/or laboratory findings.	During double blind, placebo-controlled phase and active treatment phase

AE = Adverse event; IP = Investigational Product; PT = Preferred terms; SOC = System Organ Class; TEAE = Treatment-emergent adverse event.

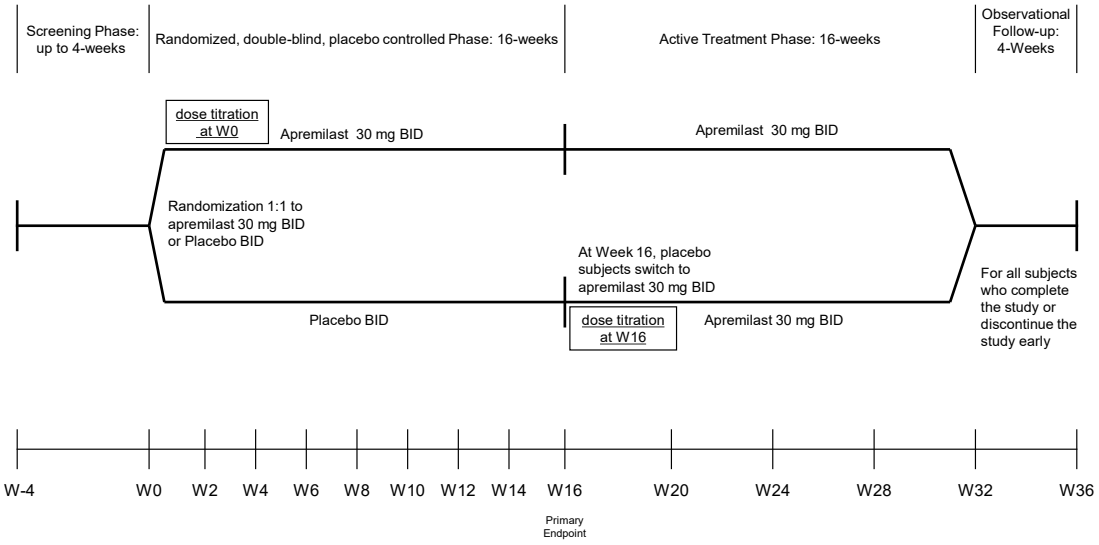
3. OVERALL STUDY DESIGN

3.1. Study Design

CC-10004-PPP-001 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study of apremilast in Japanese subjects with PPP and inadequate response to treatment with topical steroid and/or topical vitamin D3 derivative preparations.

The study design is shown in Figure 1.

Figure 1: Overall Study Design



The study includes 4 phases:

1. Screening phase for up to 4 weeks (28 days)
2. Sixteen weeks, double-blind, placebo-controlled phase (apremilast 30 mg BID and Placebo)
   a. Subjects randomized to the apremilast 30 mg BID treatment group will receive apremilast 30 mg tablets orally twice daily for the first 16 weeks
   b. Subjects randomized to the placebo treatment group will receive placebo tablets (identical in appearance to apremilast 30 mg tablets) orally twice daily for the first 16 weeks
3. Sixteen weeks, active treatment phase (apremilast 30 mg BID)
   a. Subjects randomized to the apremilast 30 mg BID treatment group will continue to receive apremilast 30 mg tablets orally twice daily for the second 16 weeks
   b. Subjects randomized to the placebo treatment group will switch to apremilast treatment in a blind manner orally twice daily for the second 16 weeks
4. Four weeks post-treatment observational follow-up phase at any time the subject completes or discontinues the trial

Subjects who meet eligibility criteria for the study will be randomized in a 1:1 ratio to one of the two treatment groups. Subject randomization for treatment assignments will be stratified according to a subject's rounded PPPASI score (≤20 / 21-30 / ≥31) at randomization, and whether a subject has any focal infection at randomization (yes/no).

Approximately 86 subjects who meet eligibility criteria for the study at Baseline visit (Week 0) will initiate IP treatments. To mitigate potential gastrointestinal (GI) side effects (primarily mild to moderate nausea and diarrhea), dose titration (using blister cards) will be implemented over a 5-day period starting at the Baseline Visit (Week 0) for subjects randomized to apremilast 30 mg BID or Placebo. Subjects randomized to placebo will receive blister cards with dummy dose titration.

The blind should be maintained for persons responsible for the ongoing conduct of the study until the final database lock at the conclusion of the study with some exceptions mentioned below. Blinded persons may include but are not limited to: Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, Clinical Research Associates.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed, and the primary data analysis will be conducted. However, unblinded data will only be made available to selected Sponsor and contract research organization (CRO) team members involved with analysis of the data. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

All subjects will be switched to (or continue with) apremilast 30 mg BID at Week 16 and will maintain this dosing through Week 32.

Observational Follow-up evaluation will be performed 4 weeks after last dose of IP. Subjects who discontinue treatment with IP or withdraw during the Treatment Phase will be also asked to enter the 4-week Observational Follow-up Phase after Early Termination assessment.

An interim Analysis is not planned. An independent committee (eg, steering committee, data monitoring committee, safety monitoring committee) is also not planned. At the end of the study, after all subjects have completed, or have been discontinued from the active treatment phase (Weeks 16 to 32) and the post-treatment observational follow-up phase, the final analysis will be performed, and a final clinical study report will be generated.

The efficacy, safety, and pharmacodynamic assessments to be performed during the study are outlined in the Schedule of Assessments (Table 5). [redacted] are an optional measurement for a subset of subjects who agree to additional informed consent (IC) at limited clinical study sites.

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

3.2. Study Duration for Subjects

This study consists of 4 phases: screening period of up to 4 weeks, 16 weeks for double blind, placebo-controlled phase, 16 weeks for active treatment phase and 4 weeks for follow-up. Total study duration per subject is approximately 40 weeks maximum.

3.3. End of Trial

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

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 86 Japanese subjects with PPP will be randomized to the apremilast 30 mg BID group or the placebo group in a 1:1 ratio (43 subjects, respectively).

4.2. Inclusion Criteria

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

1. Subject is ≥ 20 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has a diagnosis of PPP with or without PAO (not requiring treatment by immunosuppressant) for at least 24 weeks before screening, regardless of presence or absence of concurrent extra-palmoplantar lesions.

   The diagnosis criteria are as follows:

   a. Sterile pustules located on palms and/or soles,
   b. Change from blister to pustule via pustulo-vesicles with progression of disease, and
   c. Repeat recurrence at the same skin lesion and shows the chronic course profile
5. Subject has a total score of PPPASI: ≥ 12 at screening and baseline.
6. Subject has moderate or severe pustules/vesicles on palms or soles (PPPASI severity score: ≥ 2) at screening and baseline.
7. Subject has inadequate response to treatment with topical steroid and/or topical vitamin D3 derivative preparations prior to or at screening. Inadequate response to the treatment is defined as “repeated relapsing-remitting in the same lesion is observed in 6 months treatment period ".
8. Subject meets the following laboratory criteria at screening:
   a. White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L) and ≤ 14,000/mm^3 (≤ 14 x 10^9/L)
   b. Platelet count ≥ 100,000/μL (≥ 100 x 10^9/L)
   c. Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
   d. 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).
   e. Total bilirubin ≤ 2.0 mg/dL
   f. Hemoglobin > 9 g/dL
9. Subject agrees not to change his/her lifestyle habits (eg, exercise, diet, smoking) extremely.

10. Subject is in good health as judged by the Investigator, based on medical history, physical examination, clinical laboratory evaluation.
11. A female of childbearing potential[§](FCBP) must have a negative pregnancy test at Screening and Baseline. While on IP and for at least 28 days after taking the last dose of IP, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive[†]options described below:
    - Option 1[‡]: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

      OR
    - Option 2: Male or female condom PLUS, one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

4.3. Exclusion Criteria

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

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject has a diagnosis of plaque-type psoriasis.
5. Subject has the presence of pustular psoriasis in any part of the body other than the palms and soles (excluding derived from PPP).
6. Subject has obvious improvement during screening (≥ 5 PPPASI total score improvement during the screening).
7. Subject has received any procedures for focal infection (eg, tonsillectomy and dental therapy) within 24 weeks of baseline.
    a. Example of dental therapy: treatment for periodontitis includes 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).

[§] A FCBP is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).
[†] The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (ex, hormonal contraception should be initiated at least 28 days before randomization).
[‡] Hormonal contraception (injection, implant, transdermal patch) are not approved in Japan.

8. Subject has periodontitis obviously requiring treatment at screening.
    a. Treatment for periodontitis includes 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).
9. Subject has chronic or recurrent tonsillitis or sinusitis requiring any continuous treatment for a month or more at screening.
    a. 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.
10. Subject has evidence of skin conditions of hands and feet that would interfere with evaluations of the effect of study medication.
11. Subject with current or planned concurrent use of the following therapies that may have a possible effect on PPP during the course of the study:
    a. Topical therapy within 2 weeks prior to randomization, including, but not limited to, topical corticosteroids, topical retinoid or vitamin D3 analogue preparations, tacrolimus, antihistamine, antibiotics or traditional Chinese/Japanese herbal preparations.
        – Exceptions: An unmedicated skin moisturizer will be permitted as needed. Subjects should not use this treatment within 24 hours prior to clinic visit.
    b. Conventional systemic therapy within 4 weeks prior to randomization, including, but not limited to, corticosteroids, retinoids, antihistamine, antibiotics, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, dimethyl fumarate, biotin, colchicine or traditional Chinese/Japanese herbal preparations.
        – As for retinoids (etretinate), has received within 2 years prior to baseline for FCBP, 6 months prior to the baseline for males, and 4 weeks prior to baseline for non-FCBP.
    c. Granulocyte and monocyte adsorption apheresis (GMA) within 2 weeks prior to randomization.
    d. Phototherapy treatment within 4 weeks prior to randomization (ie, UVB, psoralen and ultraviolet A [PUVA]).
    e. Biologic therapy
        – TNFα or IL17 blockers such as adalimumab, brodalumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab (or biosimilars for each) within 12 weeks or 5 times of half-lives, whichever is longer duration, prior to randomization.

- Anti-IL12 or anti-IL23 monoclonal antibodies such as guselkumab, ustekinumab or tildrakizumab* and other biologics within 24 weeks or 5 times of half-lives, whichever is the longer duration, prior to randomization.

12. Subject with current or planned concurrent use of the following therapies for PAO:
    - Systemic therapy within 4 weeks prior to randomization, including, but not limited to, bisphosphonates, immunosuppressants [eg, MTX, azathioprine, cyclosporine or 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus]) and other biologics (eg, anti-IL1 antibody).

      Background stable doses of NSAIDs for treatment of PAO are permitted.
13. Subject has received prolonged sun exposure or used tanning booths or other ultraviolet light sources within 4 weeks of baseline.
    - Subjects who cannot agree to avoid prolonged sun exposure or use tanning booths or other ultraviolet light sources during the study are also excluded.
14. Subject has used strong cytochrome P450 3A4 (CYP3A4) enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) within 2 weeks or 5 times of half-lives, whichever is the longer duration, prior to randomization.
15. Subject had prior treatment with apremilast.
16. Subject has bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of signing the ICF. Any treatment for such infections must have been completed at least 4 weeks prior to randomization.
17. Subject is positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B) at screening.
    a. If negative for HBsAg and positive for anti-hepatitis B core antibody (HBcAb), hepatitis B virus deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests acute hepatitis B.
18. Subject is positive for Hepatitis C virus antibody (HCVAb) at screening:
    a. If pogative for HCVAb, hepatitis C virus ribonucleic acid (RNA) by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C.
19. Subject has active tuberculosis (TB) or a history of incompletely treated TB.
20. Subject has a prior medical history of suicide attempt at any time in the subject's lifetime prior to signing the informed consent or randomization, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent.
21. Subject has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 12 weeks or a cardiac hospitalization within the last 12 weeks before screening.
22. Subject has malignancy or history of malignancy, except for:
    a. Treated (ie, cured) basal cell or squamous cell in situ skin carcinomas.

* Not approved in Japan.

b. Treated (ie, cured) cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence within 5 years of screening.

23. Subject has a history of positive human immunodeficiency virus (HIV), or has congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
24. Subject has scheduled surgery or other interventions that would interrupt the subject's participation in the study.
25. Subject is pregnant or breastfeeding.
26. Subject has received investigational drug within 4 weeks prior to the randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever was longer).
27. Subject has a history of allergy to any component of the apremilast.
28. Subject has active substance abuse or has a history of substance abuse within 6 months prior to signing the informed consent.

5. TABLE OF EVENTS

Table 5: Schedule of Events

	Screening	Double-blind, placebo-controlled phase									Active treatment phase				Observational follow-up [a]
Visit Number	**1**	**2 [b] (Baseline)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/ET**	**15**
Week	**-4 to 0**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**4 Weeks after last dose**
Day	**-28 to 0**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**	**-**
Allowance (days)	**-**	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**	**±4**	**±4**	**±4**	**±7**
STUDY ENTRY AND GENERAL 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	-	X	-	X	-	X	X	X	X	X	-
Prior / concomitant medications and procedures [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY AND LABORATORY ASSESSMENTS															
AEs/SAEs	X	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	X
Pregnancy test for FCBP[j] and Contraception education for FCBP [j]	X	X	-	-	-	-	-	-	-	X	-	-	-	X	-
Vital signs [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height [j]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 5: Schedule of Events (Continued)

	Screening	Double-blind, placebo-controlled phase									Active treatment phase				Observational follow-up [a]
Visit Number	**1**	**2 [b] (Baseline)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/ET**	**15**
Week	**-4 to 0**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**4 weeks after last dose**
Day	**-28 to 0**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**	**-**
Allowance (days)	**-**	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**	**±4**	**±4**	**±4**	**±7**
Weight [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination [j]	X	-	-	-	-	-	-	-	-	X	-	-	-	X	-
Limited physical examination [k]	-	X	X	X	X	X	X	X	X	-	X	X	X	-	X
Hepatitis B and C [l]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical laboratory evaluations (Hematology/Chemistry) [m]	X	X	-	-	-	X	-	-	-	X	-	X	-	X	X
Clinical laboratory evaluations (Immunology/Inflammation) [m]	-	X	-	-	-	X	-	-	-	X	-	X	-	X	X
Clinical laboratory evaluations (Urinalysis) [m]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EFFICACY ASSESSMENT(S)															
PPPASI [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Modified PPPASI [o]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPSI [p]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA for palms and soles [q]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SUBJECT REPORTED OUTCOMES / QUALITY OF LIFE															
Subject's assessment for PPP signs/findings (using PPSI scale) [r]	-	X	X	X	X	X	X	X	X	X	-	X	-	X	X
Subject's VAS assessment for PPP symptoms for hands and feet [s]	-	X	X	X	X	X	-	X	-	X	-	X	-	X	X
DLQI [t]	-	X	-	-	-	X	-	-	-	X	-	X	-	X	-
EQ-5D [t]	-	X	-	-	-	X	-	-	-	X	-	X	-	X	-

Table 5: Schedule of Events (Continued)

	Screening	Double-blind, placebo-controlled phase									Active treatment phase				Observational follow-up [a]
Visit Number	**1**	**2 [b] (Baseline)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/ET**	**15**
Week	**-4 to 0**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**4 weeks after last dose**
Day	**-28 to 0**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**	**-**
Allowance (days)	**-**	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**	**±4**	**±4**	**±4**	**±7**
[redacted]															
INVESTIGATIONAL PRODUCTS (IP)															
Randomization (IRT)	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Dispense IP	-	X	-	X	-	X	-	X	-	X	X	X	X	-	-
Return and count IP tablets (IP accountability)	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-

Abbreviation: AE = Adverse event; DLQI = The Dermatology Life Quality Index; EQ-5D = Euro QOL 5 Dimension; ET = Early Termination; FCBP = Females of childbearing potential; IP = Investigational Product; IRT = Interactive Response Technology; PAO = Pustulotic arthro-osteitis; PGA = Physician's Global Assessment; PPP = Palmoplantar pustulosis; PPPASI = Palmo-Plantar Pustulosis Area and Severity Index; PPSI = Palmo-Plantar Severity Index; QOL = Quality of Life; RNA = Ribonucleic Acid; VAS = Visual Analogue Scale.

[a] Subjects who discontinue treatment with IP or withdraw during the treatment phase will be also asked to enter the 4-week observational follow-up phase after ET assessment.
[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 must be taken and must include a query about whether a subject has known active current or history of recurrent infections.
[e] Disease history will capture the following information: specific information regarding diagnosis, presence or absence of focal infection, ie, periapical pathosis, periodontitis, angina and sinusitis, Presence or absence of regular dental examination and presence or absence of PAO.
[f] Dental examination must be conducted by a dentist at Screening and obtain data if there is any dental focal infection (eg, chronic periapical periodontitis, chronic marginal periodontitis) or not, and 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 focal infection is preferred to study enrolment.
[g] Including smoking history (years/amount) and current status (yes/no and average packs/day).
[h] Inadequate response to PPP by the treatment with topical steroid and/or topical vitamin D3 derivative preparations should be confirmed.
[i] At any time when suicidal thoughts or a suicide attempt is identified, evaluate the need for referral to a psychiatrist and other actions, including discontinuation, as required in Section 6.5.2.
[j] See Section 6.5.
[k] A limited physical exam may be performed to evaluate an AE, or for any reason, at the discretion of the Investigator.

[l] See Section 6.5.6
[m] Each panel of clinical laboratory evaluations is described in Section 6.5.10. Unscheduled clinical laboratory e valuation is acceptable (eg, to follow AEs)
[n] See Appendix B.
[o] SeeAppendix F.
[p] See Appendix C.
[q] See Appendix D.
[r] Worst status between the visit in which an assessment is scheduled and the previous visit should be recorded. Indicated assessments should be performed before any tests, procedures, or other consultations (PPPASI, modified PPPASI, PPSI, and PGA for palms and soles) for that visit. See Appendix G.
[s] Worst status between the visit in which an assessment is scheduled and the previous visit should be recorded. PPP-related symptoms should be included in these assessments. Indicated assessments should be performed before any tests, procedures, or other consultations (PPPASI, modified PPPASI, PPSI, and PGA for palms and soles) for that visit. See Appendix E.
[t] Indicated assessments should be performed before any tests, procedures, or other consultations (PPPASI, modified PPPASI, PPSI, and PGA for palms and soles) for that visit. See Appendix H, Appendix I, respectively.

6. PROCEDURES

The study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use/GCP and applicable regulatory requirements. The following administrative/demographic procedures will be conducted as outlined in the Table of Events (Table 5). Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Any questions regarding the protocol should be directed to the Amgen Medical Monitor or designee.

Informed Consent

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

Inclusion / Exclusion Criteria (Eligibility Criteria)

Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study (eg, if a female subject does not require pregnancy testing and birth control because of a hysterectomy, the date of the hysterectomy must be included in the medical history).

Medical and Disease History

Relevant medical history should be recorded, including smoking and alcohol history, as well as previous relevant surgeries (please refer to the electronic Case Report Form (eCRF) Completion Guidelines for further details). Disease history includes history of PPP and PAO.

Prior/Concomitant Medications and Therapies

All medications and therapies being taken/used by the subject at the time of consent or at any time during the study should be recorded. Other key medications and therapies, such as previous treatment for TB or relevant diseases, should be recorded. Please refer to the eCRF Completion Guidelines for additional instructions.

All medications and therapies for PPP used within the last 5 years prior to the randomization, including topicals, systemics, and all other therapies, should be recorded. The stop dates for all medications and therapies prohibited in the study should be recorded. Responses to prior PPP therapies should also be recorded. Please refer to the eCRF Completion Guidelines for additional instructions.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of Baseline (Visit 2) unless noted otherwise below.

Safety laboratory analyses will be performed by the central laboratory. Screening laboratory values must demonstrate subject eligibility, but exclusionary results may be re-tested one time

within the screening window, without AmgenMedical Monitor approval. Subjects who fail initial screening may re-screen one additional time for the study.

The following assessments will be performed at screening as specified in the Table of Events (Table 5), after informed consent has been obtained:

- Demographics (year of birth, sex, race, and ethnicity-if allowed by local regulations)
- Complete medical history (all relevant medical conditions diagnosed/ occurring prior to screening should also be included)
- Disease history (including specific information regarding diagnosis, date of diagnosis, negation of plaque-type psoriasis, and of presence of pustular psoriasis in any part of the body other than the palms and soles).

  The following information is also included:

  – Presence or absence of focal infection, ie, periapical pathosis, periodontitis, Angina and Sinusitis

  – Smoking History (years/amount) and Current Status (Yes/No and average packs/day)

  – Presence or absence of regular dental examination (eg, annually at least)

  – Presence or absence of PAO
- Dental Examination and Evaluation of necessity of treatment for focal infection

  – To conduct medical examination by dentist at Screening and obtain data if there is any dental focal infection (eg, chronic periapical periodontitis, chronic marginal periodontitis) or not,

  – 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 focal infection is preferred to enrolment in the study.
- Prior/Concomitant Medications and Procedures

  – Inadequate response to PPP by treatment with topical steroid and/or topical vitamin D3 derivative preparations should be confirmed.

  – Prior and concomitant medications/procedures except for PPP and focal infection should be recorded including all procedures occurring ≤ 28 days prior to the baseline.

  – History of treatment for focal infection should be recorded within 24 weeks prior to the baseline.

  – All medications and therapies for PPP used within the last 5 years prior to the randomization, including topicals, systemics and all other therapies, should be recorded.

- AE/SAE assessment (begins when the subject signs the informed consent form)
- Psychiatric evaluation
- Serum Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG pregnancy test will be performed).
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.
- Hepatitis B and C
- Vital signs
- Height and Weight
- Complete physical examination
- Clinical laboratory evaluations
  - Hematology/Chemistry
  - Urinalysis
- PPPASI (see Section 6.4.1)
  - If obvious improvement during screening (≥ 5 PPPASI total score improvement) is observed at randomization, the initiation of study treatment is not permitted.
  - Efficacy assessments may be performed by the qualified physician who has completed the training for efficacy evaluation.
- Examination for other Inclusion / Exclusion Criteria

Randomization is performed via Interactive Response Technology (IRT).

6.2. Treatment Period (Placebo-controlled phase and Active treatment phase)

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 28 days of signing the informed consent form (ICF). For subsequent visits, an administrative window of ± 2 days until Visit 10 (Week 16) and ± 4 days for Visit 11 to 14 (Week 20 to 32) are permitted respectively. If screening assessments are performed within 72 hours of Baseline Visit, physical examinations and clinical laboratory evaluations, except for Immunology and Inflammation, need not be repeated at Baseline.

Treatment will occur as described in Section 7.3.

During the treatment period:

- Subjects must complete all SROs prior to any other study procedure being performed.
- Subjects should complete the questionnaires in the following order when applicable: 1) Subject's VAS assessment for PPP symptoms for hands and feet, 2) Subject's assessment for PPP signs/findings, 3) DLQI, 4) EQ-5D.

- Efficacy assessments may be performed by the qualified physician who has completed the training for efficacy evaluation at any time during a study visit, but only after the subject has completed all SROs assessments, when required.
- The physician performing efficacy assessments shall make independent observations at a given study visit and shall not review previous assessments or subject-derived data in advance of conducting the assessments.

The following evaluations/assessments will be performed at the frequency specified in the Table of Events (Table 5).

- Status of smoking
- Concomitant medications and procedures evaluation
- AE/SAE evaluation (continuously)
- Psychiatric evaluation
- Pregnancy test for FCBP
  - Urine dipstick pregnancy test will be performed at Baseline (within 72 hours prior to the first administration of IP)and Visit 10 (Week 16). An unscheduled urine pregnancy test should be conducted administered if the subject has missed a menstrual period. See Section 6.5.3.
- Contraception education for FCBP
- Vital signs
- Weight
- Complete or limited physical examination
- Clinical laboratory evaluations
  - Hematology/Chemistry
  - Immunology/Inflammation
- Efficacy assessment (see Section 6.4)
  - PPPASI, PPSI, PGA and modified PPPASI
- Subject reported outcomes or quality of life questionnaires (see Section 6.7)
  - Subject's VAS assessment for PPP symptom, Subject's assessment for PPP signs/findings,
  - DLQI, EQ-5D

[redacted]

[redacted]

6.2.1. End of Treatment

An end of treatment (EOT) evaluation will be performed on Visit 14 (Week 32) or for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

For Visit 15 (4 Weeks After Last Dose), an administrative window of ± 7 days is permitted.

The following evaluations will be performed as specified in the Table of Events (Table 5):

- Status of smoking
- Concomitant medications and procedures evaluation
- AE/SAE evaluation (monitored through 28 days after the last dose of IP)
- Psychiatric evaluation
- Pregnancy test for FCBP
  - Urine dipstick pregnancy test will be performed.
- Vital signs
- Weight
- Complete physical examination (source documented only)
- Clinical laboratory evaluations
  - Hematology/Chemistry
  - Immunology/Inflammation
- Efficacy assessment (see Section 6.4)
  - PPPASI, PPSI, PGA and modified PPPASI
- Subject reported outcomes or quality of life questionnaires (see Section 6.7)
  - Subject's VAS assessment for PPP symptom, Subject's assessment for PPP signs/findings,
  - DLQI, EQ-5D

[redacted]

6.3. Follow-up Period

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as any serious adverse events (SAEs) made known to the Investigator at any time thereafter, as described in Section 10.1.

6.3.1. Observational Follow-up Visit

Observational Follow-up evaluation will be performed on 28 days after last dose of IP. An administrative window of ± 7 days is permitted.

During the observational follow-up period;

- Subjects must complete all SROs prior to any other study procedure being performed.
- Efficacy assessments may be performed by the qualified physician who has completed the training for efficacy evaluation, but only after the subject has completed all SROs assessments.
- The physician performing efficacy assessments shall make independent observations at a given study visit and shall not review previous assessments in advance of conducting the assessments.

The following evaluations will be performed as specified in the Table of Events (Table 5):

- Concomitant medications and procedures evaluation
- AE/SAE evaluation (monitored through 28 days after the last dose of IP)
- Psychiatric evaluation
- Vital signs
- Weight
- Limited physical examination
- Clinical laboratory evaluations
  - Hematology/Chemistry
  - Immunology/Inflammation
- Efficacy assessment (see Section 6.4)
  - PPPASI, PPSI, PGA and modified PPPASI
- Subject reported outcomes (see Section 6.7)
  - Subject's VAS assessment for PPP symptom, Subject's assessment for PPP signs/findings

6.4. Efficacy Assessment

6.4.1. PPPASI

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

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

6.4.2. PPSI

PPSI is a disease-specific efficacy assessment tools by Investigators. See Appendix C. 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 screening.

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

6.4.3. PGA for Palms and Soles

PGA for palms and soles is a Physician's Global Assessment localized to palms and soles, which is skin lesions of PPP. Physician's Global Assessment is commonly used for assessment of the intervention. See Appendix D.

PGA for palms and soles also produces numeric score that can range from 0 to 5. A higher score indicates more severe disease.

6.4.4. Modified PPPASI

Modified PPPASI is an exploratory disease-specific efficacy assessment by Investigators, which emphasizes on pustules and vesicles. The right/left palm and right/left sole are evaluated for 4 signs of the disease (erythema, pustules, vesicle and desquamation/scale) as sub-scores. The development of vesicles followed by pustule in palm and sole is distinctive pathophysiology in PPP. See Appendix F.

The range of modified PPPASI score is from 0 to 96. A higher score indicates more severe disease.

6.5. Safety Assessment

6.5.1. Adverse Events

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

6.5.2. Psychiatric Evaluation

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

If a subject suffers from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue the subject participation to the study (see Section 11). At any time when suicidal thoughts or a suicide attempt is identified, evaluate the need for referral to a psychiatrist and other actions, including discontinuation. The result of psychiatric evaluation should be recorded in eCRF.

6.5.3. Serum and Urine Pregnancy Tests for Females of Childbearing Potential (FCBP)

A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP subjects at screening. In addition, a urine pregnancy test will be performed at the site on all FCBP subjects at the Baseline Visit, Visit 10 (Week 16) and Last Treatment Visit (Visit 14 [Week 32]). An unscheduled urine pregnancy test should be performed if the FCBP subject has missed a menstrual period. If positive results are obtained from a urine pregnancy test, a serum pregnancy test should be performed to confirm, and if positive results are obtained from a serum pregnancy test, IP should be discontinued. The event must be reported (See Section 10.4.1).

6.5.4. Contraception Education

The risks to a fetus or to a nursing child from apremilast are not known at this time. Results of animal and in vitro studies can be found in the Investigator's Brochure.

All FCBPs must use one of the approved contraceptive options as described in Section 4.2 while on IP and for at least 28 days after administration of the last dose of the IP. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (ex, hormonal contraception should be initiated at least 28 days before randomization).

At screening and at baseline, and at any time during the study when a FCBP's contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding contraception options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

6.5.5. Severe Diarrhea, Nausea and Vomiting

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

6.5.6. Hepatitis B and C

Hepatitis testing will include HBsAg, HBcAb and HCVAb.

6.5.7. Vital Signs, Height, and Weight

Vital signs, including pulse, temperature, and seated blood pressure, will be taken during the visits indicated in the Table of Events (Table 5). Weight will be measured and recorded at the Screening Visit and then as indicated in the Table of Events (Table 5); body mass index (BMI) will be calculated programmatically based on the height measured and recorded at Screening. In the event of unexplained and clinically significant weight loss, the subjects should be evaluated by the Investigator and discontinuation of treatment should be considered.

6.5.8. Complete Physical Examination

A complete physical examination includes evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems. The complete physical examination is done at screening, at Visit 10 (Week 16) and at Visit 14 (Week 32) or at Early Termination.

6.5.9. Limited Physical Examination

A limited physical exam may be performed to evaluate an AE, or for any reason, at the discretion of the Investigator.

6.5.10. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory and as indicated in Table 5.

Clinical laboratory hematology panel includes complete blood count (CBC) (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count [absolute and differential], and platelet count).

Clinical laboratory chemistry panel includes sodium, potassium, calcium, chloride, phosphorous, blood urea nitrogen (BUN), creatinine, glucose, hemoglobin A1c (HbA1c), albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase (ALT/SGPT), uric acid, lactate dehydrogenase (LDH), magnesium, total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], LDL to HDL ratio, total cholesterol to HDL ratio, triglycerides. Fasting is not required. However, if significant elevation of serum lipid(s) is observed, a fasting retest should be requested to determine whether or not the elevation was caused by food.

Clinical laboratory immunology/inflammation panel includes fibrinogen, high sensitivity C-reactive protein (hs-CRP), MMP-3, quantitative assessment of serum immunoglobulins (IgA, immunoglobulin M [IgM], and immunoglobulin G [IgG]) will also be assessed at selected visits.

Dipstick urinalysis includes specific gravity, pH, glucose, protein, blood, ketones, bilirubin, leukocyte esterase, nitrite, and urobilinogen) will be performed by the central laboratory; microscopic urinalysis (epithelial cells, casts, RBCs, and WBCs) will be performed in the event of a positive dipstick result.

6.7. Subject Reported Outcomes

These assessments should be performed before any tests, procedures, or other consultations at the visit.

6.7.1. Subject's VAS Assessment for PPP Symptom

VAS is a tool used to help a person rate the intensity of certain sensations and feelings, such as pain. Each score ranges from 0 to 100.

Subject assesses a degree of pruritus and pain as symptoms on hands and feet caused by PPP. See Appendix E. Worst status by a subject's impression between visits will be recorded. PPP-related symptoms should be included in these assessments.

6.7.2. Subject's Assessment for PPP Signs/Findings

A part of PPSI assessment is used as a questionnaire. Skin lesion for the evaluation is the same as a palm or sole identified by Investigator for evaluation of PPSI at screening. This means the evaluated skin lesion site is the same with PPSI evaluation. Three signs of the disease (erythema, pustules/vesicle and desquamation/scale) are assessed by the subject him/herself, similar to PPSI. A numeric score is produced for each sign/finding of PPP and the range is from 0 to 4 and the total score will be 0 to 12.

A subject's assessment for each sign/finding on hands or feet (erythema, pustules/vesicles and desquamation/scale) are an exploratory disease-specific efficacy assessment. See Appendix G. Worst status by a subject's own assessment between visits will be recorded.

6.7.3. Quality of Life/ Treatment Satisfaction

These assessments should be performed before any tests, procedures, or other consultations at the visit.

6.7.3.1. DLQI

DLQI is a skin disease-specific Quality of Life (QoL) questionnaire consisting of 10 items which assess the subject status over the last one week. See Appendix H.

DLQI can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI produces a numeric score that can range from 0 to 30. A higher score indicates more severe disease.

6.7.3.2. EQ-5D

EQ-5D-5L is also a general and comprehensive QoL questionnaires which assesses the subject status on the visit day. See Appendix I.

The EQ-5D is a generic health status measure composed of a descriptive system which comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a VAS asking individuals to rate their own health. A lower utility index and VAS score indicates more severe disease.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

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

Apremilast will be supplied by the Sponsor and labeled appropriately as IP for this study.

All IP will be provided in blister cards throughout the entire study. Apremilast will be provided as 10, 20, or 30 mg tablets. Placebo will be provided as identically appearing 10, 20, or 30 mg tablets. Apremilast, the IP, will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To mitigate potential GI side effects, dose titration will be implemented in the first week of this study (see Table 6).

During Week 0 (Days 1-7), subjects will be dispensed dose titration blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo tablets. The blister cards will contain all IP required for 4 weeks of treatment, with the first 7 days containing the titration supplies or matching placebo (see Table 6 Treatment Schema for Dose Titration at Visit 2 [Week 0] which details the titration supplies from Day 1 to Day 7).

At Visit 2 (Week 0), subjects who meet eligibility criteria will be randomized using a permuted block randomization in parallel 1:1 to receive either apremilast 30 mg BID or placebo, using a centralized IRT. IP will be dispensed as indicated below.

- Weeks 0 to 16: double-blind, placebo-controlled phase: apremilast 30 mg BID or placebo BID.
  - Week 0 to 1: subjects will be dose titrated as described above and detailed in Table 6.
- Weeks 16 to 32: active treatment phase: apremilast 30 mg BID
  - Week 16 to 17: Subjects will be dose titrated as described below and detailed in Table 7

Starting at Week 16, all subjects will receive apremilast. Subjects originally randomized to placebo at Week 0 will be switched to apremilast 30 mg BID at Week 16 and dose titration blister cards will be used. Dummy titration blister cards (dosing at 30 mg BID directly) will be used for subjects originally randomized to apremilast 30 mg BID. At all other visits during the active treatment phase, all subjects will receive apremilast 30 mg tablets which are to be taken twice daily.

During Weeks 16 to 32, the IP will remain blinded, to prevent study personnel and subjects from knowing the IP assignment in the double blind, placebo-controlled Phase (Week 0 to 16) and to maintain the blind regarding the initial treatment assignment, all subjects will receive dose titration cards at Visit 10 (Week 16). Although only subjects initially randomized to placebo will be dose titrated during their first week of the active treatment phase, all subjects entering the active treatment phase will receive identically-appearing titration/treatment cards as shown in Table 7.

Please refer to local apremilast prescribing information for more details on available formulations, preparation, storage conditions, the approved indications, known precautions, warnings, and adverse reactions of apremilast (see current version of Prescribing Information). The apremilast dosing schedule and dose adjustments to be followed for this study are described in Section 7.3.

Additional information may be included on the label as needed or applicable. Label(s) for IP will contain information as required per local health authority.

7.2. Description of Placebo

Placebo tablets will be provided as identically appearing apremilast 10, 20, or 30 mg tablets.

Table 6: Treatment Schema for Dose Titration at Visit 2 (Week 0)

	Week 0											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6 -7 and thereafter	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Apremilast 30 BID	10 mg A 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg P 30 mg A	30 mg A	30 mg A
Placebo	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	30 mg P	30 mg P

A=Apremilast; BID= twice daily; P= Placebo.

Table 7: Treatment Schema for Dose Titration at Visit 10 (Week 16)

	Week 16											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6 -7 and thereafter	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Apremilast 30 BID	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	10 mg P 20 mg P 30 mg A	30 mg A	30 mg A
Placebo	10 mg A 20 mg P 30 mg P	10 mg P 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg A 20 mg P 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg A 30 mg P	10 mg P 20 mg P 30 mg A	30 mg A	30 mg A

A=Apremilast; BID= twice daily; P= Placebo.

7.3. Treatment Administration and Schedule

IP will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To mitigate potential GI side effects, dose titration will be implemented in this study. During Week 0 (Days 1 to 7) and Week 16 (when placebo subjects are switched to receive apremilast 30 mg BID), subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo for the dose titration.

At all other visits where IP is dispensed, apremilast will be provided in blister cards as 10, 20, and 30 mg tablets or identically appearing placebo tablets. The treatment schema for dose titration at baseline (Week 0) and Week 16 is shown in Table 6 and Table 7, respectively.

7.3.1. Dose Modification/Interruptions

Any dose modifications outside of the dose described in Section 7.3 are not permitted in this study.

Dose interruptions are not permitted except for safety reasons. The administration of apremilast can be resumed by Investigator's judgement.

7.4. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP(s) only. Therefore, for a drug to be subject to the overdose definition it must be both required and an investigational drug. In this study the only required and investigational drug is apremilast and the control arm drug (ie, placebo), hence overdose definition will apply to only apremilast (or matching placebo).

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

AEs associated with an overdose must be collected on the AE page of the eCRF for all overdosed subjects, but the overdose itself is not considered an AE. Other required or optional non-IPs intended for prophylaxis of certain side effects, etc., are excluded from this definition.

Detailed information about overdose in this study, regardless of whether the overdose was accidental or intentional, should be reported on the drug exposure eCRF page.

7.5. Method of Treatment Assignment

At Visit 2, subjects who meet eligibility criteria will be randomized using a permuted block randomization in parallel with 1:1 ratio to receive either apremilast 30 mg BID or placebo, using a centralized IRT. Eligible subjects will be stratified according to a subject's rounded PPPASI score (≤20 / 21-30 / ≥31) at randomization, and whether a subject has or not any focal infection at randomization (yes/no). Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which give them authorization to enter the IRT to randomize subjects.

The system will present a menu of questions by which the research center personnel will identify the subject and confirm eligibility. When all questions have been answered, the IRT will assign a randomization identification number.

Confirmation of the randomization will be sent to the investigational site, Amgen, and/or its representative. During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization identification number assigned by the IRT.

7.6. Packaging and Labeling

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

7.7. Investigational Product Accountability and Disposal

7.7.1. Investigational Product Accountability

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study.

The Investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP accountability form. The Investigator(s) or designee(s) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Amgen.

At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

The IP should be stored as directed on the package label.

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

7.7.2. Record of Administration

Accurate recording of all IP administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

7.8. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. IP will be dispensed as indicated in (Table 5). The subjects will be instructed to return the IP blister cards, including any unused IP, to the study site at each visit for pill counts and reconciliation. Subjects will be asked whether they have taken their IP as instructed at each study visit. Any problems with IP compliance will be reviewed with the subject. If a subject misses 4 or more consecutive days of dosing, Amgen should be contacted to

decide whether dosing should resume or whether the subject should be terminated from the Treatment phase of the study and enter into the Observational follow-up phase.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) should be discussed with Amgen. Compliance is defined as taking between 75% and 120% of dispensed IP of the expected doses during a subject's participation while in the treatment phases (double blind, placebo-controlled phase and active treatment phase) of the study. This definition of compliance is only for the purpose of study analysis, not study conduct.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics, or excretion, please see the Investigators Brochure and/or local package insert.

8.1. Permitted Concomitant Medications and Procedures

8.1.1. Double Blind, Placebo-controlled Phase (Week 0 to Week 16)

Subjects may take any medication that is not restricted by the protocol and would not be expected to interfere with the conduct of the study or affect assessments. Chronic medication should be dosed on a stable regimen.

All medications (prescription and nonprescription), treatments and therapies taken by the subject from screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, and the date the medication started and stopped (if not ongoing) must be recorded.

The following therapies will be permitted for the duration of the study.

- Topical Therapy for PPP

  The only allowable concomitant treatments for PPP throughout the study are topical moisturizers (Vaseline). Subjects should not use moisturizers within 24 hours prior to the clinic visit.

- Treatment for focal infection

  Noninvasive dental care (eg, scaling and root planing for periodontal disease) is allowed throughout the study. About one month for treatment for acute tonsillitis or sinusitis is also allowed throughout the study. If tooth abscess and/or tooth cavity is newly recognized after starting the study, the dental therapy for them is permitted.

- Treatment for PAO

  The use of background stable doses of NSAIDs for PAO is allowed.

- Treatment for complication of disease other than PPP

  Every effort should be made to keep subjects on stable concomitant medications.

  Topical use of corticosteroids to body area other than palms and soles, inhaled, otic, ocular, nasal or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

8.1.2. Active Treatment Phase (from Week 16 to 32)

In addition to permitted concomitant medications and procedures (Section 8.1.1), subjects in the active treatment phase will have the option of adding topical therapies (including, but not limited to, topical corticosteroids, topical retinoids or vitamin D3 analogue preparations) and/or

phototherapy (excluding oral PUVA) to their treatment regimen. Dose modification is permitted for background doses of NSAIDs for PAO and concomitant medications for complication of disease other than PPP.

8.2. Prohibited Concomitant Medications and Procedures

8.2.1. Double-blind, Placebo-controlled Phase (Week 0 to Week 16)

The following treatment cannot be employed for the duration of the double-blind, placebo-controlled phase:

- Topical therapy

  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).
  Note: only use of topical antibiotics for the treatment after skin biopsy is permitted.

- Conventional systemic therapy

  Systemic therapies that could affect PPP or the efficacy evaluation (including, but not limited to corticosteroids, retinoids, antihistamine, antibiotics, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, dimethyl fumarate, biotin, colchicine or traditional Chinese/Japanese herbal preparations).

- GMA
- Phototherapy
  - UVB or PUVA
- Biologic therapies:
  - TNFα or IL17 blockers such as 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* (or biosimilars for each)
  - Other biologics that could affect PPP or the efficacy evaluation
- Treatment for focal infection

  Focal infection must be carefully assessed in all subjects, and if treatment for focal infection is obviously required, treatment for the focal infection (examples are shown in Section 4.3) should be completed prior to 24 weeks before baseline.

  Focal infection treatments for PPP below (but not limited to) except for dental therapy (see Section 8.1.1) at any time during the study.
  - Tonsillectomy for tonsillitis

* Not approved in Japan.

  - Endodontic treatment for periapical pathosis
  - Periodontal surgery for moderate to severe periodontitis

- Systemic medications for PAO

  Systemic therapy, including, but not limited to, corticosteroids, bisphosphonates, immunosuppressants [eg, MTX, azathioprine, cyclosporine or 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus]) and other biologics (eg, anti-IL1 antibody).

- Treatment for complication of disease other than PPP
  - Systemic corticosteroids
  - Disease-modifying agents such as MTX, sulfasalazine, or intramuscular (IM) gold are prohibited during the study.
- Use of strong CYP3A4 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort)
  - Coadministration of the strong CYP3A4 enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast.
- Use of any investigational drug or device
- Prolonged sun exposure or use of tanning booths or other ultraviolet light sources are also not permitted.

8.2.2. Active Treatment Phase (from Week 16 to 32)

Use of medications and procedures except for those described in Section 8.1.2 are not permitted.

8.2.3. Observational Follow-up

There is no restriction of concomitant medication during the observational follow-up phase.

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a 16-week placebo-controlled study, followed by a 16-week active treatment phase to evaluate the efficacy of apremilast (CC-10004) in Japanese subjects with PPP.

The primary efficacy endpoint, PPPASI-50 at Week 16 will be assessed and the apremilast 30 mg BID group will be compared to the placebo group.

The primary analysis will be performed when all subjects complete Week 16. Additionally, an analysis will be performed after all subjects complete the active treatment phase of the study (16 weeks of blinded treatment) and follow-up at Week 32 or discontinue early.

A Statistical analysis plan (SAP), which includes detailed list of analyses, will be written based on this protocol.

9.2. Study Population Definitions

The safety population will include all randomized subjects who received at least one dose of IP. The analysis of safety data in this study will be based on the safety population and subjects will be included in the treatment to which they actually received.

The intent-to-treat (ITT) population will be defined as all randomized subjects who received at least one dose of IP. Subjects will be included in the treatment group to which they are randomized.

The per protocol (PP) population will include all subjects in the ITT population who have no protocol deviations that may substantially affect the efficacy results during the 16 weeks placebo-controlled treatment phase. The final determination of protocol deviation criteria to define the PP population will be made prior to the unblinding of the database and will be documented separately.

9.3. Sample Size and Power Considerations

A total of approximately 86 subjects will be randomized 1:1 ratio to receive apremilast 30 mg BID or placebo. The study has 80% power (based on a chi-square test at a 2-sided significance level of 0.10) to demonstrate the superiority of apremilast 30 mg BID over placebo with respect to the primary endpoint of PPPASI-50 at Week 16, assuming the PPPASI-50 rates of 45% (apremilast 30 mg BID) and 20% (placebo), respectively. PPPASI-50 rate of 20% at Week 16 in placebo is based on the placebo rate of 21% at Week 16 in guselkumab Phase 2 study (Terui, 2018). Considering at least 20% difference as a clinically meaningful difference, apremilast 30 mg BID PPPASI rate of 45% is expected in this study. The sample-size was estimated using SAS 9.4 power procedure.

For the skin biopsy RNA expression analysis, N=13 subjects per arm will provide 80% probability to observe the lower limit of the 90% confidence interval (CI) of a decrease of IL8 mRNA expression from baseline to Week 16 in the apremilast treated arm is over -44% , based on the mean and standard deviation (SD) change observed in a 12 weeks apremilast psoriasis study CC-10004-PSOR-004 (Gottlieb, 2013). For the serum protein biomarker analysis, N=17 subjects per arm will provide 80% probability to observe the lower limit of the 90%CI of an

absolute difference from baseline to Week 16 of IL17A levels in the apremilast arm is over 60%, based on the mean and SD change observed in the psoriasis study in Japan, CC-10004-PSOR-011 (Garcet, 2018).

9.4. Background and Demographic Characteristics

Subjects' age, weight, height and other continuous demographics and baseline characteristics will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum), while gender, race, and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

9.5. Subject Disposition

Subjects disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent by phase. A summary of subjects randomized by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

9.6.1. Efficacy Evaluation for the Primary and Secondary Endpoints

All efficacy analyses will be performed using the ITT population. In addition, an analysis using the PP population will be provided for the primary efficacy endpoint. The analyses using the ITT population will be considered as the primary analysis.

9.6.1.1. Primary Efficacy Endpoint - (Weeks 0 - 16)

The primary efficacy endpoint of the proportion of subjects receiving apremilast 30 mg BID or placebo who achieve a PPPASI-50 at Week 16 from baseline will be evaluated.

The primary efficacy endpoint will be analyzed using a chi-square test. The testing will be conducted at the two-sided 0.10 significant level and the two-sided 90% CI for the treatment difference of the PPPASI-50 response rates will be provided. The two-sided 95% CI will also be provided for reference. The primary missing data handling approach for PPPASI-50 responder will be nonresponder imputation (NRI), by which a subject without sufficient data for the response determination will be considered a nonresponder. Sensitivity analysis using the PP population and/or the other missing data handling approach [eg, last observation carried forward (LOCF) method] will be performed and the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors [PPPASI total score range (≤ 20 score, 21-30 score, ≥ 31 score) and focal infection status (Yes, No) at baseline] will be conducted to support the primary analysis.

9.6.1.2. Secondary Efficacy Endpoints - (Weeks 0 - 16)

Descriptive statistics will be presented for all secondary endpoints in Table 2. Specifically, for continuous endpoints, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for baseline, Week 16 and Week 16 change from baseline will be provided. Binary endpoints will be summarized with frequency tabulations.

Treatment comparisons between the apremilast 30 mg BID and placebo will be performed for the secondary endpoints. Continuous efficacy endpoint will be analyzed using the analysis of covariance (ANCOVA) model adjusted for PPPASI total score range (≤ 20 score, 21-30 score, ≥ 31 score) and focal infection status (yes, no) at baseline as factors, and the associated baseline value as covariate, while binary endpoints will be evaluated using the CMH test previously described for the primary endpoint. The primary missing data handling approach for continuous endpoint will be multiple imputation (MI).

Secondary efficacy endpoints will be tested without multiplicity adjustment, therefore the p-value for those endpoints will be regarded as nominal. For secondary efficacy endpoints, the two-sided 95% CI will be provided.

9.6.1.3. Primary and Secondary Endpoints - (Weeks 16 - 32)

The active treatment phase runs from Week 16 to Week 32. Descriptive statistics will be provided. Specifically, for continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for baseline, specified time points and changes from baseline will be provided. Categorical variables will be summarized with frequency tabulations.

9.6.1.4. Subgroup Analysis

Subgroup analyses for comparisons of the proportion of subjects who achieve PPPASI-50 at Week 16 between apremilast 30 mg BID and placebo, based upon baseline demographic, and baseline disease characteristics, will be provided to determine the robustness of the treatment effect.

9.6.2. Efficacy Evaluation for Exploratory Endpoints - (Weeks 0 - 16)

Descriptive statistics will be presented for exploratory endpoints. Specifically, for continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for baseline, specified time points and change from baseline will be provided. Categorical variables will be summarized with frequency tabulations.

The Kaplan-Meier procedure will be used to characterize the time to achieve at least PPPASI-50 and PPPASI-75 during the double-blind placebo-controlled phase (Weeks 0-16).

9.6.3. Efficacy Evaluations for Exploratory Endpoints (Weeks 16 - 32)

The active treatment phase runs from Week 16 to Week 32. Descriptive statistics will be provided. Specifically, for continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for baseline, specified time points and changes from baseline will be provided. Categorical variables will be summarized with frequency tabulations. These data summaries will be presented according to the treatment sequence received, ie, apremilast 30 mg BID/30 mg BID, or placebo/apremilast 30 mg BID.

9.7. Safety Analysis

The safety analyses will be performed using the Safety population. Safety will be assessed by clinical review of all relevant parameters including TEAEs which are defined as any AEs that

begin or worsen on or after the first dose of IP through 28 days after the last dose of IP, laboratory tests, and vital signs; no inferential testing for statistical significance will be performed. Data from safety assessments will be summarized descriptively for the double-blind, placebo-controlled phase (Weeks 0 to 16) and the apremilast exposure period when subjects receive apremilast treatment. For safety analyses in the active treatment phase, baseline will be relative to the first dose date following randomization at Week 0. For safety analyses in apremilast exposure period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the active treatment phase (Weeks 16 to 32).

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. AEs leading to death or to discontinuation from treatment and SAEs will also be summarized and listed separately.

Laboratory data will be summarized descriptively. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges of pretreatment versus posttreatment will be provided. Associated clinical laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Baseline will be produced. To account for the different exposure to the IP, TEAEs or marked laboratory abnormalities will also be summarized using the exposure-adjusted incidence rate, in addition to the simple incidence rates.

Vital sign measurements, including weight, will be summarized descriptively by visit. In addition, shift tables showing the number of subjects with values low, normal, and high based on the specified ranges pre-treatment versus post-treatment will be provided.

The change from baseline for each of the vital signs including weight will be summarized. Incidence of abnormal vital signs parameters will be tabulated.

The detailed safety analyses will be specified in the SAP.

9.8. Interim Analysis

No interim analysis is planned for this study.

9.9. Other Topics

9.9.1. Concomitant Therapy

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

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE/SAE case report form (CRF) rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.4 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an IP should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on the paper SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the paper SAE report form and AE CRF but should not be reported as an SAE itself.

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

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

All AEs (non-serious and serious) will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study. All AEs (serious/ non- serious) will be recorded on the CRF and in the subject's source documents. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event using the paper Serious Adverse Event Report Form (refer to Appendix J) by facsimile/email of the paper SAE Form directly to Amgen Global PatientSafety.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;

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

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

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

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

All SAEs must be reported to Amgen Global Patient Safetywithin 24 hours of the investigator's knowledge of the event using the paper Serious Adverse Event Report Form in English language (refer to Appendix J) by facsimile or email of this form directly to Amgen Global Patient Safety.

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

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event based on the descriptions listed below.

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

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

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

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

10.2.4. Duration

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

10.2.5. Action Taken

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

10.2.6. Outcome

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

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

10.3. Abnormal Laboratory Values

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

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

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

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

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

10.4. Pregnancy

All pregnancies or suspected pregnancies are immediately reportable events.

10.4.1. Females of Childbearing Potential (FCBP) – Collection of Pregnancy Information

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a FCBP regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. If positive results are obtained from a serum pregnancy test, IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Global Patient Safetyimmediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Notification Form, or approved equivalent form in English language. (refer to Appendix K). The Pregnancy Notification Form in English language must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

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

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

The Investigator will follow the female subject until completion of the pregnancy and must notify Amgen Global Patient Safetyimmediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Amgen Global PatientSafety via the paper Serious

Adverse Event Report Form in English language within 24 hours of the Investigator's knowledge of the even.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported to Amgen Global Patient Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the paper SAE Report Form in English language.

Male Subjects With Partners Who Become Pregnant

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

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

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

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

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

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking IP through 28 days post last dose of IP.
- Information will be recorded on the Lactation Notification Form in English language (refer to Appendix L) and submitted by facsimile or email to Amgen Global Patient Safety witin 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study (refer to exclusion criterion # 25).

With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking IP through 28 days after discontinuing IP.

10.5. Reporting of Serious Adverse Events

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

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

Any follow-up datato the existing SAE should be resubmitted to Amgen Global Patient Safety in English language.

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

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

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

10.5.1. Safety Queries

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

10.6. Expedited Reporting of Adverse Events

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

Amgen or its authorized representative shall notify the Investigator of the following information (In Japan, Amgen KK shall notify the Heads of the Institutes in addition to the Investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, suspected unexpected serious adverse reactions [SUSARs]);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Other important safety information and periodic reports according to the local regulations.

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

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

Amgen Global Patient Safety Contact Information:

For Amgen Global Patient Safety contact information, please refer to the Serious Adverse Event Report Form (refer to Appendix J), Pregnancy Notification Form (refer to Appendix K) and/or the Lactation Notification Form (refer to Appendix L).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

- AE
- Lack of efficacy
- Non-compliance with IP
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy (of FCBP)
- Important protocol deviation
- Physician's decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

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

- Screen failure
- AE
- Lack of efficacy
- Non-compliance with IP
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy (of FCBP)
- Important protocol deviation

- Physician's decision
- Study terminated by Sponsor
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the investigator should use their medical judgement to provide appropriate medical care of clinical trial subjects.The Investigator may also contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, the investigator may also contact the Amgen Medical Information number at +1-800-772-6436. The representatives are responsible for obtaining your call-back information and contacting the on-call Amgen/contract research organization Medical Monitor, who will then contact you promptly.

12.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblended dose information.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

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

13.2. Investigator Responsibilities

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

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

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

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

The information contained in the protocol and amendments (with the exception of the information provided by Amgen on public registry websites) is considered Amgen confidential information. Only information that is previously disclosed by Amgen on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Amgen protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Amgen. Information proposed for posting on the Investigator's or their institution's website must be submitted to Amgen for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Amgen will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

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

13.4. Confidentiality

Amgen affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Amgen requires the Investigator to permit Amgen's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Amgen Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

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

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

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

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

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

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

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

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

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

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

13.8. Termination of the Study

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or Compact disc read-only memory (CD-ROM).

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Amgen standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Amgen/Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

15.1. Study Monitoring and Source Data Verification

Amgen ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Amgen representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, IP storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Amgen representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Quality, Compliance & Audit, Learning & Performance unit exists within Amgen. Representatives of this unit will conduct audits of clinical research activities in accordance with Amgen SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Pharmaceuticals and Medical Devices Agency [PMDA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

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

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

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

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

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

Clinical-Complaint-Intake@amgen.com

16. PUBLICATIONS

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

Amgen will ensure Amgen-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 2 and Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

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

Eligibility for external authorship, as well as selection of first authorship, will be in alignment with ICMJE authorship criteria and be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BID	Twice daily
BD	Behcet's disease
BMI	Body Mass Index
BSA	Body surface area
BUN	Blood urea nitrogen
cAMP	Adenosine 3', 5'-cyclic monophosphate
CBC	Complete blood count
CD-ROM	Compact disc read-only memory
CI	Confidence Interval
CIOMS	The Council for International Organizations for Medical Sciences
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CXCL	Chemokine (C-X-C motif) ligand
CYP	Cytochrome P450
DEFB	Defensin beta
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
EC	Ethics Committee
eCRF	Electronic case report form

Table 8: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EDC	Electronic data capture
EOT	End of treatment
EMA	European Medicines Agency
ET	Early Termination
EQ-5D	EuroQol 5 Dimension
EudraCT	European Clinical Trials Database
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMA	Granulocyte and monocyte adsorption apheresis
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBcAb	Anti-hepatitis B core antibody
HCVAb	Anti-hepatitis C virus antibody
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRQoL	Health-related Quality of Life
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IC	Informed consent
ICF	Informed consent form
ICH	International Council for Harmonisation
IFNG	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IM	Intramuscular

Table 8: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
ITT	Intent-to-treat
JAK	Janus kinase
KOH	Potassium hydroxide
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
modified PPPASI-50	Defined as ≥50% improvement of modified PPPASI total score from baseline.
modified PPPASI-75	Defined as ≥75% improvement of modified PPPASI total score from baseline.
MRI	Magnetic resonance imaging
mRNA	messenger RNA
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
NK	Natural killer
NRI	Nonresponder imputation
PAO	Pustulotic arthro-osteitis
PCR	Polymerase chain reaction
PDE4	Phosphodiesterase 4
PGA	Physician's Global Assessment
PIN	Personal identification number
PMDA	Pharmaceuticals and Medical Devices Agency
po	orally
PP	Per protocol
PPP	Palmoplantar pustulosis

Table 8: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PPPASI	Palmo-Plantar Pustulosis Area and Severity Index
PPPASI-50	Defined as ≥ 50% improvement in PPPASI total score from baseline.
PPPASI-75	Defined as ≥ 75% improvement in PPPASI total score from baseline.
PPSI	Palmo-Plantar Severity Index
PC	Product Complaint
QoL	Quality of Life
PsA	Psoriatic arthritis
PT	Preferred term
PUVA	Psoralen and ultraviolet A
RBC	Red blood cell count
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAPHO	Synovitis, acne, pustulosis, hyperostosis and osteitis
sc	subcutaneous
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SOP	Standard operating procedure
SRO	Subject's Reported Outcome
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th	T helper
TNF	Tumor necrosis factor
ULN	Upper limit of normal
UV	Ultraviolet
UVB	Ultraviolet B
VAS	Visual Analogue Scale

Table 8: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
WBC	White blood cell count
WHO	World Health Organization

APPENDIX B. PPPASI (PALMO-PLANTAR PUSTULOSIS AREA AND SEVERITY INDEX)

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)

Where E = erythema, P = pustular/vesicle and D = desquamation/scale

References: Bhushan, 2001.

APPENDIX C. PALMO-PLANTAR 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 screening. 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 = pustular/vesicle and D = desquamation/scale

The total score ranges from 0 to 12

Modified from: Terui, 2018.

APPENDIX D. PHYSICIAN'S GLOBAL ASSESSMENT (PGA) FOR PALMS AND SOLES

The PGA for palms and soles is used to determine the subject's palmoplantar pustulosis lesions (palms and soles) at a given time point.

<PGA for palms and soles >

Lesions on palms and soles will be graded based on the scales below.

0 = Clear

1 = Almost clear

2 = Mild

3 = Moderate

4 = Severe

5 = Very severe

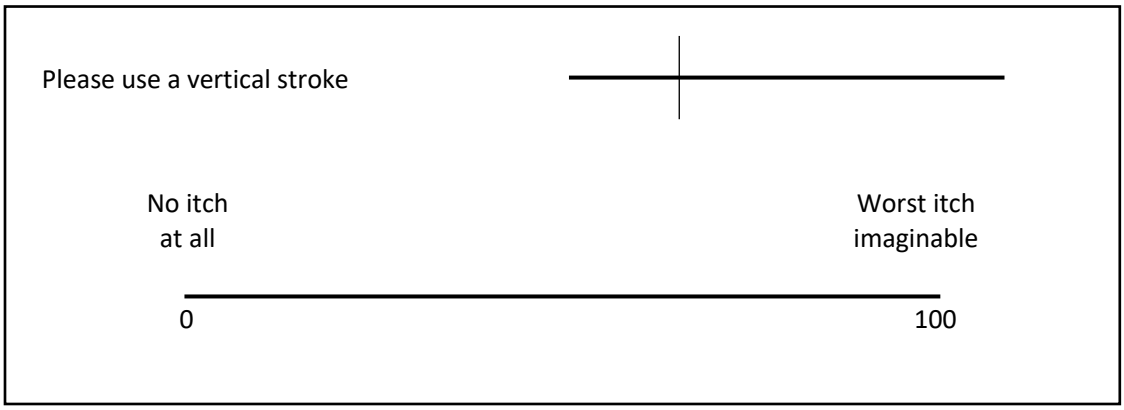
The total score ranges from 0 to 5

Modified from: Farhi, 2008; Terui, 2018.

APPENDIX E. VISUAL ANALOGUE SCALES (VAS) - PPP SYMPTOMS FOR HANDS AND FEET

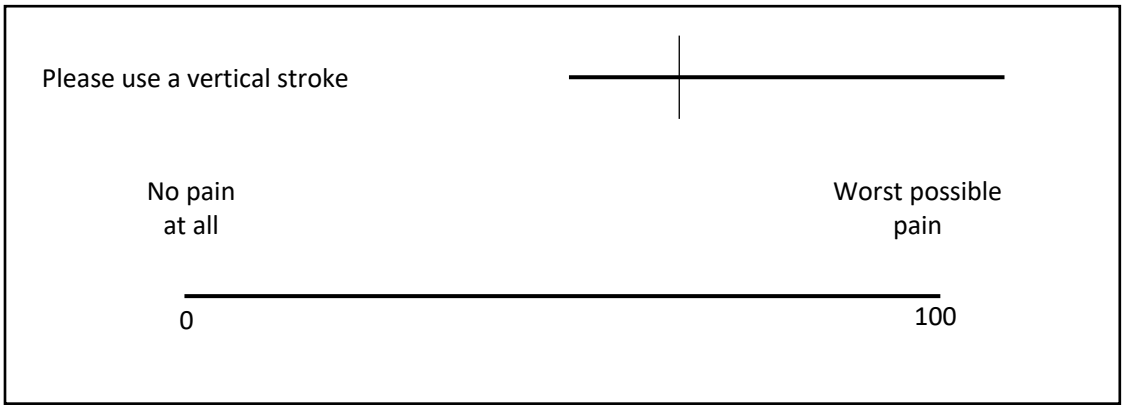
Subject's assessment for Pruritus of hands and feet

At its worst, how much itch (on hands and feet) have you had because of your condition during the last visit and this visit?



Subject's assessment for Pain of hands and feet

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



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

Reference: Sobell, 2016.

APPENDIX F. MODIFIED PPPASI

Based on characteristics that the development of vesicles followed by pustules on the palms and soles is distinctive pathophysiology in PPP, emphasizing vesicles and pustules on the palms and soles can be expected as a more sensitive assessment of PPP symptoms and that such a modification is considered to have a possibility to become a more appropriate assessment tool of PPP. Therefore, modified PPPASI is assessed as an exploratory investigation of a more appropriate endpoint for PPP.

The modified PPPASI is an exploratory system used for assessing and grading the severity and area of palmoplantar pustulosis lesions and their response to therapy. The modified PPPASI produces a numeric score that can range from 0 to 96. The severity of the disease is calculated as follows.

In the modified PPPASI system, the palms and soles are divided into 4 regions as well as normal PPPASI: the right palm, left palm, right sole, and left sole, which account for 20%, 20%, 30%, and 30% of the total body BSA of the palms and soles, respectively. Each of these areas is assessed separately for erythema, pustules, vesicles 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 modified PPPASI formula is:

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

Where E = erythema, P = pustular, V = vesicle and D = desquamation/scale

Reference: Modified from PPPASI scoring system for the signs of the disease (Appendix B).

APPENDIX G. SUBJECT'S ASSESSMENT - PPP SIGNS/FINDINGS FOR HANDS AND FEET

This assessment will be performed using the PPSI scoring system (Appendix C). A subject will evaluate skin lesion sites which are identified by either palms or soles, which has the most severe skin lesion assessed by an Investigator at screening. Any identified skin lesion site will be assessed at all subsequent visits by a subject.

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

Subject's assessment for Erythema

At its worst, how much abnormal redness of the skin on hands and feet have you had because of your condition during the last visit and this visit?

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

Subject's assessment for Pustules/Vesicle

At its worst, how many blisters and/or inflamed bumps that are filled with pus on your hands and feet have you had because of your condition during the last visit and this visit?

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

Subject's assessment for Desquamation/Scale

At its worst, how much peeling or shedding of skin and/or scabs on your hands and feet have you had because of your condition during the last visit and this visit?

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

The total score will be calculated by:

PPSI total score= (E + P + D)

Where E = erythema, P = pustular/vesicle and D = desquamation/scale

The total score ranges from 0 to 12

Reference: Modified from PPSI scoring system for the signs of the disease (Appendix C).

APPENDIX H. 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.

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Finlay, 1994.

APPENDIX I. EUROQOL 5 DIMENSION (EQ-5D)

Health Questionnaire

English version for the UK

Sample

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

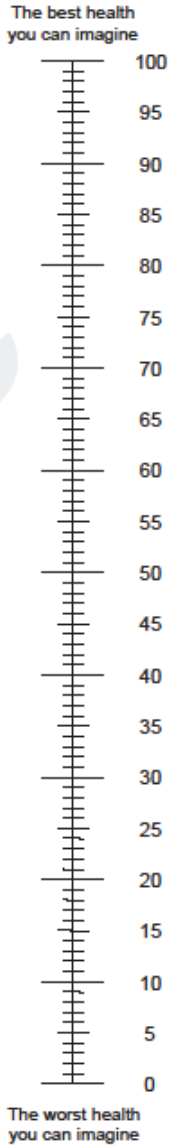
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Sample

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Sample

Source: The EuroQol Group, 1990.

APPENDIX J. SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

AMGEN CC-10004-PPP-001 Apremilast (Otezla)	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

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

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

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

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the AE/Serious Adverse Event Summary CRF*

Provide the date the investigator became aware of this Serious Adverse Event information: Day____Month___Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event co-curred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? If yes see section 10 Apremilast No✓ Yes✓	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

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

4. HOSPITALIZATION

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

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Apremilast ☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 00-April-2020*
Page 1 of 3

AMGEN CC-10004-PPP-001 Apremilast (Otezla)	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN CC-10004-PPP-001 Apremilast (Otezla)	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

APPENDIX K. PREGNANCY NOTIFICATION FORM

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: CC-10004-PPP-001 (Apremilast/Otezla)

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

APPENDIX L. LACTATION NOTIFICATION FORM

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: CC-10004-PPP-001 (Apremilast/Otezla)

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Celgene Signing Page

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

UserName: [redacted]
Title: Vice President and Head of Immunology & Fibrosis Clinical Develo
Date: Monday, 20 April 2020, 12:05 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

Signature Page for VV-TMF-13369539 v1.0

Reason for signing: Approved	Name: [redacted] Role: Records Manager Date of signature: 08-Dec-2020 16:15:51 GMT+0000

Signature Page for VV-TMF-13369539 v1.0

– SUMMARY OF CHANGES –

AMENDMENT NO. 1

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN JAPANESE SUBJECTS WITH PALMOPLANTAR PUSTULOSIS

INVESTIGATIONAL PRODUCT (IP):	**Apremilast (CC-10004)**
PROTOCOL NUMBER:	**CC-10004-PPP-001**
ORIGINAL DATE:	**08 Apr 2019**
AMENDMENT No. 1 DATE:	**02 Sep 2019**
EudraCT NUMBER:	**Not Applicable**
IND NUMBER:	**Not Applicable**

Contact Information:

Name:	[redacted]
Title:	**Dir, Clinical Research & Dev**
Address:	**JP Tower, 2-7-2 Marunouchi, Chiyoda-ku, Tokyo 100-7010, Japan**
Phone:	[redacted]
E-mail:	[redacted]

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. Description adjustment on Protocol Summary (See Underlined Part)

[redacted]

2. Description adjustment on Section 1. Introduction (See Underlined Part)

Palmoplantar Pustulosis

<original>

PPP is characterized by the mixture of blisters and pustules on the palms and soles. Pseudovesicle with pimple is observed in the center of the blister…

<revised>

PPP is characterized by the mixture of blisters and pustules on the palms and soles. Pseudovesicle with pimple and pustule are observed in the center of the blister…

Rationale: It is revised to correct the description. Pimple and pustules are typical characteristics of palmoplantar pustulosis (PPP).

Evaluation of Complication

<original>

It is necessary to evaluate if patients have any focal infection such as tonsillitis, periodontal disease, carious tooth and sinusitis. Focal infection is the infected lesion localized somewhere in the body and the infection itself is asymptomatic and mild, or the symptoms are repeated only intermittently.

<revised>

It is necessary to evaluate if patients have any focal infection such as tonsillitis, periodontal disease and sinusitis. Focal infection is the infected lesion localized somewhere in the body and the infection itself is asymptomatic and mild, or the symptoms are repeated only intermittently.

Rationale: Based on comments from Key Opinion Leaders (KOLs), 'carious tooth' is not included in Focal Infection.

Rationale for the Study Design

<original>

…Sixteen weeks without concomitant treatment for PPP has also been accepted in the study for systemic psoriasis.

<revised>

…Sixteen weeks without concomitant treatment has also been accepted in the study for systemic psoriasis.

Rationale: It is revised to correct an inconsistency within this sentence.

3. Description adjustment on Section 2. Study Objectives and Endpoints (See Underlined Part)

Table 3: Study Safety Endpoint

<original>

Name: Clinically significant changes in body weight, waist circumference, vital signs, and/or laboratory findings

Description: Frequency of clinically significant changes in body weight, waist circumference, vital signs, and/or laboratory findings.

<revised>

Name: Clinically significant changes in body weight, vital signs, and/or laboratory findings

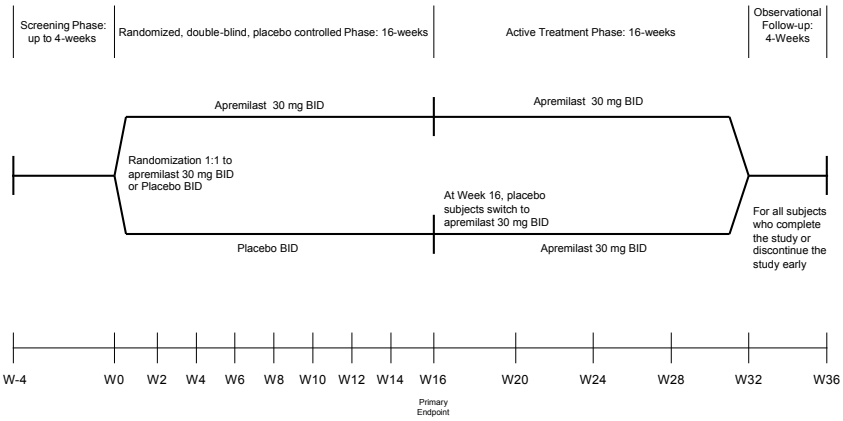
Description: Frequency of clinically significant changes in body weight, vital signs, and/or laboratory findings.

Rationale: Those are typos, because waist circumference will not be measured in this protocol.

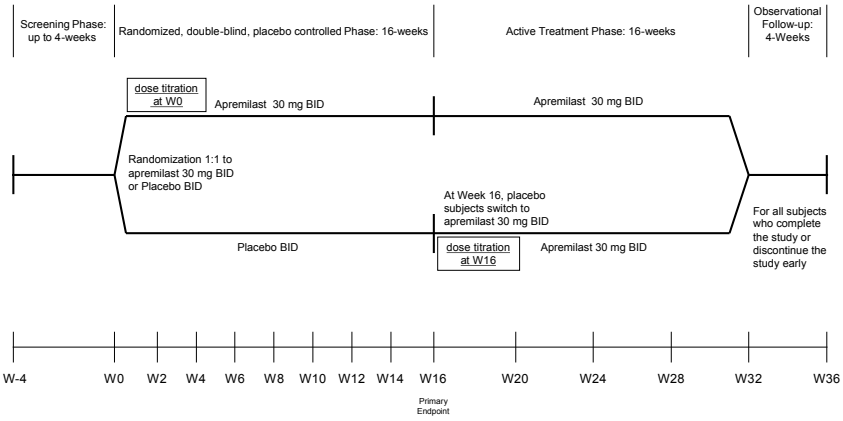
4. Description adjustment on Section 3. Overall Study Design (See Underlined Part)

Figure 1: Overall Study Design

<original>



<revised>



Rationale: It is added that "dose titration" at Week 0 and Week 16 for apremilast and placebo groups, respectively, to make it clear.

3.1 Study Design

<original>

Subjects who meet eligibility criteria for the study will be randomized in a 1:1 ratio to one of the two treatment groups. Subject randomization for treatment assignments will be stratified according to a subject's PPPASI score (≤20 / 21-30 / ≥31) at randomization, and whether a subject has any focal infection at randomization (yes/no).

<revised>

Subjects who meet eligibility criteria for the study will be randomized in a 1:1 ratio to one of the two treatment groups. Subject randomization for treatment assignments will be stratified according to a subject's rounded PPPASI score (≤20 / 21-30 / ≥31) at randomization, and whether a subject has any focal infection at randomization (yes/no).

Rationale: It is added to clarify the description for score handling.

5. Description adjustment on Section 4. Study Population (See Underlined Part)

4.2. Inclusion Criteria, Inclusion Criterion # 4

<original>

Subject has a diagnosis of PPP with or without PAO (not requiring treatment by immunosuppressant, concurrent extra-palmoplantar lesions) for at least 24 weeks before screening.

<revised>

Subject has a diagnosis of PPP with or without PAO (not requiring treatment by immunosuppressant) for at least 24 weeks before screening, regardless of presence or absence of concurrent extra-palmoplantar lesions.

Rationale: Because the sentence is confusing and unclear, the sentence is revised.

4.2. Inclusion Criteria, Inclusion Criterion # 11

<original>

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

<revised>

- Option 2: Male or female condom PLUS, one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

Rationale: Because the material of condom is deleted in the current Apremilast safety language.

4.3. Exclusion Criteria, Exclusion Criterion # 11

<original>

a. Topical therapy within 2 weeks prior to randomization, including, but not limited to, topical corticosteroids, topical retinoid or vitamin D analogue preparations, tacrolimus, or traditional Chinese/Japanese herbal preparations.

b. Conventional systemic therapy within 4 weeks prior to randomization, including, but not limited to, corticosteroids, retinoids, antibiotics, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, biotin, colchicine or traditional Chinese/Japanese herbal preparations).

<revised>

a. Topical therapy within 2 weeks prior to randomization, including, but not limited to, topical corticosteroids, topical retinoid or vitamin D3 analogue preparations, tacrolimus, antihistamine, antibiotics or traditional Chinese/Japanese herbal preparations.

b. Conventional systemic therapy within 4 weeks prior to randomization, including, but not limited to, corticosteroids, retinoids, antihistamine, antibiotics, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, dimethyl fumarate, biotin, colchicine or traditional Chinese/Japanese herbal preparations.

Rationale: It is revised to correct the description. The expression is unified as vitamin D3. Use of antihistamine as topical/conventional therapies is also excluded that could affect the efficacy evaluation. Fumaric acid derivatives is specified as dimethyl fumarate (Fumaric acid salts are excluded).

6. Description adjustment on Section 5. Table of Events (See Underlined Part)

Table 5: Table of Events

<original>

SUBJECT REPORTED OUTCOMES / QUALITY OF LIFE/ HEALTH ECONOMICS RESEARCH

<revised>

SUBJECT REPORTED OUTCOMES / QUALITY OF LIFE

Rationale: Because 'Health Economics Research' is not included in this protocol, it is deleted.

<original>

BIOMARKER (Optional)

<revised>

BIOMARKER

Rationale: It is revised because a part of biomarkers is optional but not all.

Table 5: Footnote

<original>

[d] A complete medical history must be taken and must include a query to rule out whether a subject has known active current or history of recurrent infections.

<revised>

[d] A complete medical history must be taken and must include a query about whether a subject has known active current or history of recurrent infections.

Rationale: It is revised to correct the description.

[redacted]

7. Description adjustment on Section 6. Procedures (See Underlined Part)

Prior/Concomitant Medications and Therapies

<original>

All medications and therapies for PPP, including topicals (used within the last 5 years prior to the randomization), systemics, and all medications and therapies for PAO, should be recorded.

<revised>

All medications and therapies for PPP used within the last 5 years prior to the randomization, including topicals, systemics, and all other therapies, should be recorded.

Rationale: It is revised to keep consistency with other sentences within this protocol. All medications for only PPP within the last 5 years prior to the randomization are recorded.

6.1. Screening Period

<original>

- Prior/Concomitant Medications and Procedures
  - Prior and concomitant medications/procedures except for PPP, PAO and focal infection should be recorded including all procedures occurring ≤ 28 days prior to the baseline.

- History of treatment for focal infection should be recorded within 24 weeks prior to the baseline.
- All medications and procedures for PPP used within the last 5 years prior to the randomization, including topicals, systemics including biologics, and all medications and therapies for PAO, should be recorded.

<revised>

- Prior/Concomitant Medications and Procedures
  - Prior and concomitant medications/procedures except for PPP and focal infection should be recorded including all procedures occurring ≤ 28 days prior to the baseline.
  - History of treatment for focal infection should be recorded within 24 weeks prior to the baseline.
  - All medications and therapies for PPP used within the last 5 years prior to the randomization, including topicals, systemics and all other therapies, should be recorded.

Rationale: It is revised to keep consistency within this protocol. Prior and concomitant medications for pustulotic arthro-osteitis (PAO) is recorded within ≤ 28 days prior to the baseline and prior and concomitant medications for Focal Infection is recorded within 24 weeks prior to the baseline. Medications for only PPP are recorded within the last 5 years prior to the randomization.

Also, it is revised to unify the word with other sentences in this protocol.

6.5.3. Serum and Urine Pregnancy Tests for Females of Childbearing Potential (FCBP)

<original>

A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP subjects at screening. In addition, a urine pregnancy test will be performed at the site on all FCBP subjects at the Baseline Visit, Visit 10 (Week 16) or Last Treatment Visit (Visit 14 [Week 32]). An unscheduled urine pregnancy test should be performed if the FCBP subject has missed a menstrual period. If positive results are obtained from a urine pregnancy test, a serum pregnancy test should be performed to confirm, and if positive results are obtained from a serum pregnancy test, the event must be reported and IP should be discontinued (See Section 10.4.1).

<revised>

A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP subjects at screening. In addition, a urine pregnancy test will be performed at the site on all FCBP subjects at the Baseline Visit, Visit 10 (Week 16) and Last Treatment Visit (Visit 14 [Week 32]). An unscheduled urine pregnancy test should be performed if the FCBP subject has missed a menstrual period. If positive results are obtained from a urine pregnancy test, a serum pregnancy test should be performed to confirm, and if positive results are obtained from a serum pregnancy test, IP should be discontinued. The event must be reported (See Section 10.4.1).

Rationale: It is revised to correct the description.

Rationale: Those are added to meet International Council for Harmonisation (ICH)-E18 requirement. Most of those contents are transcribed from the study informed consent form (ICF).

8. Description adjustment on Section 8. Concomitant Medications and Procedures (See Underlined Part)

8.1.1. Double Blind, Placebo-Controlled Phase (Week 0 to Week 16)

<original>

…The dose, unit, frequency, route, indication, the date the medication was started and the date the medication was stopped (if not ongoing) must be recorded. The recording of any permitted topical medications taken for PPP should also include the area of the body to which they are applied and the frequency of application.

<revised>

…The dose, unit, frequency, route, indication, and the date the medication started and stopped (if not ongoing) must be recorded.

Rationale: It is revised to correct the description. Permitted topical medications are also recorded as same as other medications.

<original>

The following therapies will be permitted duration of the study.

- Topical Therapy for PPP

The only allowable concomitant treatments for PPP throughout the study are topical moisturizers including horny softener. Subjects should not use moisturizers within 24 hours prior to the clinic visit.

<revised>

The following therapies will be permitted for the duration of the study.

- Topical Therapy for PPP

  The only allowable concomitant treatments for PPP throughout the study are topical moisturizers (Vaseline). Subjects should not use moisturizers within 24 hours prior to the clinic visit.

Rationale: Because only Vaseline can be used as topical moisturizers.

8.1.2. Active Treatment Phase (from Week 16 to 32)

<original>

In addition to permitted concomitant medications and procedures (Section 8.1.1), subjects in the active treatment phase will have the option of adding topical therapies (including, but not limited to, topical corticosteroids, topical retinoids or vitamin D analogue preparations) and/or phototherapy (excluding oral PUVA) to their treatment regimen.

<revised>

In addition to permitted concomitant medications and procedures (Section 8.1.1), subjects in the active treatment phase will have the option of adding topical therapies (including, but not limited to, topical corticosteroids, topical retinoids or vitamin D3 analogue preparations) and/or phototherapy (excluding oral PUVA) to their treatment regimen. Dose modification is permitted for background doses of NSAIDs for PAO and concomitant medications for complication of disease other than PPP.

Rationale: It is revised to correct the description. The expression is unified as vitamin D3. Dose modification of concomitant background medication is permitted during active treatment phase.

8.2.1 Double Blind, Placebo-Controlled Phase (Week 0 to Week 16)

<original>

The following psoriasis treatment cannot be employed for the duration of the study:

<revised>

The following treatment cannot be employed for the duration of the double-blind, placebo-controlled phase:

Rationale: ‘Psoriasis’ is deleted because of typo. Also, it is revised to correct the description.

<original>

- Topical therapy

  Topical therapies that could affect PPP or the efficacy evaluation (including, but not limited to, corticosteroids, vitamin D3 derivatives, tacrolimus, and antibiotics).

- Conventional systemic therapy

  Systemic therapies that could affect PPP or the efficacy evaluation (including, but not limited to corticosteroids, retinoids, antibiotics, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, biotin, colchicine or traditional Chinese/Japanese herbal preparations).

- Breastfeeding

<revised>

- Topical therapy

  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).
  Note: only use of topical antibiotics for the treatment after skin biopsy is permitted.

- Conventional systemic therapy

  Systemic therapies that could affect PPP or the efficacy evaluation (including, but not limited to corticosteroids, retinoids, antibiotics, antihistamine, JAK inhibitors, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, dimethyl fumarate, biotin, colchicine or traditional Chinese/Japanese herbal preparations.

Rationale: Antihistamine is also prohibited as topical/conventional therapies that could affect the efficacy evaluation. Fumaric acid derivatives is specified as dimethyl fumarate (Fumaric acid salts are excluded).

The note is added considering a site-specific procedure of skin biopsy. Some sites are recommending using topical antibiotics after skin biopsy.

Breastfeeding is also deleted because that is not a concomitant procedure. Subject is pregnant or breastfeeding will be excluded by exclusion criterion #25.

8.2.3. Observational Follow-Up

<original>

No description.

<revised>

There is no restriction of concomitant medication during the observational follow-up phase.

Rationale: It is revised to clarify the description.

9. Description adjustment on Section 9. Statistical Considerations (See Underlined Part)

9.7. Safety Analysis

<original>

Laboratory data will be summarized descriptively. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges of pretreatment versus posttreatment will be provided. Associated clinical laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Baseline will be produced. Associated clinical laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Baseline will be produced. To account for the different exposure to the IP, TEAEs or marked laboratory abnormalities will also be summarized using the exposure-adjusted incidence rate, in addition to the simple incidence rates.

<revised>

Laboratory data will be summarized descriptively. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges of pretreatment versus posttreatment will be provided. Associated clinical laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Baseline will be produced. To account for the different exposure to the IP, TEAEs or marked laboratory abnormalities will also be summarized using the exposure-adjusted incidence rate, in addition to the simple incidence rates.

Rationale: Duplicate sentence is removed.

10. Description adjustment on Section 10. Adverse Events (See Underlined Part)

10.4.1. Females of Childbearing Potential (FCBP)

<original>

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a FCBP regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator.

<revised>

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a FCBP regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. If positive results are obtained from a serum pregnancy test, IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. …

Rationale: It is revised to correct the description.

11. Description adjustment on Appendix C. PALMO-PLANTAR PUSTULOSIS SEVERITY INDEX (PPSI) (See Underlined Part)

<original>

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

0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe.

References: Terui, 2018.

<revised>

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.

Modified from: Terui, 2018.

Rationale: Expression of the scoring system for the signs of the disease is adjusted with the Primary Endpoint (Palmo-Plantar Pustulosis Area and Severity Index [PPPASI]).

12. Description adjustment on Appendix E. VISUAL ANALOGUE SCALES (VAS) - PPP SYMPTOMS FOR HANDS AND FEET (See Underlined Part)

Subject's assessment for Pruritus of hands and feet

<original>

On average, how much itch (on hands and feet) have you had because of your condition during the last visit and this visit?

<revised>

At its worst, how much itch (on hands and feet) have you had because of your condition during the last visit and this visit?

Rationale: It is revised to keep consistency within this protocol. Worst score during visits is captured.

Subject's assessment for Pain of hands and feet

<original>

On average, how much skin discomfort/pain (on hands and feet) have you had because of your condition during the last visit and this visit?

<revised>

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

Rationale: It is revised to keep consistency within this protocol. Worst score during visits is captured.

Other minor editorial changes were made throughout the document. (ex. changing "Sibject" to "Subject" in the Exclusion Criteria #9(a)). All editorial changes are captured in the document below.