A PHASE 4, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE IMPACT OF APREMILAST (CC-10004) ON MRI OUTCOMES IN SUBJECTS WITH PSORIATIC ARTHRITIS

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Printed Name of Celgene Therapeutic Area Head and Title By my signature, I indicate I have reviewed this protocol and find its content to be acceptable. By my signature, I indicate I have reviewed this protocol and find its content to be acceptable. **NOTE: Signed by Celgene based on Approval from Amgen Therapeutic Head** [redacted]

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PROTOCOL SUMMARY

Study Title

A Phase 4, Multicenter, Single-Arm, Open-Label Study to Evaluate the Impact of Apremilast (CC-10004) on MRI Outcomes in Subjects with Psoriatic Arthritis

Indication

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatologic disorder characterized by peripheral arthritis, affecting 6% to 39% of patients suffering from psoriasis. PsA is classified as a seronegative spondyloarthropathy (SpA) because it shares certain features with other conditions included in that group. Indeed, spinal involvement has been reported in approximately 50% of patients with PsA. In addition, PsA is associated with enthesitis and dactylitis, which are extra-articular features common to SpA. Finally, the majority of patients with PsA are negative for the rheumatoid factor (Gladman, 2005; Kruithof, 2005).

Apremilast (CC-10004) is an oral phosphodiesterase enzyme (PDE) inhibitor. It is highly selective for PDE4, which is the dominant PDE in inflammatory cells. Through inhibiting PDE4, apremilast elevates intracellular cyclic adenosine monophosphate levels, leading to a partial inhibition of the production of many pro-inflammatory mediators, as well as an increase in some anti-inflammatory mediators. A recent study in subjects with PsA indicated that apremilast was associated with reductions in tumor necrosis factor–α (TNF-α), interleukin (IL)-17, IL-23, IL-6, IL-8, macrophage inflammatory protein-1β, and monocyte chemoattractant protein 1, as well as increases in anti-inflammatory mediators, including IL-10 and the IL-1 receptor antagonist (Schafer, 2015). It is believed, therefore, that apremilast exerts its therapeutic benefits through the modulation of multiple inflammatory pathways.

Following a comprehensive clinical development program, apremilast has been approved for the treatment of PsA and it is under clinical investigation for the treatment of Behçet's syndrome and inflammatory bowel disease.

Apremilast has been shown to be efficacious in halting inflammation and reducing signs and symptoms of PsA, as well as improving physical function (Cutolo, 2016; Edwards, 2016; Kavanaugh, 2014; Nash, 2018). A question that remains to be addressed is whether apremilast can impact the structural progression of the disease. In addition, the extent of its structure modifying effects remains to be characterized using axial PsA specific imaging techniques and methodologies.

Magnetic resonance imaging (MRI) has gained importance as a promising tool for early diagnosis and increasing acceptance as an outcome measure in clinical trials of different inflammatory arthritides. It is highly sensitive (Althoff, 2007; Braun, 2004; Hermann, 2005; Hermann, 2006) and superior to conventional radiography in depicting inflammatory bone lesions of the peripheral arthritis and axial skeleton. Moreover, it can detect soft tissue inflammation, bone erosion, and proliferation. As such, this study is designed to assess the efficacy of apremilast on MRI outcomes in subjects with active PsA, with less than 5 years of disease duration (since diagnosis), and who are naïve to biologic therapies.

Objectives

Primary Objective

- To evaluate the efficacy of apremilast 30 mg twice per day (BID) on inflammation indices, assessed by MRI of the hand

Secondary Objectives

- To evaluate the efficacy of apremilast 30 mg BID on imaging outcomes associated with structural progression, assessed by MRI of the hand
- To evaluate the efficacy of apremilast 30 mg BID on disease activity and functionality, assessed by clinical outcomes
- To evaluate the efficacy of apremilast 30 mg BID on inflammation indices of peripheral arthritis and enthesitis, total (sum of arthritis and enthesitis) and separately, assessed by whole-body MRI (WB-MRI)
- To evaluate the efficacy of apremilast 30 mg BID on PsAID-12
- To evaluate the safety and tolerability of apremilast 30 mg BID

Exploratory Objectives

Study Design

This is a Phase 4, single-arm, multicenter, open-label study to evaluate the impact of apremilast (CC-10004) either in monotherapy or with stable methotrexate (MTX) on MRI outcomes in subjects with active PsA with up to 5 years of disease duration (since diagnosis).

Approximately 120 subjects will receive apremilast 30 mg BID, after a 5-day titration period, with or without stable MTX. All subjects will be permitted to take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or low-dose oral glucocorticoids (prednisone ≤ 10 mg/day or equivalent) throughout the study. The NSAIDs and low-dose oral glucocorticoids must be on a stable regimen for at least 4 weeks prior to baseline. MTX (≤ 25 mg/week) will be permitted if duration of treatment is ≥ 6 months and on a stable regimen for at least 3 months prior to baseline. In addition, the stable doses of MTX, NSAIDs, and low-dose glucocorticoids must be continued from Day 1 through the Week 24 Visit. Change in doses, increase or decrease, and/or discontinuation will not be allowed except for safety reasons or for lack of availability. After the Week 24 Visit, the doses of MTX, NSAIDs, or glucocorticoids may be adjusted as clinically required.

This is a 56-week study comprising of 3 phases:

- Screening Phase – up to 4 weeks
- Single-arm, Open-label Treatment Phase – Weeks 0 to 48
  - 120 subjects will receive apremilast 30 mg BID (after a 5-day titration period) for the entire duration of this phase.

- All subjects who complete the study or discontinue early will participate in the 4-week Post-treatment Observational Follow-up Phase. Henceforth, this will be referred to as the Observational Follow-up Phase.

The study will be conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.

Study Population

The study population will consist of male or female subjects, ≥ 18 years of age, with active PsA with up to 5 years of disease duration, who have not been previously treated with TNF blockers or other biologic disease-modifying antirheumatic drugs (DMARDs). Prior treatment with 2 non-biologic conventional synthetic DMARDs (csDMARDs) is permitted. Subjects who are taking MTX (≤ 25 mg/week) for at least 6 months and on stable doses for at least 3 months will be allowed to maintain such treatment. Subjects who are still taking a csDMARD at the time of screening must discontinue their treatment at least one day prior to their Baseline Visit (ie, Visit 2; Day 1), except for those subjects taking MTX, leflunomide, and cyclosporine. Subjects taking MTX at screening who do not meet the criteria above will require a 28 day-washout. Subjects taking leflunomide will require a 12-week washout or treatment with cholestyramine in accordance with the leflunomide prescribing label (ie, 8 g cholestyramine 3 times daily for 11 days). Subjects taking cyclosporine at screening will require a 28 day-washout to participate in the study. Subjects who have been previously treated with more than 2 csDMARD or any

biologic treatment for rheumatic or dermatologic diseases will not be allowed to participate in the study. At screening, subjects must have a documented diagnosis of PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR), with disease duration ≥ 3 months and ≤ 5 years. In addition, subjects must have ≥ 3 swollen (out of 76) AND ≥ 3 tender (out of 78) joints, with hand involvement (defined as ≥ 1 swollen joint or dactylitis [each clinically active joint of a dactylitic digit is counted as one joint]), and at least 1 active enthesitis site (either one of the Spondyloarthritis Research Consortium of Canada or Leeds Enthesitis Index sites) at screening. Subjects may or may not have axial involvement in conjunction with peripheral PsA.

Length of Study

Subjects will spend up to a total of 56 weeks in this study: up to 4 weeks in the Screening Phase, 48 weeks in the open-label active treatment phase, and 4 weeks in the Observational Follow-up Phase.

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

Apremilast will be provided in blister cards for a 5-day titration period. Dose titration cards will be provided at Week 0 to all subjects.

After the 5-day titration, subjects will be required to take one 30 mg tablet twice daily (morning and evening), approximately 12 hours apart, with or without food. All subjects will receive apremilast supplied in high-density polyethylene bottles until the end of study or early discontinuation.

Overview of Key Efficacy Assessments

Overview of Efficacy Assessments on Imaging

The following will be used for assessing clinical efficacy on MRI outcomes:

- Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS)
- WB-MRI generated indices, such as WB-MRI inflammation indices of peripheral arthritis and enthesitis, the Canada-Denmark and the Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging Scoring Indices for the axial involvement (Krabbe, 2017; Maksymowych, 2005), the Hip Inflammation Magnetic Resonance Imaging Scoring System (HIMRISS) (Maksymowych, 2016), the Knee Inflammation Magnetic Resonance Imaging Scoring System (KIMRISS) (Jaremko, 2017), and the OMERACT Heel Enthesitis Magnetic Resonance Imaging Scoring System

[redacted]

Overview of Clinical Efficacy Assessments

The following will be used for assessing clinical efficacy:

- 76 Swollen Joint and 78 Tender Joint Score
- Clinical Disease Activity Index for Psoriatic Arthritis (c-DAPSA)
- Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Assessment (Maksymowych, 2009)
- Leeds Enthesitis Index (LEI)
- Leeds Dactylitis Index (LDI)
- Psoriatic Arthritis Disease Activity Score (PASDAS) (Coates, 2014)
- Patient's (Subject's) and Physician's (Evaluator's) Global Assessment of Disease Activity
- Subject's Pain Assessment
- Health Assessment Questionnaire–Disability Index (HAQ-DI)

[redacted]

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), for subjects deemed to have PsA spondylitis by the investigator and with BASDAI item 2 ≥ 4 at baseline

Overview of Subject-reported Outcomes

The following will be used for assessing health-related quality of life, impact of disease, fatigue, and work productivity:

- Psoriatic Arthritis Impact of Disease 12-domain questionnaire (PsAID-12)

[redacted]

Overview of Key Safety Assessments

The following will be used for assessing safety:

- Adverse events/
- Physical examination, vital signs, weight
- Clinical laboratory evaluations

Statistical Methods

Sample size calculation for this single-arm study was based on the confidence interval (CI) approach. Efficacy parameters including MRI, clinical, and subject-reported outcomes will be analyzed descriptively and 95% CIs will be provided as appropriate. Safety analyses will be performed for all subjects who receive at least one dose of study medication.

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1.1. Disease Background

1.1.1. Psoriatic Arthritis

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatologic disorder characterized by inflammatory arthritis, enthesitis, dactylitis and spondylitis, affecting 6% to 39% of the patients suffering from psoriasis.

The exact prevalence of PsA is unknown. Estimates of incidence vary from 0.3% to 1% of the population. Disease onset typically occurs between the ages of 30 and 55 years, and affects both genders equally (Gladman, 2005).

PsA is classified as a seronegative spondyloarthropathy (SpA) because it shares certain features with other conditions included in that group. Indeed, spinal involvement has been reported in approximately 50% of patients with PsA. In addition, PsA is associated with enthesitis and dactylitis, which are extra-articular features common to SpA. Finally, the majority of patients with PsA are negative for the rheumatoid factor (RF) (Gladman, 2005; Kruithof, 2005).

Recent studies have challenged the assertion that PsA is a more benign disease than rheumatoid arthritis (RA). There is an increasing body of evidence that suggests that PsA patients experience progressive joint destruction over a relatively short period of time. The results from these studies indicate that PsA is erosive and deforming in nearly half of the patients, with joint damage appearing in the first years of disease onset. Other investigators later confirmed that 41% of the patients developed erosive disease within 2 years of onset of symptoms (Helliwell, 2015).

PsA is also associated with a high burden of disease. PsA has been shown to have a similar impact on physical function, quality of life (QoL) and ability to work as RA. When compared to patients with psoriasis alone, patients with PsA had a further diminished QoL. Lastly, PsA was associated with a significantly higher (60%) risk of mortality than that of the general population; the risk increased with increasing severity of the disease (Gladman, 2008; Rosen, 2012; Sokoll, 2001).

1.2. Compound Background

1.2.1. Apremilast

Apremilast (CC-10004) is an oral phosphodiesterase enzyme (PDE) inhibitor. It is highly selective for PDE4, which is the dominant PDE in inflammatory cells. Through inhibiting PDE4, apremilast elevates intracellular cyclic adenosine monophosphate levels, leading to a partial inhibition of the production of many pro-inflammatory mediators, as well as an increase in some anti-inflammatory mediators. Indeed, a recent study in subjects with PsA indicated that apremilast was associated with reductions in tumor necrosis factor–α (TNF-α), interleukin (IL)-17, IL-23, IL-6, IL-8, macrophage inflammatory protein-1β, and monocyte chemoattractant protein 1, as well as increases in anti-inflammatory mediators, including IL-10 and the IL-1 receptor antagonist (Schafer, 2015). It is believed, therefore, that apremilast exerts its therapeutic benefits through the modulation of multiple inflammatory pathways.

Following a comprehensive clinical development program, apremilast has been approved for the treatment of PsA and psoriasis. It is under clinical investigation for the treatment of Behçet's syndrome and inflammatory bowel disease.

Whether apremilast can impact the structural progression of PsA has yet to be addressed. In addition, the extent of its effects on axial imaging parameters remains to be characterized in subjects with axial PsA.

1.2.2. Key Findings from Clinical Studies

The safety and efficacy of apremilast for the treatment of PsA were demonstrated in a comprehensive clinical development program. Subjects enrolled in Phases 3 and 3b studies included disease-modifying antirheumatic drug (DMARD)-naïve, DMARDs-experienced, biologic-naïve, and biologic-experienced subjects [redacted]The results from these studies indicated that apremilast is safe and effective, both as monotherapy and in combination with conventional synthetic DMARDs (csDMARDs).

Table 1: Apremilast Phase 3 and 3b Studies

Study	Population	Treatment Arms	Subjects Randomized Who Received ≥ 1 Dose of Study Medication
PALACE 1/ CC-10004-PSA-002	csDMARD- and/or biologic-experienced	Apremilast 20 mg/30 mg BID + concomitant csDMARDs vs. PBO + concomitant csDMARDs	504
PALACE 2/ CC-10004-PSA-003	csDMARD- and/or biologic-experienced	Apremilast 20 mg/30 mg BID + concomitant csDMARDs vs. PBO + concomitant csDMARDs	484
PALACE 3/ CC-10004-PSA-004	csDMARD- and/or biologic-experienced with > 1 psoriatic skin lesion > 2 cm	Apremilast 20 mg/30 mg BID + concomitant csDMARDs vs. PBO + concomitant csDMARDs	505
PALACE 4/ CC-10004-PSA-005	csDMARD-naïve and biologic-naïve	Apremilast monotherapy vs. PBO	527
ACTIVE/ CC-10004-PSA-006	Maximum 1 prior csDMARD, biologic-naïve	Apremilast monotherapy vs. PBO	219

BID = twice daily; csDMARD = conventional synthetic disease-modifying antirheumatic drug; PBO = placebo; vs = versus.

1.2.2.1. Efficacy

1.2.2.1.1. Efficacy Data From Phase 3 Studies CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2), and CC-10004-PSA-004 (Palace 3) Through Week 24 in Subjects With Prior csDMARDs and/or Biologic DMARDs

Apremilast was first evaluated in 3 multicenter, randomized, double-blinded, placebo-controlled, Phase 3 pivotal studies (Studies CC-10004-PSA-002 [Palace 1], CC-10004-PSA-003 [Palace 2], and CC-10004-PSA-004 [Palace 3]) (Cutolo, 2016; Edwards, 2016; Kavanaugh, 2014). The studies were similarly designed. Adult subjects with active PsA (≥ 3 swollen and ≥ 3 tender joints) despite prior csDMARD and/or biologic TNF therapy were enrolled in the studies (TNF blockers efficacy failures were limited to < 10% of subjects). Subjects were excluded if they had previously failed > 3 agents for PsA or > 1 TNF inhibitor. Stable baseline concomitant methotrexate (MTX [≤ 25 mg/week]), sulfasalazine (SSZ [≤ 2 g/day]), leflunomide (LEF [≤ 20 mg/day]), low-dose oral glucocorticoids (equivalent to ≤ 10 mg of prednisone a day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed during the trials.

In the 3 pivotal studies, 1493 subjects were randomized equally to placebo (N = 496), apremilast (APR) 20 twice per day (BID) (N = 500), or APR 30 BID (N = 497). Placebo subjects whose tender and swollen joint counts (TJC and SJC, respectively) had not improved by ≥20% were re-randomized 1:1 in a blinded fashion to either apremilast 20 mg or 30 mg twice daily at Week 16, while apremilast subjects remained on their initial treatment.

All 3 studies achieved their primary endpoint (Table 2); a statistically significantly higher percentage of subjects in the APR 30 BID treatment group achieved the primary endpoint of American College of Rheumatology (ACR) 20 at Week 16 compared with placebo. Apremilast was also associated with statistically significant improvements in physical function and improvements in skin manifestations at Weeks 16 and 24 among subjects with body surface area (BSA) for psoriasis ≥ 3 % at baseline.

Table 2: Primary (ACR20) and Major Secondary Endpoints of Studies CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2), and CC-10004-PSA-004 (Palace 3) (Full Analysis Set)

	Study CC-10004-PSA-002		Study CC-10004-PSA-003		Study CC-10004-PSA-004	
	Placebo N = 168	APR 30 BID N = 168	Placebo N = 159	APR 30 BID N = 162	Placebo N = 169	APR 30 BID N = 167
ACR 20 – NRI						
Week 16 n (%)	32 (19.0)	64 (38.1)	30 (18.9)	52 (32.1)	31 (18.3)	68 (40.7)
Week 24 n (%)	22 (13.1)	59 (35.1)***	25 (15.7)	40 (24.7)*	26 (15.4)	52 (31.3)***
ACR 50 – NRI						
Week 16 n (%)	10 (6.0)	27 (16.1)**	8 (5.0)	17 (10.5)	14 (8.3)	25 (15.0)
Week 24 n (%)	7 (4.2)	32 (19.0)***	14 (8.8)	19 (11.7)	13 (7.7)	27 (16.2)*

Table 2: Primary (ACR20) and Major Secondary Endpoints of Studies CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2), and CC-10004-PSA-004 (Palace 3) (Full Analysis Set) (Continued)

	Study CC-10004-PSA-002		Study CC-10004-PSA-003		Study CC-10004-PSA-004	
	Placebo N = 168	**APR 30 BID N = 168**	**Placebo N = 159**	**APR 30 BID N = 162**	**Placebo N = 169**	**APR 30 BID N = 167**
ACR 70 – NRI						
Week 16 n (%)	2 (1.2)	7 (4.2)	1 (0.6)	2 (1.2)	4 (2.4)	6 (3.6)
Week 24 n (%)	1 (0.6)	17 (10.1)***	5 (3.1)	4 (2.5)	6 (3.6)	9 (5.4)
HAQ – LOCF[a]						
Week 16 mean change from Baseline (SE)[b]	-0.086 (0.0360)	-0.244 (0.0364)**	-0.053 (0.0358)**	-0.193 (0.0354)	-0.065 (0.0335)	-0.192 (0.0339)**
Week 24 mean change from Baseline (SE)[b]	-0.076 (0.0369)	-0.258 (0.0371)***	-0.085 (0.0377)	-0.206 (0.0372)*	-0.053 (0.0350)	-0.192 (0.0353)**
BSA ≥ 3 at Baseline	**Placebo N = 68**	**APR 30 BID N = 82**	**Placebo N = 74**	**APR 30 BID N = 77**	**Placebo N = 89**	**APR 30 BID N = 90**
PASI 50 – LOCF						
Week 16 n (%)	11 (16.2)	36 (43.9)***	10 (13.5)	33 (42.9)***	22 (24.7)	38 (42.2)*
Week 24 n (%)	12 (17.6)	41 (50.0)***	11 (14.9)	35 (45.5)***	22 (24.7)	39 (43.3)**
PASI 75 – LOCF						
Week 16 n (%)	3 (4.4)	18 (22.0)**	2 (2.7)	17 (22.1)***	7 (7.9)	20 (22.2)**
Week 24 n (%)	3 (4.4)	17 (20.7)**	3 (4.1)	21 (27.3)***	10 (11.2)	23 (25.6)**

ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response; APR = apremilast; BID = twice daily; BSA = body surface area; DMARD = disease-modifying antirheumatic drugs; HAQ-DI = Health Assessment Questionnaire Disability Index (HAQ-DI score: 0 = best, 3 = worst; measures the subject's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity); LOCF = last observation carried forward; NRI = non-responder imputation; PASI 50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index; SE = standard error.

***p < 0.001 for apremilast versus placebo. **p < 0.01 for apremilast versus placebo. *p < 0.05 for apremilast versus placebo.

[a] Subjects with a baseline value and at least 1 postbaseline value at or prior to Week 16 are included.

[b] Least-squares mean (SE) and p-value based on an analysis of covariance model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and (for Study PSA-004 only) involvement of ≥ 3% BSA with psoriasis at baseline as factors, and the baseline value as a covariate.

For subjects who discontinued from the study prior to Week 16, the last available postbaseline value observed prior to discontinuation was carried forward to Weeks 16 and 24. For subjects who entered early escape (EE) at Week 16 or who did not enter EE but discontinued from the study between Weeks 16 and 24, the last available postbaseline value observed prior to EE or discontinuation, respectively, was carried forward to Week 24. Missing values for subjects who did not discontinue or enter EE were imputed using the latest available postbaseline value prior to the visit in question. Subjects who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as non-responders.

1.2.2.1.2. Efficacy Data From Phase 3 Study CC-10004-PSA-005 (Palace 4) Through Week 24 in Subjects Naïve to csDMARDs and Biologic DMARDs

The efficacy of apremilast in subjects naïve to csDMARDs therapy was investigated in a multicenter, randomized, double-blinded, placebo-controlled Phase 3 study (CC-10004-PSA-005 [Palace 4]) (Wells, 2013). Subjects enrolled had a diagnosis of PsA for ≥3 months and active disease (defined by ≥ 3 swollen and ≥ 3 tender joints). Previous treatment with csDMARDs or biologics was not allowed. Subjects could receive stable doses of prednisone (equivalent to ≤ 10 mg/day) and/or NSAIDs. The use of other csDMARDs, including MTX, SSZ, LEF, or biologics was prohibited during the trial. Subjects were randomized 1:1:1 to placebo, APR 20 BID, or APR 30 BID treatment groups.

In total, 527 subjects were randomized to the placebo (n = 176), APR 20 BID (n = 175), or APR 30 BID (n = 176) group. Subjects whose TJCs and SJCs had not improved by ≥20% at Week 16 were required to enter the early escape (EE) to blinded active treatment. Placebo subjects who met the EE criteria were re-randomized 1:1 in a blinded fashion to APR 20 BID or APR 30 BID. Apremilast subjects remained on their initial treatment.

A statistically significantly higher percentage of subjects in the APR 30 BID treatment group achieved the primary endpoint of ACR 20 at Week 16 compared with placebo (Table 3). Apremilast was also associated with statistically significant improvements in physical function and improvements in skin manifestations at Weeks 16 and 24 among subjects with BSA for psoriasis ≥ 3% at baseline.

Table 3: Primary and Major Secondary Endpoints of Study CC-10004-PSA-005 (Full Analysis Set)

	Study CC-10004-PSA-005	
	Placebo N = 176	**APR 30 BID N = 176**
ACR 20 – NRI		
Week 16 n (%)	28 (15.9)	54 (30.7)**
Week 24 n (%)	23 (13.1)	43 (24.4)***
ACR 50 – NRI		
Week 16 n (%)	8 (4.5)	20 (11.4)*
Week 24 n (%)	11 (6.3)	22 (12.5)*
ACR 70 – NRI		
Week 16 n (%)	2 (1.1)	7 (4.0)
Week 24 n (%)	7 (4.0)	8 (4.5)
HAQ - LOCF[a]		
Week 16 mean change from Baseline (SE)[b]	0.012 (0.0350)	-0.205 (0.0350)***
Week 24 mean change from Baseline (SE)[b]	0.012 (0.0370)	-0.207 (0.0369)***

Table 3: Primary and Major Secondary Endpoints of Study CC-10004-PSA-005 (Full Analysis Set) (Continued)

	Study CC-10004-PSA-005	
BSA ≥ 3 at Baseline	**Placebo N = 93**	**APR 30 BID N = 103**
PASI 50 – LOCF		
Week 16 n (%)	18 (19.4)	51 (46.8)***
Week 24 n (%)	23 (24.7)	53 (48.6)***
PASI 75 – LOCF		
Week 16 n (%)	10 (10.8)	29 (26.6)**
Week 24 n (%)	11 (11.8)	28 (25.7)*

ACR 20/50/70 = American College of Rheumatology 20%/50%/70% response; APR = apremilast; BID = twice daily; BSA = body surface area; DMARD = disease-modifying antirheumatic drugs; HAQ-DI = Health Assessment Questionnaire Disability Index; LOCF = last observation carried forward; NRI = non-responder imputation; PASI 50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index; SE = standard error.
***p < 0.001 for apremilast versus placebo. **p < 0.01 for apremilast versus placebo. *p < 0.05 for apremilast versus placebo.
[a] Subjects with a baseline value and at least 1 postbaseline value at or prior to Week 16 are included.
[b] Least-squares mean (SE) and p-value based on an analysis of covariance model for the change from baseline at the respective time point, with treatment group and baseline DMARD use as factors, and (for Study PSA-004 only) involvement of ≥ 3% BSA with psoriasis at baseline as factors, and the baseline value as a covariate.

Health Assessment Questionnaire–Disability Index (HAQ-DI) score: 0 = best, 3 = worst; measures the subject's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

For subjects who discontinued from the study prior to Week 16, the last available postbaseline value observed prior to discontinuation was carried forward to Weeks 16 and 24. For subjects who entered EE at Week 16 or who did not enter EE but discontinued from the study between Weeks 16 and 24, the last available postbaseline value observed prior to EE or discontinuation, respectively, was carried forward to Week 24. Missing values for subjects who did not discontinue or enter EE were imputed using the latest available postbaseline value prior to the visit in question. Subjects who did not have sufficient data (observed or imputed) for a determination of response status at the respective visits were counted as non-responders.

Improvements in enthesitis and dactylitis among subjects with baseline enthesitis and/or dactylitis at baseline are shown in Table 4.

Table 4: Summary of Secondary Efficacy Endpoints Related to Enthesitis and Dactylitis at Week 16 (FAS; LOCF)

Secondary Endpoints	**Placebo N = 176**	**APR 30 BID N = 176**
MASES mean change from baseline (SE)	-0.5 (0.24)	-1.5 (0.25)**
MASES = 0 n (%)	22 (19.1)	41 (36.9)**
Dactylitis mean change from baseline (SE)	-1.0 (0.25)	-1.7 (0.26)*
Dactylitis score = 0 n (%)	30 (33.3)	34 (40.5)

APR = apremilast; BID = twice daily; FAS = Full Analysis Set; LOCF = last observation carried forward; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; SE = standard error.
MASES evaluated only subjects with pre-existing enthesopathy (N = 115 and 111 for placebo and APR 30 BID, respectively).
Dactylitis score evaluated only in subjects in pre-existing dactylitis (N = 90 and 84 for placebo and APR 30 BID, respectively).
Note: **p < 0.01 for apremilast versus placebo. *p < 0.05 for apremilast versus placebo.

1.2.2.1.3. Efficacy Data From Phase 3 CC–10004-PSA-006 (ACTIVE) Through Week 24 in Subjects With an Inadequate Response to ≤1 csDMARDs and Who Received Apremilast Monotherapy

The rapid onset of efficacy of apremilast monotherapy in biologic-naïve subjects who had received ≤1 csDMARDs was demonstrated in the ACTIVE study (CC-10004-PSA-006) (Nash, 2018), a Phase 3b multicenter, parallel-group study with 1 active treatment; overall treatment duration was 2 years. The study randomized 219 patients (APR 30 mg, n=110; placebo [PBO], n=109). At Week 16 (time of the primary endpoint), all subjects whose improvement was < 10% in both tender and swollen joint counts were eligible to enroll into an EE to active treatment with apremilast 30 mg BID. After 24 weeks of treatment, all subjects entered the active-treatment phase, in which they received apremilast 30 mg BID.

A separation in the proportion of ACR20 responders to APR versus PBO was noted at Week 2 (16.4% versus 6.4%; *P*=0.0252), the first Post-baseline Visit. Early onset of response to APR was observed across clinical assessments, with improvements in the Disease Activity Score (DAS)-28 C-reactive protein (CRP), SJC, HAQ-DI, enthesitis, and morning stiffness severity. Dactylitis and skin responses were not assessed in CC-10004-PSA-006.

A statistically significantly greater proportion of subjects in the APR 30 BID treatment group achieved the primary endpoint of ACR 20 response at Week 16 compared to placebo. A nominally significantly greater proportion of subjects in the APR 30 BID treatment group achieved an ACR 50 or ACR 70 response at Week 16 than in the placebo group (Table 5). Significant reduction in PsA disease activity/manifestations versus placebo was also demonstrated by changes in DAS-28 (CRP) (*P*<0.0001), SJC (*P*≤0.0001), and HAQ-DI (Table 6).

Table 5: ACR 20/50/70 Responses at Weeks 16 and 24 During the Placebo-controlled Period in Study CC-10004-PSA-006 (FAS; NRI)

	Study CC-10004-PSA-006	
	Placebo N = 109	**APR 30 BID N = 110**
ACR 20		
Week 16 n (%)	22 (20.2)	42 (38.2)**
Week 24 n (%)	27 (24.8)	48 (43.6)**

Table 5: ACR 20/50/70 Responses at Weeks 16 and 24 During the Placebo-controlled Period in Study CC-10004-PSA-006 (FAS; NRI) (Continued)

	Study CC-10004-PSA-006	
	Placebo N = 109	**APR 30 BID N = 110**
ACR 50		
Week 16 n (%)	5 (4.6)	20 (18.2)**
Week 24 n (%)	12 (11.0)	22 (20.0)
ACR 70		
Week 16 n (%)	0 (0.0)	7 (6.4)*
Week 24 n (%)	5 (4.6)	8 (7.3)

ACR 20/50/70 = American College of Rheumatology 20%/50%/70%; APR = apremilast; BID = twice daily; FAS = Full Analysis Set; NRI = non-responder imputation.
Note: **p < 0.01 for apremilast versus placebo. *p < 0.05 for apremilast versus placebo.

Table 6: HAQ-DI Score (0 to 3) Change From Baseline at Weeks 16 and 24 (FAS; MMRM)

Visit Treatment Group	**n[a]**	**Change From Baseline LS Mean (SE)[b]**
Week 16		
Placebo	109	-0.055 (0.0513)
APR 30 BID	109	-0.205 (0.0523)*
Week 24		
Placebo	109	-0.169 (0.0581)
APR 30 BID	109	-0.273 (0.0572)

APR = apremilast; BID = twice daily; DMARD = disease-modifying antirheumatic drug; EE = early escape; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire – Disability Index; LS = least-squares; MMRM = mixed-effects model of repeated measures; SE = standard error.
[a] Subjects with a baseline value and at least 1 postbaseline value (after exclusion of data for EE subjects) during the Placebo-controlled Phase are included in the MMRM analysis.
[b] The LS mean (SE) and 2-sided p-value are based on an MMRM analysis for the change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD use and baseline oral glucocorticoids (prednisone or equivalent) use as factors and the baseline value as a covariate. An unstructured covariance matrix that is homogeneous across treatment groups was used. The p-values in italics are < 0.05 and are considered nominally significant, as hierarchical testing was stopped after the first secondary endpoint.

Among subjects with enthesitis at baseline, significant improvements from baseline in Gladman Enthesitis Index (GEI) score were observed with APR 30 mg (-1.1) versus placebo (-0.4) at Week 2 (P=.0354), as well as at Weeks 16 and 24 (Table 7).

In addition, numerically greater proportions of subjects treated with APR 30 mg (48.2%) compared to placebo (33.3%) achieved GEI scores of 0 at Week 24.

Table 7: Gladman Enthesitis Index Change From Baseline at Weeks 16 and 24 During the Placebo-controlled Period in Subjects With Pre-existing Enthesopathy (FAS; MMRM)

Treatment Group	n[a]	Change From Baseline	
		Week 16 LS Mean (SE)[b]	Week 24 LS Mean (SE)[b]
Placebo	48	-0.4 (0.26)	-0.5 (0.27)
APR 30 BID	49	-1.5 (0.26)**	-1.5 (0.26)**

APR = apremilast; BID = twice daily; DMARD = disease-modifying antirheumatic drug; EE = early escape; FAS = Full Analysis Set; GEI = Gladman Enthesitis Index; LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error.

[a] Subjects with a baseline value and at least 1 postbaseline value at or prior to the respective visits are included.

[b] The LS mean and 2-sided p-value is based on an MMRM analysis for the change from baseline, with treatment group, time, treatment-by-time interaction, and previous DMARD use and baseline oral glucocorticoids (prednisone or equivalent) use as factors and the baseline value as a covariate. An unstructured covariance matrix that is homogeneous across treatment groups was used. The p-values in italics are < 0.05 and are considered nominally significant, as hierarchical testing was stopped after the first secondary endpoint.

Note: **p < 0.01 for apremilast versus placebo. For subjects who EE at Week 16, data obtained after EE are excluded from the MMRM analysis. The GEI is a count from 0 to 6. A higher count represents greater enthesitis burden, and a negative change from baseline indicates improvement. Pre-existing enthesopathy was defined as subjects who had a baseline GEI score of greater than 0. Joints temporarily or permanently inaccessible at baseline were excluded from joint count. For other unassessed joints at baseline, the joint assessment at the Screening Visit, if assessed, was used as the baseline assessment; otherwise, the joint was excluded from joint count. The last observed joint assessment (at baseline or postbaseline) is used for joints unassessed at the time point.

1.2.2.1.4. Long-term Efficacy Data From Phase 3 Study CC-10004-PSA-002 (Palace 1)

The 5-year efficacy of apremilast in subjects with active PsA despite prior csDMARD and/or biologic anti-TNF therapy was assessed using data from the Phase 3 Study CC-10004-PSA-002 (Palace 1) (TNF blockers efficacy failures were limited to < 10% of subjects). Data were based on observed analyses from subjects who received apremilast 30 mg BID and who were still attending study visits.

ACR20/50/70 responses were achieved by 71.7%, 48.6%, and 28.4% of subjects, respectively, attending the Week 260 Visit (Kavanaugh, 2018). Psoriasis Area and Severity Index (PASI) 50 and 75 were achieved by 69.4% and 46.9% of subjects, respectively. At Week 260, 61.5% of the subjects achieved HAQ-DI improvements >0.3, which corresponds to the minimal clinically important difference (MCID) (Mease, 2004).

Apremilast was also associated with sustained responses and improvements in enthesitis and dactylitis among subjects still attending study visits. At 5 years, 54.5% of subjects achieved a Maastricht Ankylosing Spondylitis Enthesitis Score of 0 and 80% achieved a dactylitis count of 0.

1.2.2.1.5. Long-term Efficacy Data From Phase 3 Study CC-10004-PSA-005 (Palace 4) in csDMARD-naïve Subjects

The long-term efficacy profile of APR monotherapy in DMARD-naïve subjects was reported for ≤ 208 weeks. ACR20/50/70 responses were achieved by 68.2%, 43.4%, and 23.1% of subjects, respectively, attending the Week 208 Visit (Wells, 2017). PASI 50 and 75 were achieved by 67.6% and 40.5%. At Week 208, half of the subjects achieved HAQ-DI improvements greater than 0.3, which corresponded to the MCID (Mease, 2004).

Apremilast monotherapy was also associated with sustained responses and improvements in enthesitis and dactylitis among subjects still attending study visits.

1.2.2.1.6. Long-term Efficacy Data From Phase 3 Study CC-10004-PSA-006 (ACTIVE)

In biologic-naïve PsA subjects who may have had exposure to 1 prior csDMARD, sustained improvements were observed with the continued exposure to apremilast in monotherapy among subjects still attending study visits through Week 52: ACR20/50/70 responses were achieved by 63.3%, 32.4%, and 14.0% respectively (Nash, 2018); also, 45.6% achieved HAQ-DI improvements >0.3, which corresponded to the MCID (Mease, 2004). It is noteworthy that 62.8% of subjects who were initially randomized to receive APR 30 mg with baseline enthesitis (GEI >0) achieved a GEI of 0 at Week 52.

1.2.2.2. Safety

1.2.2.2.1. Pooled Safety 16-Week Data From Phase 3 Studies CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2), CC-10004-PSA-004 (Palace 3), and CC-10004-PSA-005 (Palace 4)

The safety data from the Palace 1, 2, 3, and 4 studies were pooled and summarized for the first 16 weeks of exposure to placebo or apremilast (Celgene, 2017; Wells, 2013). The analyses conducted on the apremilast population included subjects started on apremilast at baseline and subjects switched from placebo to apremilast at Weeks 16 or 24. Analysis included all data during the time subjects were exposed to apremilast, regardless of the time apremilast exposure started.

Approximately half of the subjects (50.7%) experienced ≥1 treatment-emergent adverse event (TEAE) during the first 16 weeks of exposure to apremilast. The incidence of TEAE was higher among subjects who received apremilast than placebo (42.9%) (Table 8). The most frequently reported TEAEs were diarrhea, nausea, headache, and upper respiratory tract infection. The subject incidence of diarrhea, nausea, and headache was higher in the APR 30 BID group than in the APR 20 BID group, suggesting a dose effect.

Table 8: Treatment-emergent Adverse Events Reported in ≥2% of Subjects in Any Treatment Group, First 16 Weeks of Exposure (Studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005; Subjects As Treated)

	Weeks 0 to 16	First 16 Weeks of Apremilast Treatment[b]		
Preferred Term[a]	Placebo Subjects n (%) (N = 671)	APR 20 BID n (%) (N = 972)	APR 30 BID n (%) (N = 973)	APR Total n (%) (N = 1945)
Any TEAE	**288 (42.9)**	**470 (48.4)**	**516 (53.0)**	**986 (50.7)**
Diarrhea	17 (2.5)	86 (8.8)	128 (13.2)	214 (11.0)
Nausea	26 (3.9)	71 (7.3)	114 (11.7)	185 (9.5)
Headache	24 (3.6)	53 (5.5)	77 (7.9)	130 (6.7)
Upper Respiratory Tract Infection	16 (2.4)	42 (4.3)	37 (3.8)	79 (4.1)
Vomiting	5 (0.7)	17 (1.7)	29 (3.0)	46 (2.4)
Nasopharyngitis	12 (1.8)	28 (2.9)	17 (1.7)	45 (2.3)
Hypertension	15 (2.2)	17 (1.7)	25 (2.6)	42 (2.2)
Dyspepsia	8 (1.2)	21 (2.2)	19 (2.0)	40 (2.1)
Abdominal Pain Upper	1 (0.1)	19 (2.0)	18 (1.8)	37 (1.9)

AE = adverse event; APR = apremilast; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] Preferred terms are coded using MedDRA Version 14 and are presented in descending order of subject incidence in the APR Total group. A subject with multiple occurrences of an AE is counted only once in the AE category.

[b] The first 16 weeks of exposure are included regardless of when apremilast exposure started.

Treatment-emergent AEs were predominantly mild or moderate in severity. The most frequently reported TEAEs (ie, diarrhea, nausea, upper respiratory tract infection, and headache) were primarily mild in severity. Severe diarrhea was reported by 1 (0.1%) subject in the placebo group, 4 (0.4%) in the APR 20 BID group, and 3 (0.3%) in the APR 30 BID group. Severe nausea was reported by 0 subjects in the placebo group, 2 (0.2%) in the APR 20 BID group, and 3 (0.3%) in the APR 30 BID group. Severe headache was reported by 1 (0.1%) subject in the placebo group, 2 (0.2%) in the APR 20 BID group, and 1 (0.1%) in the APR 30 BID group. No events of severe upper respiratory tract infection were reported in any treatment group. Treatment with apremilast was associated with an increase in adverse reactions of depression. During the 0-to-16-week placebo-controlled period of Palace 1, 2, and 3, 1.0% (10/998) of subjects treated with apremilast reported depression or depressed mood and 0.8% (4/495) treated with placebo.

Body weight was measured routinely in Studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005. At the end of the placebo-controlled period, median (mean) weight change from baseline was 0.00 (0.13) kg in the placebo group, -0.50

(-1.05) kg in the APR 20 BID group, and -0.60 (-0.97) kg in the APR 30 BID group. Weight loss > 5% was observed in 2.1% of subjects in the placebo group, 4.7% in the APR 20 BID group, and 4.9% in the APR 30 BID group.

Serious TEAEs were reported for 22 (3.3%) subjects who received placebo and 44 (2.3%) who received apremilast during the first 16 weeks of exposure (Table 9). The incidence of serious adverse events (SAEs) was comparable across treatment groups, ie, 3.3% of subjects in the placebo group, 2.4% in APR 20 BID group, and 2.2% in the APR 30 BID group.

Table 9: Treatment-emergent Serious Adverse Events Reported in >1 Subject in Any Treatment Group, First 16 Weeks of Exposure (Studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005; Subjects As Treated)

Preferred Term[a]	Weeks 0 to 16	First 16 Weeks of Apremilast Treatment[b]		
	Placebo n (%) (N = 671)	APR 20 BID n (%) (N = 972)	APR 30 BID n (%) (N = 973)	APR Total n (%) (N = 1945)
Any SAE	22 (3.3)	23 (2.4)	21 (2.2)	44 (2.3)
Atrial Fibrillation	0	0	2 (0.2)	2 (0.1)
Acute Myocardial Infarction	1 (0.1)	2 (0.2)	0	2 (0.1)
Deep Vein Thrombosis	0	0	2 (0.2)	2 (0.1)
Myocardial Ischemia	0	2 (0.2)	0	2 (0.1)
Psoriatic Arthropathy	3 (0.4)	1 (0.1)	1 (0.1)	2 (0.1)
Hypertensive Crisis	2 (0.3)	0	1 (0.1)	1 (0.1)
Pancreatitis Acute	2 (0.3)	0	0	0

AE = adverse event; APR = apremilast; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

[a] Preferred terms are coded using MedDRA Version 14 and are presented in descending order of subject incidence in the APR Total group and then alphabetically. A subject with multiple occurrences of an AE is counted only once in the AE category.

[b] The first 16 weeks of exposure are included regardless of when apremilast exposure started.

During the first 16 weeks, 1 death was reported in Study PSA-002 (Palace 1). The event occurred in a subject randomized to the APR 20 BID treatment group, who died due to multi-organ failure on Day 73 of the study. The subject was diagnosed with anemia due to vitamin B_{12} deficiency before the first dose of apremilast and was receiving concomitant MTX for the treatment of PsA. The death certificate indicated that the direct cause of death was "multiple organ failure," specifying that severe B_{12} deficiency anemia led to the event of multiple organ failure.

TEAEs leading to drug withdrawal were reported in 3.6% of subjects in the placebo group, 4.5% in the APR 20 BID group, and 5.2% in the APR 30 BID group. The most frequently reported TEAEs leading to withdrawal of apremilast were diarrhea, nausea, and headache. Among subjects who were taking placebo, the most frequently reported TEAEs that led to drug

withdrawal were diarrhea and nausea. There was no evidence of an increased incidence of TEAEs leading to drug withdrawal with continued apremilast treatment when the incidence rate was adjusted for exposure.

1.2.2.2.2. Long-term Safety Data From CC-10004-PSA-006 (ACTIVE), CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2) and CC-10004-PSA-004 (Palace 3)

The long-term safety of apremilast monotherapy in subjects who had received ≤ 1 csDMARD was assessed in the ACTIVE study over a period of 52 weeks (Nash, 2018). The overall incidence of adverse events (AEs) in the placebo-controlled period was generally similar for APR monotherapy and placebo. The most commonly reported AEs (≥ 5% of pts) with APR versus placebo were nasopharyngitis (8.3% versus 6.4%, respectively), nausea (8.3% versus 1.8%), headache (7.3% versus 3.7%), hypertension (6.4% versus 6.4%), and diarrhea (subject- or investigator-reported) (14.7% versus 11.0%); using a protocol-defined characterization of diarrhea (≥ 2 watery/liquid stools/day), overall incidence was lower for APR and placebo (11.0% and 8.3%). Serious AEs were lower with APR than placebo (2.8% versus 4.6%). No opportunistic infections, reactivations of tuberculosis (TB), or cases of marked depression were seen. In general, no increase was seen in AE incidence/severity with longer-term exposure to APR up to 52 weeks. Apremilast was generally well tolerated.

The long-term safety of apremilast, with or without concomitant csDMARDs, over 4 years was assessed in a pooled analysis of the Palace 1, 2, and 3 studies (Mease, 2017). Results from this analysis suggested a favorable and consistent safety profile over time. Importantly, the frequency of gastrointestinal AEs decreased with longer exposure to apremilast, and the frequency of other common AEs either decreased or remained stable with prolonged exposure (Table 10). The rates of infections did not increase over time, nor did the data indicate a need for specific laboratory monitoring. Treatment with apremilast was associated with an increase in adverse reactions of depression; 0.3% (4/1441) of subjects treated with apremilast discontinued treatment due to depression or depressed mood versus 0 placebo-treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to apremilast versus 0 placebo-treated subjects (0/495). Two subjects who received placebo committed suicide versus 0 apremilast-treated subjects. Importantly, the rates of depression remained low over time.

Table 10: Frequency of Common AEs Over 208 Weeks of Exposure

	Weeks 0 to ≤ 52	**Weeks > 52 to ≤ 104**	**Weeks > 104 to ≤ 156**	**Weeks > 156 to ≤ 208**
Subjects, n (%)	**APR30 N=721**	**APR30 n=520**	**APR30 n=443**	**APR30 n=401**
≥ 1 AE	524 (72.7)	316 (60.8)	284 (64.1)	234 (58.4)
≥ 1 SAE	47(6.5)	35 (6.7)	40 (9.0)	28 (7.0)
AE leading to drug withdrawal	56 (7.8)	13 (2.5)	7 (1.6)	7 (1.7)
Death	0 (0.0)	1[§] (0.2)	0 (0.0)	2[‡,‖] (0.5)

Table 10: Frequency of Common AEs Over 208 Weeks of Exposure (Continued)

	Weeks 0 to ≤ 52	**Weeks > 52 to ≤ 104**	**Weeks > 104 to ≤ 156**	**Weeks > 156 to ≤ 208**
Subjects, n (%)	**APR30 N=721**	**APR30 n=520**	**APR30 n=443**	**APR30 n=401**
AEs in ≥ 5% of subjects, n (%)				
Diarrhea	112 (15.5)	20 (3.8)	12 (2.7)	4 (1.0)
Nausea	108 (15.0)	11 (2.1)	10 (2.3)	3 (0.7)
Headache	75 (10.4)	17 (3.3)	12 (2.7)	7 (1.7)
Upper respiratory tract infection	60 (8.3)	27 (5.2)	24 (5.4)	21 (5.2)
Nasopharyngitis	41 (5.7)	31 (6.0)	20 (4.5)	26 (6.5)

AE = adverse event; APR30 = apremilast 30 mg twice daily; SAE = serious adverse event.
* Includes all subjects who received APR during the time interval relative to the start of APR treatment. §Motor vehicle accident on Day 489. ‡Cerebrovascular accident on Day 1,330 in a 69-year-old man, considered unrelated to study drug; subject had history of myocardial infarction, atrial fibrillation, and cerebrovascular accident. ‖Stroke on Day 1,224 in a 58-year-old woman, considered unrelated to study drug; subject had a history of chronic ischemic heart disease, hypertension, alcoholism, and atrial fibrillation.

Most AEs were mild or moderate in severity. Rates were very low for major cardiac events, malignant neoplasms, and serious opportunistic infections. It is noteworthy that systemic opportunistic infections did not occur with long-term exposure to apremilast. Marked laboratory abnormalities were infrequent, and most returned to baseline values with continued treatment.

In a pooled analysis of Palace 1, 2, 3, and 4 (Celgene, 2017) for subjects receiving long-term treatment with APR 30 BID, the median (mean) weight change from baseline was -1.00 (-1.25) kg and -1.30 (-1.68) kg, respectively, at Week 52, and -1.00 (-1.70 kg) and -2.00 (-2.14) kg at Week 78. At the end of treatment, weight loss > 5% was observed in 14.8% of subjects receiving apremilast 20 mg BID and 16.5% receiving apremilast 30 mg BID. Overall, no overt clinical consequences were seen with the weight loss observed with apremilast.

The 5-year safety of apremilast was evaluated in a long-term analysis of the Palace 1 study (Kavanaugh, 2018). No new safety concerns were identified. For subjects entering the fifth year of apremilast 30 mg BID exposure, AEs occurring in ≥5% were upper respiratory tract infection, nasopharyngitis, and urinary tract infection; most AEs were mild or moderate in severity. Apremilast 30 mg BID continued to demonstrate a favorable safety profile and was generally well tolerated.

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

1.3. Rationale

1.3.1. Study Rationale and Purpose

1.3.1.1. Unmet Medical Need

In 2016, the European League Against Rheumatism and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published updated recommendations for the management of PsA. The GRAPPA recommendations are based on the following goals of therapy: 1) To achieve the lowest possible level of disease activity; 2) To optimize functional status and improve QoL, and prevent structural damage, and 3) To avoid or minimize complications, both from untreated active disease and from therapy.

Apremilast has been extensively investigated for the treatment of PsA. It is associated with improvements in clinical outcomes across several core PsA domains, physical function and QoL. However, its impact on imaging outcomes associated with structural progression in patients with PsA remains to be determined. In addition, the extent of its effects on axial parameters remains to be characterized in subjects with axial PsA.

Importantly, recent studies have failed to demonstrate substantial radiographic progressions in most PsA subjects studied over short periods of time (Gladman, 1995a; Gladman, 1995b; Queiro-Silva, 2003). These studies enrolled subjects who were at high risk for structural disease progression, such as patients with ≥3 swollen joints, elevated CRP, and evidence of erosive disease of peripheral joints at baseline. Subjects were treated with biologics or Janus kinase (JAK) inhibitors, or were receiving placebo. Taken together, the limited amount of radiographic progression observed in these studies may reflect a change in the expression of the disease over time, which can be explained by improvements in the care of PsA. This may also highlight the limitations of conventional radiographic imaging to assess structural changes.

1.3.1.2. Magnetic Resonance Imaging (MRI) in PsA and Study Rationale

Magnetic resonance imaging (MRI) has gained importance as a promising tool for early diagnosis and increasing acceptance as an outcome measure in clinical trials of different inflammatory arthritides (Ostergaard, 2009; Weber, 2007; Weber, 2009). It is highly sensitive (Althoff, 2007; Braun, 2004; Hermann, 2005; Hermann, 2006) and superior to conventional radiography in depicting inflammatory bone lesions of peripheral arthritis and the axial skeleton. Moreover, it can detect soft tissue inflammation, bone erosion, and proliferation. Since there is lack of ionizing radiation, an MRI is also well suited for young patients and repetitive follow-up exams.

Results from studies in RA indicate that bone marrow edema (BME) is a predictor of erosive progression. A similar relationship is also suggested in PsA (Poggenborg, 2015c). Indeed, a close relationship between erosions and BME was found in a cross-sectional MRI study of erosive PsA patients. These data suggest that BME is a “forerunner” of structural joint damage in PsA (Tan, 2009). In a 48-week longitudinal study of PsA patients, BME detected by MRI predicted subsequent erosive progression as detected by computed tomography (relative risk of erosion progression of 10 [95% CI, 2.1-49] versus joints without BME) (Poggenborg, 2014).

The potential use of MRI to monitor treatment outcomes has encouraged research in this field. In 2015, the Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) was validated in a randomized placebo-controlled trial with 40 subjects who received placebo or abatacept for 6 months. The results showed numerical improvements in the inflammatory variables of PsAMRIS, with high responsiveness, especially for synovitis and tenosynovitis, during abatacept but not placebo therapy. The scoring system (Glinatsi, 2015) assesses metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of fingers 2 to 5, quantifying synovitis (score 0-3), flexor tenosynovitis (score 0-3), periarticular inflammation (absent or present), bone edema (score 0-3), bone erosion (score 0-10), and bone proliferation/enthesophytes (absent or present). The PsAMRIS is a new outcome measure for clinical trials (Coates, 2012). The scoring system provides an objective measure of disease activity, being able to identify responses earlier than clinical assessments.

Poggenborg, et al (Poggenborg, 2014) showed that MRI is useful in quantifying improvements in tenosynovitis, synovitis, and osteitis after treatment with an anti-TNF agent. In contrast, in the same trial, MRI scores of periarticular inflammation did not change significantly after 24 weeks. As a result, the impact of apremilast on the PsAMRIS composite score of BME, synovitis, and tenosynovitis was chosen as the primary endpoint of this study, due to its sensitivity to change in response to treatment.

Dynamic contrast-enhanced MRI (DCE-MRI) is a distinct MRI technique that quantifies the patterns of enhancement within pre-determined regions of interest, after injection of intravenous contrast agent (Cimmino, 2012). Such dynamic imaging allows the capture of the tissue vascularity and quantifies the inflammation in the studied joint. It has been validated in RA for measuring inflammation, but has been used less frequently in studies in PsA. It seems to be a sensitive tool to assess inflammation in PsA, correlating significantly with PsAMRIS total inflammation score (Poggenborg, 2012). In this study, DCE-MRI will be performed in the most affected hand as an optional assessment. Furthermore, we aim to compare standard MRI and DCE-MRI for monitoring inflammation, determining differences in responsiveness between both.

Undoubtedly, physical examination is the basis of clinical evaluation. Nevertheless, the routine clinical exam, especially of enthesitis, is often inconclusive, making the decision to initiate or adapt therapy very difficult. Therefore, more objective methods demonstrating inflammation at tendons, ligaments, and fascia at their insertion in bone and/or the adjacent soft tissue are needed (Poggenborg, 2015a). However, standard MRI can only be used to scan a small anatomical area at a time. This is a limitation when assessing PsA, which has a heterogeneous phenotype, being diverse and widespread in terms of disease manifestations. Whole-body MRI (Althoff, 2007) (WB-MRI) is a promising method for improving enthesitis assessment by evaluating all entheses from "head-to-toe" in one examination (Mager, 2009; Meaney, 2010). A prospective, cross-sectional pilot study of patients with PsA (n=18) and axial SpA (n=18) by Poggenborg and colleagues showed that enthesitis can be detected on WB-MRI, with moderate agreement between WB-MRI and clinical examination at the entheseal level (Poggenborg, 2015a). It is important to emphasize that, although clinical examination is considered the gold standard, previous studies have documented a moderate reliability of clinical assessment among rheumatologists with expertise in SpA. This undoubtedly contributes to the lack of association with MRI findings (Gladman, 2007). Poggenborg's study showed that enthesitis was frequently

observed, mostly occurring at the greater femoral trochanter, supraspinatus, and Achilles tendon insertions. Moreover, by performing WB-MRI, it may be possible to differentiate between enthesitis and fibromyalgia, enabling the rheumatologist to choose the appropriate treatment (Weckbach, 2011).

Involvement of the axial skeleton is a characteristic feature of spondyloarthritis (SpA). It is present in between 25% (early disease and clinical assessment only) and 75% (late disease and sophisticated imaging) of PsA patients, with an impact as great as that seen in ankylosing spondylitis (Jadon, 2017). MRI is widely accepted as the most sensitive imaging modality to detect early inflammatory lesions of the axial skeleton (Weber, 2008). WB-MRI is capable of detecting axial involvement in PsA patients, because it evaluates multiple possible areas of involvement in a single procedure. WB-MRI has been validated against standard MRI for scoring acute inflammatory lesions in the sacroiliac joints of 32 SpA patients with established and active disease (30 had primary ankylosing spondylitis and 2 had Crohn's disease, all fulfilling the modified New York criteria) (Weber, 2009). Results showed a strong correlation and comparable reliability for the detection of inflammatory lesions.

Thus, although relatively new, WB-MRI is a very promising tool for the assessment of disease activity and damage in PsA, with significant potential as a measure of the overall burden of the disease (Ostergaard, 2017; Poggenborg, 2015b). As a result, WB-MRI will be used in the current study to assess the impact of apremilast on MRI parameters of axial joints in subjects with suspected axial PsA. Its impact on entheses and peripheral joints will also be investigated.

The concept that MRI more accurately identifies clinically relevant synovitis than clinical assessment is well established. One hypothesis for why MRI might be a useful predictive biomarker for clinical response is that some patients may have elevated disease activity measures driven by comorbid conditions, rather than solely by active joint inflammation (Baker, 2017). Conversely, patients with greater MRI-detected activity might be expected to have a big proportion of their clinical disease activity explained by active PsA. Finally, since the evidence for the prognostic value of MRI in PsA is still scarce (Mathew, 2017), this study intends to investigate the correlation between specific imaging features and structural progression in this population.

1.3.2. Rationale for the Study Design

Psoriatic arthritis may vary from a mild nonprogressive oligoarthritis to severe polyarticular disease, with great disability and reduced quality of life. These diverse clinical manifestations undermine general predictions regarding outcomes. Although PsA has been historically conceived as a more benign arthropathy, in some patients it follows a particularly aggressive and deforming course. Hence, early diagnosis and treatment may have a significant beneficial effect on the natural course of this disease.

This study is designed to determine the impact of apremilast on imaging outcomes, assessed by both MRI of the most affected hand and WB-MRI, in biologic-naïve subjects with active PsA, with ≥ 3 months and ≤ 5 years of disease duration, who had inadequate response to 2 or less csDMARDs. The purpose of the single-arm design of this trial is to obtain preliminary evidence of the impact of apremilast on MRI outcomes and structural progression of the disease.

A placebo-controlled study was not deemed necessary since current evidence in the literature shows that inflammation, as assessed by MRI, is not expected to significantly improve without an intervention in PsA. Moreover, a comparison arm with methotrexate was not pursued as the efficacy of MTX in PsA has not been convincingly proven in a randomized placebo-controlled trial.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

After a dose titration over a 5-day period, an oral dose of apremilast 30 mg BID will be given to all subjects. This is the approved dosing regimen of apremilast for the treatment of PsA.

In the Phase 3 PsA studies, a statistically significantly greater proportion of subjects in the apremilast 30 mg BID treatment group achieved the primary endpoint of ACR 20 response at Week 16 versus placebo. The statistically significant ACR 20 responses observed at Week 16 were maintained at Week 24 in the APR 30 BID group in all 3 pivotal studies. Therefore, the 24-week treatment period with frequent visits and assessments will provide adequate time to reasonably assess the effect of apremilast on clinical parameters and subject-reported outcomes, but especially on inflammatory and bony lesions classically associated with PsA, as assessed by MRI. This is also consistent with the design of clinical trials that evaluated the effect of biologic drugs in subjects with PsA through MRI assessments that have selected their primary endpoints at Week 24 in order to assess efficacy. The long-term effects of apremilast will be evaluated at Week 48. Indeed, results from the above-mentioned studies indicate that a longer follow-up is needed to detect changes in erosions with MRI.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 11: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy of apremilast 30 mg twice a day (BID) on inflammation indices, assessed by magnetic resonance imaging (MRI) of the hand.
Secondary Objective(s)
The secondary objectives of the study are to evaluate: • The efficacy of apremilast 30 mg BID on imaging outcomes associated with structural progression, assessed by MRI of the hand. • The efficacy of apremilast 30 mg BID on disease activity and functionality, assessed by clinical outcomes • The efficacy of apremilast 30 mg BID on inflammation indices of peripheral arthritis and enthesitis, total (sum of arthritis and enthesitis) and separately, assessed by whole-body MRI (WB-MRI) • The efficacy of apremilast 30 mg BID on The European League Against Rheumatism Psoriatic Arthritis Impact of Disease 12 domains (PsAID-12) • The safety and tolerability of apremilast 30 mg BID
Exploratory Objective(s)
[redacted]

Table 12: Study Endpoints

Endpoint	Name	Description	Time Frame
Primary	Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) Inflammation Score of bone marrow edema [BME] + synovitis + tenosynovitis	Change from baseline in the composite score of BME, synovitis, and tenosynovitis assessed by PsAMRIS	Week 24
Secondary	Efficacy		
	PsAMRIS Inflammation Score of BME + Synovitis + Tenosynovitis	Change from baseline in the composite score of BME, synovitis, and tenosynovitis assessed by PsAMRIS	Week 48
	PsAMRIS BME + Synovitis	Change from baseline in the composite score of BME and synovitis assessed by PsAMRIS	Week 24 Week 48
	PsAMRIS Total Inflammation Score (BME + Synovitis + Tenosynovitis + Periarticular Inflammation)	Change from baseline in the PsAMRIS total inflammation score	Week 24 Week 48
	PsAMRIS BME	Change from baseline in BME assessed by PsAMRIS	Week 24 Week 48
	PsAMRIS Synovitis	Change from baseline in synovitis assessed by PsAMRIS	Week 24 Week 48
	PsAMRIS Tenosynovitis	Change from baseline in tenosynovitis assessed by PsAMRIS	Week 24 Week 48
	PsAMRIS Periarticular Inflammation	Change from baseline in periarticular inflammation assessed by PsAMRIS	Week 24 Week 48
	PsAMRIS Total Damage Score (erosion + bone proliferation)	Change from baseline in the PsAMRIS total damage score (erosion + bone proliferation)	Week 24 Week 48
	PsAMRIS Erosion	Change from baseline in bone erosion assessed by PsAMRIS	Week 24 Week 48
	PsAMRIS Bone Proliferation	Change from baseline in bone proliferation/enthesophytes assessed by PsAMRIS	Week 24 Week 48
	Swollen Joint Count (SJC)	Change from baseline in the SJC	Week 24 Week 48
	Tender Joint Count (TJC)	Change from baseline in the TJC	Week 24 Week 48

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Time Frame
	Clinical Disease Activity Index for Psoriatic Arthritis (c-DAPSA)	Change from baseline in the c-DAPSA Score	Week 24 Week 48
	Spondyloarthritis Research Consortium of Canada (SPARCC)	Change from baseline in SPARCC, in subjects with preexisting enthesopathy	Week 24 Week 48
	Leeds Enthesitis Index (LEI)	Change from baseline in the LEI, in subjects with preexisting enthesopathy	Week 24 Week 48
	Enthesitis improvement to 0	Proportion of subjects with baseline enthesitis whose enthesitis improves to 0	Week 24 Week 48
	Leeds Dactylitis Index (LDI)	Change from baseline in the LDI, in subjects with preexisting dactylitis	Week 24 Week 48
	Dactylitis improvement to 0	Proportion of subjects with baseline dactylitis whose tender dactylitis count improves to 0	Week 24 Week 48
	Psoriatic Arthritis Disease Activity Score (PASDAS)	Change from baseline in the PASDAS	Week 24 Week 48
	Evaluator's Global Assessment of Disease Activity	Change from baseline in the evaluator's global assessment of disease activity	Week 24 Week 48
	Subject's Global Assessment of Disease Activity	Change from baseline in the subject's global assessment of disease activity	Week 24 Week 48
	Subject's Assessment of Pain	Change from baseline in the subject's assessment of pain	Week 24 Week 48
	Health Assessment Questionnaire-Disability Index (HAQ-DI)	Change from baseline in physical function (HAQ-DI score)	Week 24 Week 48
	WB-MRI Peripheral Enthesitis Inflammation Index	Change from baseline in the peripheral enthesitis inflammation index assessed by WB-MRI	Week 24 Week 48
	WB-MRI Peripheral Joints Inflammation Index	Change from baseline in peripheral joints inflammation index assessed by WB-MRI	Week 24 Week 48
	WB-MRI Total Peripheral Inflammation Index	Change from baseline in the total peripheral (joints and enthesitis) inflammation index assessed by WB-MRI	Week 24 Week 48

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Time Frame
	BASDAI	Change from baseline in the BASDAI (for subjects deemed to have PsA spondylitis by the investigator and with BASDAI item 2 ≥ 4 at baseline)	Week 24 Week 48
	The European League Against Rheumatism Psoriatic Arthritis Impact of Disease 12 domains (PsAID-12)	Change from baseline in the PsAID-12	Week 24 Week 48
	Safety		
	The following parameters will be evaluated throughout the duration of the study:		
	Adverse events (AEs)	Type, frequency, severity and relationship of AEs to study medication	-
	Discontinuation due to AEs	Number of subjects who discontinue study medication due to any AE	-
	Clinically significant changes in physical examination, vital signs, and/or laboratory findings	Frequency of clinically significant changes in physical examination, vital signs, and/or laboratory findings	-
Exploratory	[redacted]		

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Time Frame
	[redacted]		

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Time Frame
	[redacted]		

3. OVERALL STUDY DESIGN

3.1. Study Design

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements. For all regions, the local Regulatory Label must be followed.

This is a Phase 4, multicenter, single-arm, open-label study to evaluate the impact of apremilast, either in monotherapy or with stable MTX, on MRI outcomes in subjects with active PsA with up to 5 years of disease duration (since diagnosis).

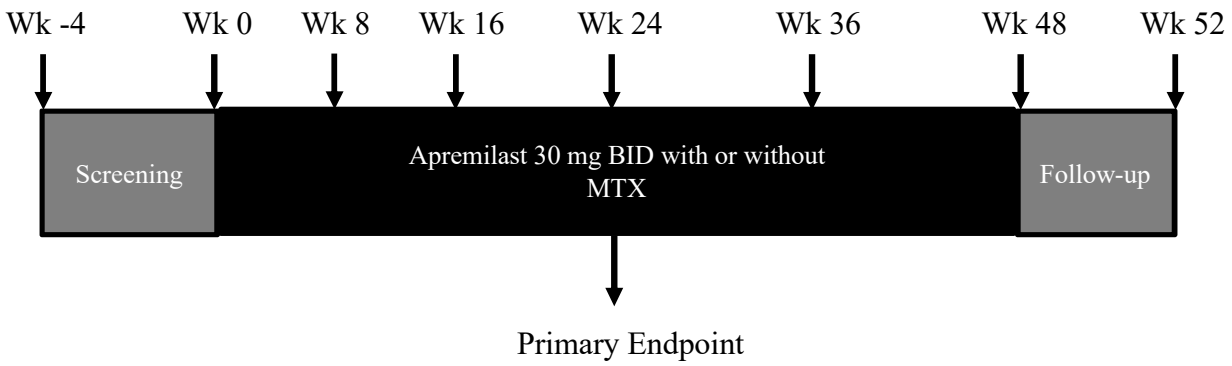
Approximately 120 subjects will receive apremilast 30 mg BID, after a 5-day titration period, with or without stable MTX. All subjects will be permitted to take NSAIDs and/or low-dose oral glucocorticoids (prednisone ≤ 10 mg/day or equivalent) throughout the study. The NSAIDs and low-dose oral glucocorticoids must be on a stable regimen for at least 4 weeks prior to baseline. MTX (≤ 25 mg/week) will be permitted if treatment duration is ≥ 6 months and on a stable regimen for at least 3 months prior to baseline. In addition, the stable doses of MTX, NSAIDs, and low-dose glucocorticoids must be continued from Day 1 through the Week 24 Visit. Change in doses, increase or decrease, and/or discontinuation will not be allowed, except for safety reasons or for lack of availability. After the Week 24 Visit, the doses of MTX, NSAIDs, or glucocorticoids may be adjusted as clinically required.

This is a 56-week study which will consist of 3 phases, as shown in Figure 1:

- Screening Phase – up to 4 weeks
- Single-arm, Open-label Treatment Phase – Weeks 0 to 48
  - 120 subjects will receive apremilast 30 mg BID (after a 5-day titration period) for the entire duration of this phase

- All subjects who complete the study or discontinue early will participate in the 4-week Post-treatment Observational Follow-up Phase. Henceforth, this will be referred to as the Observational Follow-up Phase.

Figure 1: Overall Study Design



BID = twice daily; MTX = methotrexate; Wk = Week.

3.2. Study Duration for Subjects

Subjects who complete the study will spend up to a total of 56 weeks in this study:

- Up to 4 weeks in the Screening Phase
- Weeks 0 to 48 (ie, 48 weeks) in the Open-label, Single-arm, Treatment Phase
- 4 weeks in the Observational Follow-up Phase

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.

Study completion is defined as the date of the last visit of the last subject in this clinical study. Study completion for an individual subject is defined as reaching Visit 7/48 weeks of treatment, and finishing the Observational Follow-up Visit at Week 52. A subject not meeting this definition is considered under early discontinuation (see Section 6.3). For the purpose of analyses, study completion for an individual subject is defined as reaching the Week 48 Visit.

4. STUDY POPULATION

Subjects must meet all inclusion criteria (Section 4.3) and must not have any of the conditions specified in the exclusion criteria (Section 4.4) 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).

4.1. Medical and Disease History

Relevant medical history should be recorded, including smoking and alcohol history, as well as previous relevant surgeries. Disease history should include history of psoriasis and PsA.

4.2. Number of Subjects

Approximately 120 subjects will be enrolled worldwide.

4.3. Inclusion Criteria

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

1. Males or females, aged ≥ 18 years at time of consent
2. For all regions, the local Regulatory Label for treatment with apremilast must be followed. For example, subjects in the EU must have had inadequate response or intolerance to a prior csDMARD.
3. Must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted
4. Able to adhere to the study visit schedule and other protocol requirements
5. Have a documented diagnosis of PsA of ≥ 3 months AND ≤ 5 years in duration, meeting the CASPAR criteria for PsA (Appendix B, Taylor, 2006) at the time of Screening Visit
6. Have ≥ 3 swollen AND ≥ 3 tender joints, with hand involvement (defined as ≥ 1 swollen joint or dactylitis [each clinically active joint of a dactylitic digit is counted as one joint]).
7. Have at least 1 active enthesitis site (one of the SPARCC or LEI sites)
8. Must not have been treated previously with a TNF blocker or other biologic drug for PsA treatment
9. Must not have been treated with more than 2 csDMARDs
10. Subjects taking csDMARDs, with the exception of MTX, cyclosporine, or LEF (see Section 4.4, Exclusion Criterion 18, 19 and 20), do not require a washout period. However, they must discontinue the csDMARD treatment at least one day prior to their Baseline Visit (ie, Visit 2, Day 1)
11. Subjects who have been previously treated with MTX for < 6 months and who are not on stable doses for at least 3 months will require a 28-day washout prior to the Baseline Visit (ie, Visit 2, Day 1) to participate in the study

12. Subjects who have been previously treated with LEF will require a 12-week washout prior to the Baseline Visit (ie, Visit 2, Day 1), or treatment with cholestyramine, per LEF prescribing label (ie, 8 g cholestyramine 3 times daily for 11 days)
13. Subjects who have been previously treated with cyclosporine will require a 28-day washout prior to the Baseline Visit (ie, Visit 2, Day 1) to participate in the study
14. If taking MTX (≤ 25 mg/week), continuity of treatment will be allowed if duration of treatment is ≥ 6 months and on a stable dose for at least 3 months prior to the Baseline Visit (ie, Visit 2, Day 1)
15. If taking oral glucocorticoids, must be on a stable dose of prednisone ≤ 10 mg/day or equivalent for at least 4 weeks prior to the Baseline Visit (ie, Visit 2, Day 1)
16. If taking NSAIDs or narcotic analgesics, must be on stable dose for at least 4 weeks prior to Baseline Visit (ie, Visit 2, Day 1)
17. 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, a FCBP who engages in activity in which conception is possible must use one of the approved contraceptive[§] options described below:

    Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device; tubal ligation; or partner's vasectomy;

    OR

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

    Note: Option 2 may not be acceptable as a highly effective contraception option in all countries, per local guidelines/recommendations.

    [†] An FCBP is defined as a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).
    [§] The female subject's chosen form of contraception must be effective by the time the female subject is screened into the study (for example, hormonal contraception should be initiated at least 28 days before screening).
18. Must be in general good health (except for PsA) as judged by the investigator, based on medical history, physical examination, and clinical laboratories. (Note: The definition of good health means a subject does not have uncontrolled significant comorbid conditions).

4.4. Exclusion Criteria

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

1. Contraindication to MRI examination including, but not limited to, intracranial metal clips, heart pacemakers, insulin pumps, implanted hearing aids, neurostimulators, metal hip replacements, profound claustrophobia or inability to lie in the MRI machine in an

appropriate position to obtain quality images, history of hypersensitivity to gadolinium contrast agent

2. Severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft–Gault equation), which would prevent the use of gadolinium enhancement
3. History of clinically significant (as determined by the investigator) cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease
4. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
5. Prior history of suicide attempt at any time in the subject's lifetime prior to signing the informed consent, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent.
6. Pregnant or breast feeding
7. Active substance abuse or a history of substance abuse within 6 months prior to screening
8. History of allergy or hypersensitivity to any component of the IP
9. History of rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption
10. History of positive human immunodeficiency virus (HIV), or congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease)
11. Active tuberculosis or a history of incompletely treated tuberculosis
12. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of screening. Any treatment for such infections must have been completed and the infection cured, at least 4 weeks prior to screening and no new or recurrent infections prior to the Baseline Visit
13. Malignancy or history of malignancy or myeloproliferative or lymphoproliferative disease within the past 3 years, except for treated (ie, cured) basal cell or squamous cell in situ skin carcinomas
14. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following Baseline Visit
15. Rheumatic autoimmune disease other than PsA, including, but not limited to: systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia
16. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, RA, ankylosing spondylitis, Lyme disease), which confounds the ability to interpret data from the study
17. Prior treatment with any biologic DMARD
18. Prior treatment with more than 2 csDMARDs

19. Use of the following systemic therapy(ies) within 28 days of the Baseline Visit (ie, Visit 2, Day 1): cyclosporine or other calcineurin inhibitors, glucocorticoids exceeding 10 mg daily prednisone equivalent, as well as mycophenolate
20. Use of MTX within 4 weeks of the Baseline Visit (ie, Visit 2, Day 1), unless subject is on stable doses for at least 3 months and total treatment duration with MTX is ≥ 6 months
21. Use of LEF within 12 weeks of the Baseline Visit (ie, Visit 2, Day 1), unless subject has taken cholestyramine, 8 g three times daily × 11 days after stopping LEF
22. Previous treatment with a JAK inhibitor (including tyk2 inhibitor)
23. Prior treatment with apremilast, or participation in a clinical study involving apremilast
24. Use of intra-articular (IA) glucocorticoid injection within 8 weeks before the Baseline Visit (ie, Visit 2, Day 1).
25. Use of any investigational drug within 4 weeks of the Baseline Visit, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer)

5. TABLE OF EVENTS

Table 13: Table of Events

								Early Termination [j]	Observational Follow-up
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**Assessments performed for Early Termination**	**8 (or subsequent to Early Termination Visit)**
Week	**Days -28 to 0**	**0**	**8 (+/-1 week)**	**16 (+/-1 week)**	**24 (+/-1 week)**	**36 (+/-1 week)**	**48 (+/-1 week)**	**-**	**Week 52 or 4 weeks (+/-1 week) after Early Termination)**
Study Entry and General Assessments									
Informed Consent	x	-	-	-	-	-	-	-	-
Demographics	x	-	-	-	-	-	-	-	-
Medical History	x	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	x	x	-	-	-	-	-	-	-
Prior/concurrent Medications	x	x	x	x	x	x	x	x	x
Prior/concurrent Procedures	x	x	x	x	x	x	x	x	x
Biomarkers and Safety Assessments									
[redacted]									
Vital Signs	x	x	x	x	x	x	x	x	-
Height	x	-	-	-	-	-	-	-	-

Table 13: Table of Events (Continued)

								Early Termination [j]	Observational Follow-up
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**Assessments performed for Early Termination**	**8 (or subsequent to Early Termination Visit)**
Week	**Days -28 to 0**	**0**	**8 (+/-1 week)**	**16 (+/-1 week)**	**24 (+/-1 week)**	**36 (+/-1 week)**	**48 (+/-1 week)**	**-**	**Week 52 or 4 weeks (+/-1 week) after Early Termination)**
Weight	x	x	x	x	x	x	x	x	-
Assessment of Diarrhea	-	x	x	x	x	x	x	x	-
Complete Physical Exam [a]	x	-	-	-	x	-	x	x	-
Limited Physical Exam [a]	-	x	x	x	-	x	-	-	-
Complete Blood Count	x	x	x	x	x	x	x	x	-
Serum Chemistries	x	x	x	x	x	x	x	x	-
[redacted]									
Hemoglobin A1c	-	x	-	-	x	-	x	x	-
Urinalysis	x	x	-	-	x	-	x	x	-
Pregnancy Test [c] (FCBP only)	x	x	-	-	-	-	x	x	-
Contraception Education [d]	x	x	-	-	-	-	-	-	-
Adverse Events [e]	x	x	x	x	x	x	x	x	x
Efficacy Assessments									
Tender Joint Count (0-78)	x	x	x	x	x	x	x	x	-
Swollen Joint Count (0-76)	x	x	x	x	x	x	x	x	-
Subject Global Assessment of Disease Activity	x	x	x	x	x	x	x	x	-

Table 13: Table of Events (Continued)

								Early Termination [j]	Observational Follow-up
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**Assessments performed for Early Termination**	**8 (or subsequent to Early Termination Visit)**
Week	**Days -28 to 0**	**0**	**8 (+/-1 week)**	**16 (+/-1 week)**	**24 (+/-1 week)**	**36 (+/-1 week)**	**48 (+/-1 week)**	**-**	**Week 52 or 4 weeks (+/-1 week) after Early Termination)**
Evaluator Global Assessment of Disease Activity	-	x	x	x	x	x	x	x	-
Subject Assessment of Pain	x	x	x	x	x	x	x	x	-
HAQ-DI	-	x	x	x	x	x	x	x	-
c-DAPSA (for eligibility) [f]	x	x	-	-	-	-	-	-	-
SPARCC	x	x	x	x	x	x	x	x	-
LEI	x	x	x	x	x	x	x	x	-
Dactylitis Assessment [g]	x	x	x	x	x	x	x	x	-
[redacted]									
BSA	x	x	-	-	x	-	x	x	-
BASDAI [h]	-	x	x	-	x	-	x	x	-
MRI of the Most Affected Hand [i]	-	x	-	-	x	-	x	x	-
Whole-body MRI [i]	-	x	-	-	x	-	x	x	-
[redacted]									

Table 13: Table of Events (Continued)

								Early Termination [j]	Observational Follow-up
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**Assessments performed for Early Termination**	**8 (or subsequent to Early Termination Visit)**
Week	**Days -28 to 0**	**0**	**8 (+/-1 week)**	**16 (+/-1 week)**	**24 (+/-1 week)**	**36 (+/-1 week)**	**48 (+/-1 week)**	**-**	**Week 52 or 4 weeks (+/-1 week) after Early Termination)**
SRO									-
PsAID-12	-	x	x	-	x	-	x	x	-
[redacted]									
Dosing									-
Dispense Investigational Product	-	x	x	x	x	x	-	-	-
Investigational Product Accountability	-	-	x	x	x	x	x	x	-

[redacted]; ACR = American College of Rheumatology; BASDAI = Bath Ankylosing Spondylitis Activity Index; BSA = body surface area; c-DAPSA = Clinical Disease Activity Index for Psoriatic Arthritis; CRP = C-reactive protein; [redacted]; [redacted] FCBP = female of childbearing potential; HAQ-DI = Health Assessment Questionnaire – Disability Index; IP = investigational product; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MRI = magnetic resonance imaging; PASI = Psoriasis Area and Severity Index; [redacted] PsA = psoriatic arthritis; PsAID = PsA Impact of Disease; [redacted]; SPARCC = Spondyloarthritis Research Consortium of Canada; SRO = Subject-reported Outcomes; [redacted].

[a] During the Observational Follow-up Visit, a complete or limited physical exam may be done at the discretion of the study physician, although not required as per protocol.

[b] High-sensitivity CRP will also be performed as one of the efficacy assessments.

[c] An FCBP† must have a negative pregnancy test at screening and baseline. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening, and urine β-hCG pregnancy test will be performed at baseline. Urine pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP (negative results required for dispensing IP). Pregnancy tests should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed. At the last treatment visit, or in case of early termination, a serum β-hCG pregnancy test will be performed.

[d] See Section 4.3 and Appendix T.

[e] See Section 6.5.8.
[f] At screening (and to be confirmed at baseline), c-DAPSA will be calculated, for eligibility. Half of the subjects must have moderate disease activity or below. Eligibility for each patient will be confirmed by IWRS.
[g] For dactylitis assessment at screening, only a binary evaluation is needed (yes/no). As per inclusion criteria, subjects must have ≥ 3 swollen AND ≥ 3 tender joints, with hand involvement (defined as ≥1 swollen joint OR dactylitis). For the subsequent visits, LDI is needed.
[h] BASDAI will be performed for all subjects.
[i] The clinical and the MRI assessments should be performed on the same day, with the MRI scans always performed after the clinical visit. Exceptionally, MRI scans can be performed within 7 days after the clinical assessments. The baseline MRI must be performed within 7 days after the first administration of IP. The subsequent MRIs should be performed at Week 24 + 7 days and Week 48 + 7 days.
[j] As per protocol, in case of early termination, the site must perform all due assessments, including the MRI scans, to the best of its ability. Early termination MRI assessments will not be performed if the previous MRI scans have been done within the last 8 weeks before the early termination visit.

6. PROCEDURES

The following procedures will be conducted as outlined in the Table of Events, Section 5.

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 first dosing unless noted otherwise below.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses and all assessments will be performed centrally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

Chest radiography can be performed at the investigator's discretion, however it is not required as per protocol.

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

- Inclusion/Exclusion criteria
- Medical history (including specific information regarding diagnosis and additional needed details)
- Demographics (include year of birth, sex, race, and ethnicity-if allowed by local regulations)
- Prior disease therapies: includes surgery, systemic or any other therapy for the subject's disease
- Complete medical history (all relevant medical conditions diagnosed/ occurring prior to screening should also be included)
- Prior and concomitant procedures (including all procedures occurring ≤ 28 days before screening)
- Prior and concomitant medication evaluation (including those taken ≤ 28 days before screening, except for those taken for disease)
- Complete physical examination (can be source documented only), height, weight and BSA
- c-DAPSA (for eligibility, to be confirmed at Baseline Visit). Half of the subjects must have moderate disease activity or below
- SPARCC, LEI and dactylitis assessment (for eligibility, to be confirmed at Baseline Visit)
- Vital signs (including blood pressure, temperature, and heart rate)

- Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential), and platelet count
- Chemistry panel including sodium, potassium, calcium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) and lipid profile

[redacted]

- Urinalysis
- Pregnancy test is required for all FCBP subjects. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening. Urine pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP (negative results required for dispensing IP)
- Contraception education: counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted (see Section 4.3)
- Adverse event assessment begins when the subject signs the informed consent form.

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 28 days of signing the informed consent form (ICF).

The following will be performed at the frequency specified in the Table of Events, Table 13.

- Inclusion/Exclusion criteria
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Physical examination
- Vital signs
- Weight (see Section 6.5.2)
- Hematology panel including complete blood count (CBC) with differential and platelet count
- Chemistry panel
- Hemoglobin A1c

[redacted]

- Urinalysis
- Subject-reported outcomes
- Adverse event evaluation (continuously)
- Assessment of diarrhea (see Section 6.5.5)
- Efficacy assessments, including MRI (see Section 6.4)
- Pregnancy test (prior to dosing on Day 1 and as specified in the Table of Events)
- A pregnancy test should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed
- Contraception education: counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted (see Section 4.3)
- Dispensing IP
- IP accountability

6.2.1. End of Treatment/Early Termination Visit

An Early Termination Visit will be performed for subjects who are withdrawn from treatment for any reason, as soon as possible, after the decision to permanently discontinue treatment has been made.

The following will be performed as specified in the Table of Events:

- Complete physical examination (source documented only), weight
- Vital signs
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Subject-reported outcomes
- Adverse event/Serious Adverse Event evaluation/assessment
- Assessment of diarrhea
- Hematology panel including complete blood count (CBC) with differential and platelet
- Chemistry panel
- Hemoglobin A1c
- [redacted]
- Urinalysis
- Serum β-hCG (for FCBP subjects)
- Efficacy assessments, including MRI
- IP accountability

6.3. Observational Follow-up Period

6.3.1. Safety Follow-up

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as any SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study t, as described in Section 10.1. Safety assessments are specified in the Table of Events, Table 13.

6.4. Efficacy Assessments

The following assessments will be conducted as outlined in the Table of Events, Section 5.

6.4.1. Magnetic Resonance Imaging (MRI)

The MRI assessments will be conducted following the procedures outlined in the MRI manual, at scheduled visits according to Section 5 (Table of Events). The clinical and the MRI assessments should be performed on the same day, with the MRI scans always performed after the clinical visit. Exceptionally, MRI scans can be performed within 7 days after the clinical assessments. The baseline MRI must be performed within 7 days after the first administration of IP. The subsequent MRIs should be performed at Week 24 + 7 days and Week 48 + 7 days. All MRI visits should be scheduled well in advance to allow for proper planning. In addition, it is recommended to schedule 2 MRI visits (an initial and a repeat visit) for each MRI time point in order to be assured of a high-quality MRI scan at each protocol-specified time point. The initial and repeat MRI visits should be scheduled approximately 7 to 14 days apart to allow enough time for confirmation of quality scans from the initial MRI. If the initial MRI scans are of acceptable quality, then the scheduled repeat MRI session can be canceled.

All MRI technicians will receive training on specific MRI positioning and joint placement, further details of which are provided in the Study Procedures Manual. The MRI technician will ensure the quality of each MRI prior to the subject leaving the radiology facility.

The adjudication of the results, when two readers are involved, will be done through the consensus procedure between the two readers. The readers will be able to share the screen and discuss the data, then amend the final scoring. All data, the original and the consented results will be recorded and stored in the imaging database and later incorporated into the clinical database to be available for statistical analysis.

Refer to Appendix P, Appendix Q and [redacted] for details of MRI indices.

For more detailed information on the specific procedures and the consistent acquisition of MRI images, see the MRI Manual.

6.4.2. MRI of the Most Affected Hand

The OMERACT PsAMRIS is a validated scoring system that assesses metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of fingers 2 to 5, evaluating synovitis (score 0-3), flexor tenosynovitis (score 0-3), periarticular inflammation (absent or present), bone edema (score 0-3), bone erosion (score 0-10) and bone proliferation/enthesophytes (absent or present). It will be obtained by MRI of the most affected hand (Appendix P).

6.4.3. WB-MRI

Selected peripheral joints and entheses, the sacroiliac joints (SIJ) and the spine will be assessed by WB-MRI (Appendix Q).

Selected peripheral joints will be scored at each side (right and left) for synovitis and BME, including glenohumeral, acromioclavicular, sternoclavicular, hip and knee. Selected entheses will be scored bilaterally for entheseal BME and entheseal soft tissue inflammation. The entheses will include supraspinatus tendon insertion at humerus, ischial tuberosity, pubic symphysis, greater femoral trochanter, tendon insertions at the knee, calcaneal Achilles tendon insertion and plantar fascia insertion.

The final WB-MRI assessment protocol will be developed based on the prevalent recommendations by the OMERACT MRI in arthritis working group at the time of reading initiation. The final detailed MRI manual will be available before any reading starts.

6.4.3.1. Definition of WB-MRI Indices

WB-MRI indices will be constructed to assess synovitis, BME, and soft tissue inflammation per regions, including pre-specified entheses and peripheral joints, SIJ and the spine.

The final list of WB-MRI indices may be updated based on the prevalent knowledge, including recommendations by the OMERACT MRI in arthritis working group, at the time of reading initiation. The final detailed imaging charter with a reading manual will be available before any reading starts.

[redacted]

6.4.5. Clinical Efficacy Assessments

6.4.5.1. Joint Assessments

A modified ACR joint count that includes the distal interphalangeal joints of the fingers and toes (the "78 tender and 76 swollen" joint scores; Appendix C) will be performed at every visit. The joints to be evaluated are illustrated in Figure 2. Joint tenderness and swelling will be noted as "present" or "absent," with no quantitation of severity.

In case of digit(s) with dactylitis, each joint of the affected digit must be evaluated for tenderness and swelling.

Joints that are swollen or tender should be marked with a tick.

In the event that a joint is injected with intra-articular glucocorticoid (allowed only after Week 24 assessments are completed, and up to the Week 36 Visit), this joint should be marked by an "X" and won't be assessed if the study visit occurs within 4 weeks (28 days) of the intra-articular (IA) injection.

In order to maintain consistency throughout the study, the same evaluator should perform the joint assessments for a given subject at a study site at each study visit.

[redacted]

6.4.5.2. Subject and Evaluator's Global Assessments of Disease Activity

The Patient's (Subject's) and Physician's (Evaluator's) Global Assessments of Disease Activity are assessments of how active a subject's PsA was on average during the past week. Both, subjects and evaluators should mark the box with an X on a 0- to-10-unit numeric rating scale (NRS), on which the left-hand box of 0 represents "not active," and the right-hand box represents "very active" (Appendix D; Felson, 1995; Sieper, 2009).

6.4.5.3. Subject's Pain Numeric Rating Scale

The pain NRS is the subject's assessment of how much pain he/she had, on average, during the past week in his/her joints due to PsA. The subject will be asked to mark the box with an X on a 0- to 10-unit NRS, on which the left-hand box of 0 represents "no pain," and the right-hand box represents the "pain as bad as you can imagine" (Appendix D; Felson, 1995; Sieper, 2009; Hjermstad, 2011).

6.4.5.4. HAQ-DI

The HAQ-DI (Appendix E; Fries, 1980) is a 20-question, self-administered instrument that measures the subject's functional ability on a 4-level difficulty scale (0 to 3, with 0 representing normal or no difficulty; and 3 representing an inability to perform). Eight categories of functioning are included: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities (Bruce, 2003). This scale is sensitive to change and is a good predictor of future disability (Aletaha, 2006).

[redacted]

6.4.5.7. Enthesitis

Enthesitis, or the inflammation of the sites where tendons or ligaments insert into the bone, is a prominent clinical manifestation in subjects with PsA. In this study, 2 clinical indices will be used to evaluate entheseal inflammation. The Leeds Enthesitis Index (Appendix F; Healy, 2008b) will be assessed through physical examination of the following sites. Tenderness (yes/no) will be assessed at 6 sites of tendon insertions (0-6) as depicted below:

- Lateral epicondyle, left and right
- Medial femoral condyle, left and right
- Achilles tendon insertion, left and right

Tenderness on physical examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0 to 6. Higher count represents a greater enthesitis burden.

The SPARCC Enthesitis Index (Appendix G) will be assessed through physical examination of the following sites:

- Medial epicondyle (left/right [L/R])
- Lateral epicondyle (L/R)
- Supraspinatus insertion into greater tuberosity of humerus (L/R)
- Greater trochanter (L/R)
- Quadriceps insertion into superior border of patella (L/R)
- Patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R)
- Achilles tendon insertion into calcaneum (L/R)
- Plantar fascia insertion into calcaneum (L/R)

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 16 sites, for an overall score range of 0–16. Higher count represents greater enthesitis burden.

6.4.5.8. Dactylitis

Dactylitis ("sausage digit") is characterized by the swelling of the entire finger or toe. It will be assessed using the Leeds Dactylitis Index (LDI) (Appendix H; Helliwell, 2005).

The score is a function of finger circumference and tenderness, assessed and summed across all dactylitic digits.

6.4.5.9. Clinical Disease Activity Index for Psoriatic Arthritis (c-DAPSA)

The c-DAPSA is a measure of PsA disease activity, associated with functional and structural outcomes (Aletaha, 2017). It will be performed programmatically by summing four disease activity variables: TJC and SJC, subject global and pain assessment. Cut-offs for cDAPSA are:

- ≤ 4: remission
- > 4 and ≤ 13: low disease activity
- > 13 and ≤ 27: moderate disease activity
- > 27: high disease activity.

6.4.5.10. Psoriatic Arthritis Disease Activity Score (PASDAS)

The PASDAS is a weighted index comprising assessments of joints, function, acute phase response, QoL, and patient and physician visual analogue scores (VAS) (Coates, 2014).

Note: This study does not utilize VASs, but rather NRSs. The patient's and physician's global assessment of disease activity captured on a NRS will be multiplied by a factor of 10 to derive the VAS, used to calculate PASDAS.

The calculation of the PASDAS will be performed programmatically using the formula below:

PASDAS =(((0.18×√physician global VAS)+(0.159×√patient global VAS)−(0.253×√SF36−PCS)+(0.101×LN (SJC +1))+(0.048×LN (TJC +))+(0.23×LN (Leeds enthesitis count+1))+(0.377 LN (dactylitis count+1))+(0.102× LN (CRP+1))+2)*1.5.

CRP = C-reactive protein; LN = natural logarithm; PCS = physical component summary scale of SF36; SF36 = Medical Outcomes Study Short Form-36; SJC = swollen joint count; TJC = tender joint count; VAS = visual analogue scale. All VAS scores are 0–100 mm. Swollen joint count is 66 joints, and tender joint count 68.

The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores. Response criteria for the Psoriatic Arthritis Disease Activity Score (PASDAS) is detailed below.

	Improvement		
Final PASDAS Score	> 1.6	< 1.6 but > 0.8	< 0.8
≤ 3.2	1	2	3
> 3.2 but < 5.4	2	2	3
≥ 5.4	2	3	3

1: good response; 2: moderate response; 3: poor response.

[redacted]

6.4.5.12. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is a composite score based on a subject self-administered survey of six questions using a 0- to 10-unit NRS that assesses the subject's five major symptoms relevant to spondyloarthropathies: 1) fatigue; 2) spinal pain; 3) peripheral joint pain/swelling; 4) areas of localized tenderness; 5) morning stiffness severity upon wakening; 6) morning stiffness duration upon wakening (Appendix J; Calin, 1999; Sieper, 2009). The subject will be asked to mark with an X a 0- to 10-unit NRS for each of the six questions. To give each of the five symptoms equal weighting, the mean of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. A BASDAI score of 4 or greater is considered to be indicative of active disease.

6.5. Safety Assessments

In addition to daily safety monitoring conducted by investigators and individual study personnel, AEs, serious adverse events (SAEs), discontinuations and laboratory findings will be reviewed internally by the study team at Amgen.

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

The following assessments will be conducted as outlined in the Table of Events, Section 5.

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

A serum pregnancy test with a sensitivity of ≤ 15 mIU/mL will be required for FCBP subjects at screening, at the last treatment visit or the Early Termination Visit for subjects who discontinue

before Week 48 Visit. Urine pregnancy test will be performed on all FCBP subjects at the Baseline Visit at the site. Urine pregnancy test kit will be provided by the central laboratory. Pregnancy tests should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed.

In addition to the assessments specified in Section 5, the Investigator will follow country guidelines regarding the monitoring of pregnancy testing at any scheduled or unscheduled visit and will document the test result in the source document. At the discretion of the Investigator, a serum pregnancy may be done.

6.5.2. Vital Signs, Height and Weight

Vital signs, including temperature, pulse, and seated blood pressure, will be taken during the visits indicated in Section 5, Table of Events. Height will be measured and recorded at screening; weight will be measured and recorded at every visit.

In the event of unexplained and clinically significant weight loss, subjects should be evaluated and discontinuation of study treatment should be considered by the investigator.

6.5.3. Complete/Limited Physical Examination

A complete physical examination includes evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems. A complete physical examination is done at screening and other designated visits as indicated in Section 5. A limited physical examination includes evaluations of skin, lymph nodes, and respiratory, cardiovascular, and musculoskeletal systems. A limited physical examination is done at Baseline Visit and other designated visits as indicated in Section 5.

6.5.4. Psychiatric Evaluation

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

If a patient suffers from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue study treatment (see Section 11).

6.5.5. Diarrhea, Nausea and Vomiting

Apremilast has been associated with AE reports of diarrhea in clinical trials. Most diarrhea events were of mild or moderate severity and reported within the first 2 weeks of treatment, usually resolving within 4 weeks without medical intervention.

Diarrhea is the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual (World Health Organization [WHO], 2013). Following the definition of diarrhea by the WHO and taking a more conservative approach, the AE of diarrhea in this protocol is defined as having two or more watery/liquid stools in a day.

To better characterize diarrhea and to distinguish similar events coding to the Medical Dictionary of Regulatory Activities (MedDRA) preferred term of diarrhea, subjects reporting diarrhea or similar events (eg, frequent bowel movements, loose bowels, etc.) will be asked whether they have had two or more watery/liquid stools in a day. Subjects who respond "yes" to this question will be further asked how often, on average, have they experienced two or more watery/liquid stools in a day. Subjects who respond "no" to the question will not be asked any further questions.

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.

Subjects 65 years of age or older and those taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications. Subjects should be monitored for the occurrence of severe diarrhea, nausea and vomiting. If subjects develop severe diarrhea, nausea and vomiting, discontinuation of treatment with study treatment may be necessary (see Section 11).

6.5.6. Tuberculosis

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

6.5.7. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by the central laboratory, and as indicated in Section 5. Clinical laboratory evaluations include: RF, CBC (RBC count, hemoglobin, hematocrit, WBC count and differential, absolute WBC counts, platelet count); serum chemistries (total protein, albumin, calcium, phosphorous, glucose, triglycerides, total cholesterol [TC], total and direct bilirubin, alkaline phosphatase, AST, ALT], sodium, potassium, chloride, bicarbonate [carbon dioxide, CO_2], BUN, creatinine, creatinine clearance, lactate dehydrogenase [LDH], and magnesium); [redacted]; hemoglobin A1c (HbA1c); and urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen). Urinalysis will be performed by the central laboratory; microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the urinalysis is abnormal.

6.5.8. Adverse Events

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

All AEs will be recorded by the investigator from the time the subject signs informed consent to 28 days after the last dose of IP. AEs and SAEs will be recorded on the AE page of the case report form (CRF), the paper SAE reporting form (SAEs) and in the subject's source documents.

All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event using the paper Serious Adverse Event Report Form by facsimile/email of the paper SAE Report Form directly to Amgen Global Patient Safety

Details of AE/SAE reporting can be found in Section 10 of the protocol.

It should be noted that worsening of a subject's PsA should be considered as worsening of disease under study and should not be captured as an adverse event.

6.6. Biomarkers

[redacted]

6.7. Subject-reported Outcomes

The following assessments will be conducted as outlined in the Table of Events, Section 5.

6.7.1. Psoriatic Arthritis Impact of Disease 12-domain Questionnaire (PsAID-12)

The PsAID is a validated score reflecting the impact of disease in PsA. The PsAID-12 is a 12-item, self-administered questionnaire that reflects the impact of PsA from the perspective of the patient. It is composed of 12 physical and psychological domains. Each domain is rated from 0 to 10 with a different weighting. The total score is divided by 20. The final score has a range from 0 (best status) to 10 (worst status) with a cut-off of 4 (Appendix K; Gossec, 2014).

[redacted]

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

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

Apremilast will be provided by Amgen Inc. and labelled appropriately as IP for this study.

Apremilast will be provided as 10, 20, or 30 mg tablets in blister cards for dose titration purposes. Apremilast will also be provided as 30 mg tablets in high-density polyethylene (HDPE) bottles (approximately 80 tablets) with child-resistant caps. The apremilast dosing schedule and dose adjustments to be followed for this study are described in Section 7.2. Please refer to the IB for more details on approved indications, known precautions, warnings, and adverse reactions of apremilast.

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. Treatment Administration and Schedule

Tablets will be taken by mouth twice daily, in the morning (AM) and in the evening (PM), approximately 12 hours apart, with no food restrictions. To mitigate potential gastrointestinal (GI) adverse events, dose titration shall be implemented over a 5-day period (Table 14). At the Week 0 Visit, subjects will be dispensed a blister card with 10, 20, and 30 mg apremilast tablets for the dose titration. Subjects will be dispensed bottles with 30 mg apremilast tablets at designated visits.

Table 14: Treatment Schema for Dose Titration at Baseline

Week 0											
Day 1		Day 2		Day 3		Day 4		Day 5		Day 6	
AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	-	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Pictures of the blister card configurations are shown in Appendix S. Since dose modifications are not permissible in this study, if a subject develops severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft–Gault equation), interruption of study medication is required.

7.2.1. 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 there is no control arm drug, hence overdose definition will apply to only apremilast. Other required or optional non-study drugs intended for prophylaxis of certain side effects, etc, are excluded from this definition.

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

Adverse Events associated with an overdose must be collected on the Adverse Events page of the CRF (see Section 10) for all overdosed subjects, but the overdose itself is not considered an AE.

7.3. Method of Treatment Assigned

After the informed consent is signed, subjects will be assigned a subject identification number using a centralized interactive web response system (IWRS). At the Baseline Visit, a centralized schema will be applied to assign subjects who meet the inclusion and none of the exclusion criteria to receive apremilast 30 mg BID, after a 5-day titration period. In addition, half of the subjects must have moderate disease activity or below, as assessed by c-DAPSA.

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

7.4. Packaging and Labeling

For the titration period, apremilast will be supplied by Amgen Inc. to the principal investigator as blister cards. For the remaining of the study, apremilast 30 mg tablets will be supplied in HDPE bottles with child-resistant caps.

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.

7.5. Investigational Product Accountability and Disposal

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

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 record the information in the IRT.

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

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

7.5.1. Dosing

7.5.1.1. Study Medication Dispensing and Counting

After the informed consent is signed, subjects will be assigned a subject identification number using a centralized interactive web response system (IWRS). At the Baseline Visit, a centralized schema will be applied to assign subjects who meet the inclusion and none of the exclusion criteria to receive apremilast 30 mg tablets. Study medication will be dispensed as specified in Section 5, Table of Events. The tear-off label from each blister card should be pasted into the drug accountability document in each subject's record. Subjects must be instructed to return all previously issued empty blister card(s), empty study drug bottle(s) and/or unused study medication at the time that new medication is issued. A detailed record of tablets issued and returned at each visit must be maintained in the subject's record.

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

7.6. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. Investigational product will be dispensed as noted in the Table of Events, Section 5. The subjects will be instructed to return the IP containers, including any unused medication, to the study site at each visit for tablet counts and reconciliation. 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 the subject misses 4 or more consecutive days of dosing, Amgen must 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.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications and therapies being taken/used by the subject up to 30 days prior to the Screening Visit (Visit 1) or at any time during the study should be recorded. Prior medications for the treatment of PsA must be recorded at any time. Other key medications and therapies, such as previous treatment for TB or relevant diseases, should be recorded.

All medications and therapies, including physical therapy, for PsA and their reasons for discontinuation, should be recorded. The stop dates for all medications and therapies prohibited in the study should be recorded. Additional instructions can be found in the CRF Completion Guidelines.

8.1. Permitted Concomitant Medications and Procedures

All medications (prescription and non-prescription), 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 CRF. 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. Subjects may continue receiving standard of care therapy (eg, folic acid for those on MTX) if not explicitly prohibited as per protocol. The following concomitant medications and procedures are permitted:

- Oral glucocorticoids, (on a stable dose of prednisone ≤ 10 mg/day or equivalent for at least 4 weeks prior to Baseline Visit [ie, Day 1]).
- Note: The stable dose of glucocorticoids must be continued and maintained from Day 1 through the Week 24 Visit. Change in doses, increase or decrease, and/or discontinuation of glucocorticoids will not be allowed except for safety reasons or for lack of availability. After the Week 24 Visit, the dose of glucocorticoids may be adjusted as clinically required.
- MTX (≤ 25 mg/week, if total treatment duration is ≥ 6 months and on a stable dose for at least 3 months prior to baseline).
- At Week 12, subjects will be allowed to receive IA glucocorticoids, administration of up to 2 injections of ≤ 40 mg triamcinolone hexacetonide or equivalent (each joint).
- NSAIDs or narcotic analgesics (must be on a stable dose for at least 4 weeks prior to the Baseline Visit [ie, Day 1]).
- Note: The stable dose of NSAIDs or narcotic analgesics must be continued and maintained from Day 1 through the Week 24 Visit. Change in doses, increase or decrease, and/or discontinuation of NSAIDs or narcotic analgesics will not be allowed except for safety reasons or for lack of availability. After the Week 24 Visit, the dose of NSAIDs or narcotic analgesics may be adjusted as clinically required.
- NSAIDs or narcotic analgesics that are administered on an as needed basis (PRN) should be recorded on the Prior/Concomitant Medications page of the CRF.
- Loperamide and antidiarrheal drugs with antisecretory effect (eg, racecadotril).

- Low dose aspirin (acetylsalicylic acid, up to 325 mg per day) for cardiovascular prophylaxis.
- Birth control medications/barrier methods for FCBP subjects.
- Low-potency topical glucocorticoids (or locally available equivalent) as background therapy for treatment of psoriasis on the face, axillae and groin in accordance with the manufacturers' suggested usage during the course of the study.
- Coal tar shampoo and/or salicylic acid scalp preparations on scalp psoriasis lesions.
- A nonmedicated skin emollient (eg, Eucerin® cream) for body psoriasis lesions only.

Medications for conditions other than PsA and psoriasis, which are not prohibited in Section 8.2, are permitted and must be recorded in the subject's source documents and as a concomitant medication on the CRF.

The following therapy will be permitted after the Week 24 Visit for subjects with worsening arthritic symptoms of PsA:

- Change of NSAID type and/or dose
- Administration of no more than 40 mg intramuscular (IM) or intra-articular (IA) glucocorticoid (triamcinolone hexacetonide or equivalent) at a single visit, up to Week 36, not to exceed two glucocorticoid IM and/or IA administrations in any 6 month-interval. Injected joints should not be counted during the visits that will take place within 4 weeks of the intra-articular injection.
- Short course (≤ 2 weeks) of low-dose oral glucocorticoids (prednisone ≤ 10 mg/day or equivalent), to be completed up to Week 36 and not to exceed one course in a 6-month interval

In order to minimize the impact on ongoing efficacy assessments, the investigator should use the least intensive regimen to ameliorate the subject's worsening PsA symptoms. After Week 24, if subjects experience a decrease in PsA clinical disease activity, the investigator may opt to taper the background treatment; however, only one agent may be reduced or tapered at any one time. After the first agent's taper has been completed (not required to be zero), the dose must be stable for at least 4 weeks prior to starting the taper of the next agent. Subjects are recommended to have a reduction of background therapy in the following order: first MTX, second glucocorticoids and third NSAIDs or other pain medication. If clinically indicated, the investigator may opt to reduce the medications in a different order. Any further questions/concerns regarding dose reductions can be discussed with the Sponsor.

All other prohibited medications listed in Section 4.4 (Exclusion Criteria) and Section 8.2 (Prohibited Concomitant Medications and Procedures) remain in effect through the end of the subject's participation in the study.

8.2. Concomitant Medications Not Recommended

It has been observed that co-administration with strong cytochrome P450 3A4 (CYP3A4) enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of strong CYP3A4 enzyme

inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with study treatment is not recommended.

8.3. Prohibited Concomitant Medications and Procedures

The following concomitant medications and concomitant procedures are prohibited, except as permitted in Section 8.1.

- DMARDs (conventional synthetic or biologic) for treatment of PsA, except for MTX (≤ 25 mg/week) if on stable dose at least 3 months prior to Baseline Visit and with total treatment duration ≥ 6 months.
- Treatment with IA glucocorticoids outside the time points specified in Section 8.1, or administration of more than 2 injections of ≤ 40 mg triamcinolone hexacetonide or equivalent (each joint)

8.4. Required Concomitant Medications and Procedures

There are no required concomitant medications or procedures.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This section outlines the statistical analysis strategy for the data collected in the study. A detailed Statistical Analysis Plan (SAP), including data handling and imputation rules, will be prepared and finalized before database lock or any analysis procedures are conducted.

9.2. Study Population Definitions

The Full Analysis Set (FAS) will consist of all subjects who are enrolled in the study. Among the FAS, specific analysis populations will be defined in detail in the SAP.

The Per Protocol (PP) population will consist of all subjects who receive at least one dose of study medication and have no major protocol deviations during the first 24-week period. The final determination of major protocol deviation criteria will be made prior to the database lock and will be documented.

The Safety population will consist of all subjects who received at least one dose of study medication.

9.3. Sample Size and Power Considerations

While no MRI data are available for apremilast, assumptions used for the sample size calculation are primarily derived from the literature (Glinatsi, 2015). With an approximate 20% dropout rate, a sample size of 120 is required to produce a two-sided 95% confidence interval, for the expected change from baseline in the composite score of BME, synovitis, and tenosynovitis, with a distance from the mean to the limit equal to 1.24, assuming the standard deviation is 6.2.

9.4. Background and Demographic Characteristics

Subject's age, weight, height and other continuous demographic and baseline characteristics will be summarized using descriptive statistics (mean, standard deviation, minimum and maximum), while gender, race, and other categorical variables will be summarized with frequency tabulations. Medical history data will be classified using the MedDRA classification system and summarized using frequency tabulations by system organ class and preferred term. Treatment history (including previous csDMARD and investigational agents) will be summarized using 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.

9.5. Subject Disposition

Subject disposition (subjects enrolling into and completing or discontinuing from the study, along with primary reason for discontinuation) will be summarized using frequency and percent by study phase. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

9.6.1. Primary Endpoint

The primary endpoint, change from baseline in the composite score of BME, synovitis, and tenosynovitis assessed by PsAMRIS at Week 24, will be analyzed descriptively. The 95% confidence interval will be provided for the mean change, and the composite score over time will be presented graphically.

9.6.2. Secondary Endpoints

All secondary efficacy endpoints listed in Section 2 will be analyzed descriptively, with summary statistics for continuous endpoints and frequency distribution for binary endpoints. The 95% confidence intervals will also be provided. Separate analyses for the responders and non-responders will also be performed for each imaging endpoint. The PsAMRIS will also be analyzed separately based on the presence or absence of different imaging parameters at baseline. In addition, data will be reported based on the proportion of subjects above or below the smallest detectable changes (SDC).

9.6.3. Exploratory Endpoints

[redacted]

9.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 10.2.

Adverse events will be classified using the MedDRA classification system. All adverse events will be summarized by system organ class and preferred term; in addition, also by severity separately. Adverse events leading to death or to discontinuation from treatment, serious adverse events, study drug-related adverse events, and events of interest will be summarized separately. A subject having the same event more than once will be counted only once using the maximum severity.

Laboratory data will be summarized by visit descriptively (mean, standard deviation, median, minimum, and maximum). Number and percentage of subjects with marked laboratory abnormalities will be provided. In addition, shift tables showing the number of subjects with values low, normal, and high based on the normal ranges pre-treatment versus post-treatment will be provided.

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

To account for the exposure to the study medication, the exposure adjusted incidence rate will also be calculated for adverse events and marked laboratory abnormalities.

9.8. Other Topics

9.8.1. Investigational Product Compliance (Tablets)

Study medication information will be summarized and subject listings will be provided. Compliance will be estimated by the proportion of subjects who take between 75% and 120% of the intended quantity of study medication.

9.8.2. Concomitant Therapy

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

9.8.3. Steering Committee

Guidance in protocol development and interpretation of data analysis will be provided by a scientific steering committee (SSC). Details for the SSC are pre-specified in a separate SSC charter.

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 page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to apremilast 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 7.2.1 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an IP which meets the definition of an adverse event should be reported as an AE on the CRF. If the sequelae of an overdose meet serious criteria, then it must be marked as serious on the CRF and the paper SAE Report form. The overdose itself should not be reported as an AE.

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

10.1.1. Monitoring, Recording, and Reporting AEs of Diarrhea

The PDE4 inhibitors, including apremilast, have been associated with AE reports of diarrhea. To better characterize and understand all reported AEs of diarrhea, further information will be collected as described in Section 5, in the Table of Events. Please refer to Section 10.1 for further details on how to record such AEs.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

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

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

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

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

- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the paper SAE Report Form must be completed. All SAEs must be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge by submitting the paper SAE report form via facsimile/email directly to Amgen Global Patient Safety.

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

10.2.2. Severity/Intensity

For each AE, the Investigator must assess the severity/ intensity of the event.

Mild

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

Moderate

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

Severe (could be non-serious or serious)

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

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

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

10.2.3. Causality

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

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

Causality should be assessed and provided for each AE 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 non-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 each AE, 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 apremilast as a result of each AE, as applicable (eg, discontinuation or interruption, 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 each AE.

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 an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

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

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

10.4. Pregnancy

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

10.4.1. Collection of Pregnancy and Infant Health Information

Pregnancies and suspected pregnancies (including elevated β-subunit of human chorionic gonadotropin [β-hCG] or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, must be reportable within 24 hours. Investigational product 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 Safety immediately by facsimile, email or other appropriate method, using the Pregnancy Notification Form or approved equivalent form (refer to Appendix V). The Pregnancy Notification Form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

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

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

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

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Amgen Global Patient Safety using the paper Serious Adverse Event Report Form within 24 hours of the Investigator's knowledge of the event.

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

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

10.4.2. 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 (refer to Appendix V). The form must be submitted to Amgen Global Patient Safety with 24 hours of the investigator's/site's awareness of the pregnancy (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

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

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

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

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

10.4.3. Collection of Lactation Information

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

10.5. Reporting of Serious Adverse Events

Any AE that meets any seriousness criterion must be reported as an SAE 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.

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

All SAEs must be reported directly to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of the event by facsimile or email via the paper Serious Adverse Event Report form, in addition, ensuring the event is recorded on the CRF as well.

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

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

- Facsimile transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information. If facsimile is unavailable, the email method to transmit this information is acceptable (refer to Appendix U).
- 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 U**).**

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated/generated from Amgen Global Patient Safety to the site via Amgen's safety query paper process or other appropriate method. Pertaining, to urgent queries (eg, missing causality assessment), these may be handled by phone, facsimile or email.

10.6. Expedited Reporting of Adverse Events

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

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area, Amgen or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on IPs for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

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

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

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

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

For Amgen Global Patient Safety contact information, please refer to your site's paper Serious Adverse Event Report Form, paper Pregnancy Notification Form and/or paper Lactation Notification Form (Appendix V, Appendix U, Appendix W).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

- Adverse event(s)
- Lack of efficacy
- Non-compliance with study drug
- Withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Pregnancy
- Death
- Protocol deviation
- Other (to be specified on the CRF)

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

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

The decision to discontinue a subject from treatment can be taken at any time and remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor 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
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- 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- 800-77-AMGEN (1 800-772-6436**)**. The representatives are responsible for obtaining your call-back information and contacting the on-call /contract research organization Medical Monitor, who will then contact you promptly.

12.2. Emergency Identification of Investigational Products

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

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Amgen, its authorized representative, and Investigator abide by 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 of Amgen information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an 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 adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the 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 CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Amgen standard operating procedures (SOPs). These 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 , 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 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, an 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 (egg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Amgen immediately.

15.3. Product Complaint

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

investigational products or devices supplied by Amgen are to be reported according to the instructions provided in the Investigational Product Instruction Manual or equivalent.
If you become aware of a suspected PC, you are obligated to report the issue within 24 hours of discovery or notification of the concern or irregularity. Amgen requires notification of any concern or irregularity at any stage of the study.

15.3.1. How to Report a Product Complaint to Amgen:

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

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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 15: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
ACR	American College of Rheumatology
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase
APR	Apremilast
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
β-hCG	Serum beta human chorionic gonadotropin
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BID	Twice per day
BME	Bone marrow edema
BSA	Body surface area
BUN	Blood urea nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CBC	Complete blood count
c-DAPSA	Clinical Disease Activity Index for Psoriatic Arthritis
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DAS	Disease Activity Score
[redacted]	[redacted]
DEMRIQ	Dynamic Contrast-enhanced MRI Quantification
DMARD	Disease-modifying antirheumatic drug
EC	Ethics Committee
EDC	Electronic data capture
EE	Early escape
EULAR	European League Against Rheumatism

Table 15: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
FAS	Full Analysis Set
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEI	Gladman Enthesitis Index
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire–Disability Index
HDPE	High-density polyethylene
HIMRISS	Hip Inflammation Magnetic Resonance Imaging Scoring System
HLA	Human leukocyte antigen
[redacted]	[redacted]
IA	Intra-articular
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IM	Intramuscular
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive web response system
JAK	Janus kinase
KIMRISS	Knee Inflammation Magnetic Resonance Imaging Scoring System
LDI	Leeds Dactylitis Index
LEF	Leflunomide
LEI	Leeds Enthesitis Index
LOCF	Last observation carried forward
L/R	Left/right
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities

Table 15: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
MRI	Magnetic resonance imaging
MTX	Methotrexate
NRI	Non-responder imputation
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
[redacted]	[redacted]
PBO	Placebo
PDE	Phosphodiesterase enzyme
PP	Per protocol
PC	Product Complaint
PsA	Psoriatic arthritis
PsAID-12	Psoriatic Arthritis Impact of Disease 12-domain questionnaire
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Score
QoL	Quality of life
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIJ	Sacroiliac joint
SJC	Swollen joint count
SOP	Standard operating procedure
SpA	Spondyloarthropathy
SPARCC	Spondyloarthritis Research Consortium of Canada

Table 15: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
SRO	Subject-reported outcomes
SSC	Scientific steering committee
SSZ	Sulfasalazine
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
VAS	Visual analog scale
vs	versus
WBC	White blood cell
WB-MRI	Whole-body magnetic resonance imaging
WHO	World Health Organization
[redacted]	

APPENDIX B. THE CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS (CASPAR) CRITERIA

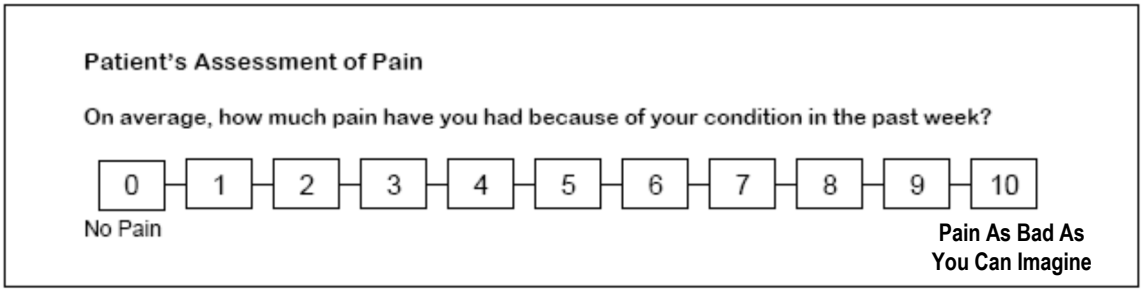
To meet the CASPAR[1] criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.[2]
   - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

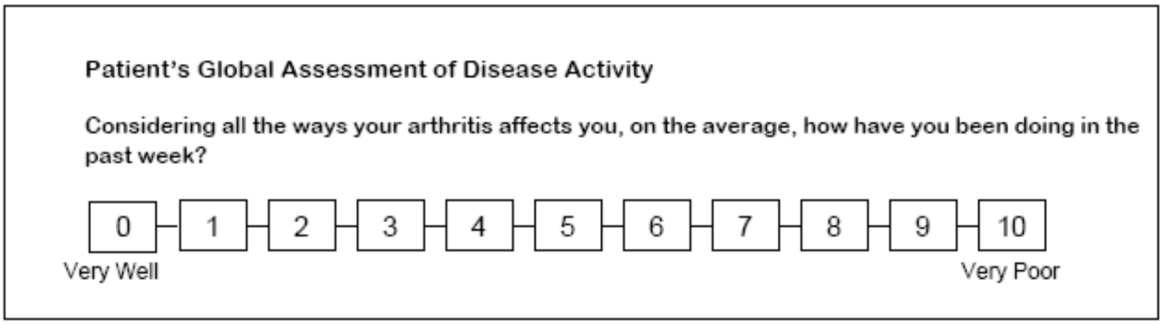
[1] The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.
[2] Current psoriasis is assigned a score of 2; all other features are assigned a score of 1 (from Taylor, 2006).

APPENDIX D. NUMERICAL RATING SCALES

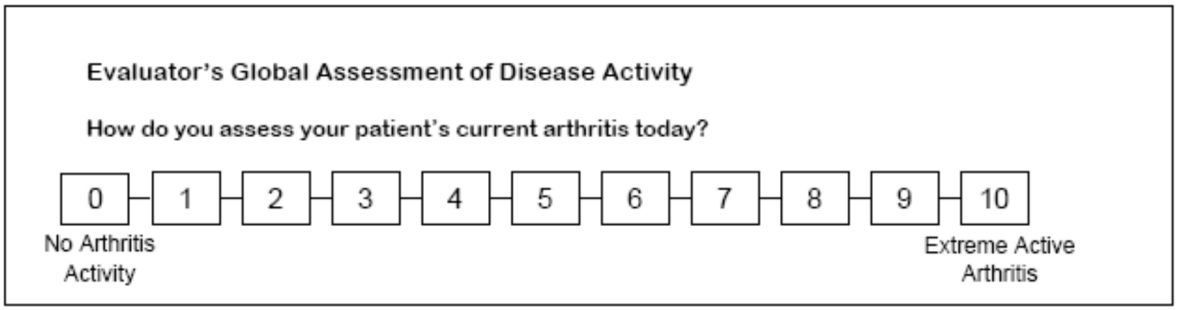
Subject's Assessment of Pain



Subject's Global Assessment of Disease Activity



Evaluator's Global Assessment of Disease Activity



Adapted from Felson, 1995.

APPENDIX E. DISABILITY INDEX OF THE HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)

_____ Built up or special utensils

_____ Special or built up chair

_____ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming

_____ Arising

_____ Eating

_____ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE				
Are you able to:				
- Wash and dry your body?	_____	_____	_____	_____
- Take a tub bath?	_____	_____	_____	_____
- Get on and off the toilet?	_____	_____	_____	_____
REACH				
Are you able to:				
- Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____
GRIP				
Are you able to:				
- Open car doors?	_____	_____	_____	_____
- Open jars which have been previously opened?	_____	_____	_____	_____
- Turn faucets on and off?	_____	_____	_____	_____
ACTIVITIES				
Are you able to:				
- Run errands and shop?	_____	_____	_____	_____
- Get in and out of a car?	_____	_____	_____	_____
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Raised toilet seat	_____Bathtub bar
_____ Bathtub seat	_____Long-handled appliances for reach
_____Jar opener (for jars previously opened)	_____Long-handled appliances in bathroom
	_____ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Hygiene	_____Gripping and opening things
_____ Reach	_____Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness**.**

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0		SEVERE PAIN 100

Source: Bruce, 2003.
STANFORD-RA (MAY99 - Phase 31) – English, USA
HAQ-DI - United States/English - Mapi.
HAQ-DI_AU1.0-eng-USori.doc

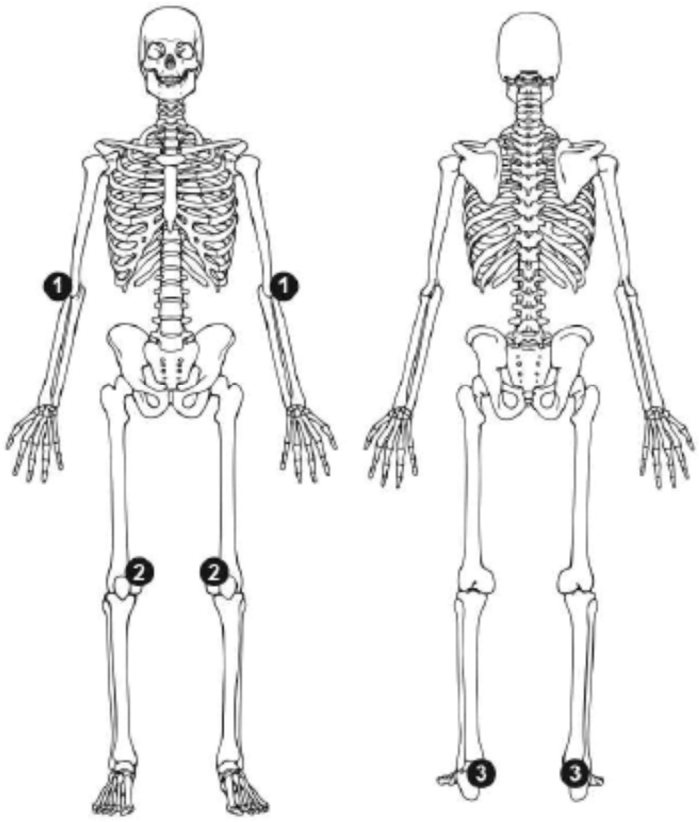
APPENDIX F. LEEDS ENTHESITIS INDEX (LEI)

Leeds Enthesitis Index (Healy, 2008b):

Enthesitis is measured by physical examination of the following joints. Tenderness (yes/no) will be assessed at 6 sites of tendon insertions (0-6) as depicted below:

- Lateral epicondyle, left and right
- Medial femoral condyle, left and right
- Achilles tendon insertion, left and right

Tenderness on physical examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0 to 6. Higher count represents a greater enthesitis burden.



APPENDIX G. THE SPONDYLOARTHRITIS RESEARCH CONSORTIUM OF CANADA (SPARCC) ENTHESITIS INDEX

Entheseal sites examined include:

- Medial epicondyle (left/right [L/R])
- Lateral epicondyle (L/R)
- Supraspinatus insertion into greater tuberosity of humerus (L/R)
- Greater trochanter (L/R)
- Quadriceps insertion into superior border of patella (L/R)
- Patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R)
- Achilles tendon insertion into calcaneum (L/R)
- Plantar fascia insertion into calcaneum (L/R)

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 16 sites, for an overall score range of 0–16. Higher count represents greater enthesitis burden.

The video describing the approach to the physical exam can be seen at www.carearthritis.com under “Physician Tools”.

Source: Maksymowych, 2009.

APPENDIX H. LEEDS DACTYLITIS INDEX (LDI)

The LDI (Healy, 2008a; Helliwell, 2005) measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit. The ratio of circumference is multiplied by a tenderness score.

Affected fingers are marked on a diagram displaying fingers and toes. Circumferences of the affected and contralateral fingers are then measured around the proximal phalanx, as close as possible to the web space, using either a measuring tape or a pre-calibrated loop.

The clinician then squeezes the affected fingers with moderate pressure and documents the patient's response: 0 = no tenderness, 1 = tender, 2 = tender and winces, and 3 = tender and withdraws.

APPENDIX H. LEEDS DACTYLITIS INDEX (LDI) (CONTINUED)

The ratio of circumference between an affected finger and the contralateral unaffected finger is recorded. If both sides are affected, the circumference of the affected finger is compared to normative data supplied in a table. The tenderness score (0-3) for a finger with dactylitis is recorded, and a total score is generated for each finger. If multiple fingers are affected, each score is added together to produce a total for the patient.

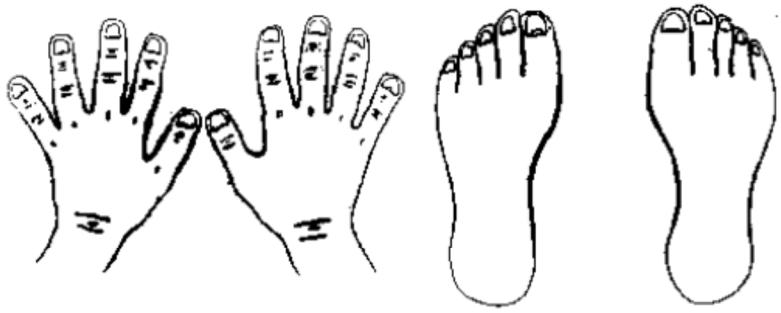
In addition, as part of the LDI, number of affected digits will be evaluated. Each digit on the hands and feet will be rated as zero for no dactylitis or 1 for dactylitis present. The dactylitis score is the sum of the individual scores for each digit.

DACTYLITIS SCORE SHEET

Addressograph Label

Date:

Please indicate dactylitic joints



Finger or toe	Circumference involved digit (A)	Circumference contralateral Digit (or Tables) (B)	Tenderness score (C)	Final score: [{(A/B) - 1} x 100] x C
TOTAL				

Standard reference. Table - hands

Digit	Men	Women
Thumb	70	58
Index	65	54
Middle	65	54
Ring	59	50
Little	52	44

Table - feet

Digit:	Men	Women
Great toe	82	72
Second	52	46
Middle	50	44
Fourth	50	44
Little	52	45

Tenderness score: response to squeeze
0 no tenderness
1 tender
2 tender and wince
3 tender and withdraw

APPENDIX J. BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI)

Please check the box that represents your answer. (i.e. )

All questions refer to the **last 7 days**.

1. How would you describe your overall level of fatigue/tiredness?

0	1	2	3	4	5	6	7	8	9	10

none very severe

2. How would you describe your overall level of **neck, back or hip** pain resulting from AS?

0	1	2	3	4	5	6	7	8	9	10

none very severe

3. How would you describe your overall level of pain/swelling in joints **other than** the neck, back or hips?

0	1	2	3	4	5	6	7	8	9	10

none very severe

4. How would you describe your overall level of discomfort from any areas tender to the touch or pressure?

0	1	2	3	4	5	6	7	8	9	10

none very severe

5. How would you describe your overall level of morning stiffness from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

none very severe

6. How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

0 hr	1 hr	2 or more hrs

Source: Calin, 1999; Sieper, 2009.

BASDAI - United States/English - Version of 09 Dec 15 - Mapi.
ID051206/ BASDAI_TS1.0_eng-US2.doc

APPENDIX K. THE EULAR PSORIATIC ARTHRITIS IMPACT OF DISEASE 12 DOMAINS (PSAID-12) QUESTIONNAIRE

The PsAID-12 questionnaire is a 12-item, self-administered questionnaire that reflects the impact of PsA from the perspective of the patient. It is composed of 12 physical and psychological domains. Each domain is rated from 0 to 10 with a different weighting. The total score is divided by 20. The final score has a range from 0 (best status) to 10 (worst status), with a cut-off of 4.

The outputs of the PsAID calculation should be printed and added to the source documents.

We want you to indicate how much your psoriatic arthritis impacts your health. Please tell us how you have been feeling this last week.

1. Pain

Circle the number that best describes the pain you felt due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

2. Fatigue

Circle the number that best describes the overall level of fatigue due to your psoriatic arthritis you have experienced during the last week:

No fatigue	0	1	2	3	4	5	6	7	8	9	10	Totally exhausted

3. Skin problems

Circle the number that best describes the skin problems including itching you felt due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

APPENDIX K: THE EULAR PSORIATIC ARTHRITIS IMPACT OF DISEASE 12 DOMAINS (PSAID-12) QUESTIONNAIRE (CONTINUED)

4. Work and/or leisure activities

Circle the number that best describes the difficulties you had to participate fully in work and/or leisure activities due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

5. Functional capacity

Circle the number that best describes the difficulty you had in doing daily physical activities due to your psoriatic arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

6. Discomfort

Circle the number that best describes the feeling of discomfort and annoyance with everyday tasks due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

7. Sleep disturbance

Circle the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your psoriatic arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

APPENDIX K: THE EULAR PSORIATIC ARTHRITIS IMPACT OF DISEASE 12 DOMAINS (PSAID-12) QUESTIONNAIRE (CONTINUED)

8. Coping

Considering your psoriatic arthritis overall, how well did you cope (manage, deal, make do) with your psoriatic arthritis during the last week?

Very well	0	1	2	3	4	5	6	7	8	9	10	Very poorly

9. Anxiety, fear and uncertainty

Circle the number that best describes the level of anxiety, fear and uncertainty (for example about the future, treatments, fear of loneliness) due to your psoriatic arthritis you have experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

10. Embarrassment and/or shame

Considering your psoriatic arthritis overall, circle the number that best describes the level of embarrassment and/or shame due to your appearance experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

11. Social participation

Circle the number that best describes the difficulties you had to participate fully in social activities (including relationships with family and/or people very close to you) due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

APPENDIX K: THE EULAR PSORIATIC ARTHRITIS IMPACT OF DISEASE 12 DOMAINS (PSAID-12) QUESTIONNAIRE (CONTINUED)

12. Depression

Circle the number that best describes the level of depression due to your psoriatic arthritis you have experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

THANK YOU FOR ANSWERING THIS QUESTIONNAIRE

Source: Gossec, 2014.

APPENDIX K: THE EULAR PSORIATIC ARTHRITIS IMPACT OF DISEASE 12 DOMAINS (PSAID-12) QUESTIONNAIRE (CONTINUED)

PsAID-12 SCORING AND CALCULATION RULES

The PsAID is calculated based on 12 NRS questions. Each NRS is assessed as a number between 0 and 10.

Calculators and translations are available at
http://www.eular.org/index.cfm?framePage=/st_com_clinical_tools.cfm.

1. Calculation

PsAID final value =

(PsAID1 (pain) NRS value (range 0-10) x 3)

+ (PsAID2 (fatigue) NRS value (range 0-10) x 2)

+ (PsAID3 (skin) NRS value (range 0-10) x 2)

+ (PsAID4 (Work and/or leisure activities) NRS value (range 0-10) x 2)

+ (PsAID5 (function) NRS value (range 0-10) x 2)

+ (PsAID6 (discomfort) NRS value (range 0-10) x 2)

+ (PsAID7 (sleep) NRS value (range 0-10) x 2)

+ (PsAID8 (coping) NRS value (range 0-10) x 1)

+ (PsAID9 (anxiety) NRS value (range 0-10) x 1)

+ (PsAID10 (embarrassment) NRS value (range 0-10) x 1)

+ (PsAID11 (social life) NRS value (range 0-10) x 1)

+ (PsAID12 (depression) NRS value (range 0-10) x 1)

The total is divided by 20. Thus, the range of the final PsAID value is 0-10, where higher figures indicate worse status.

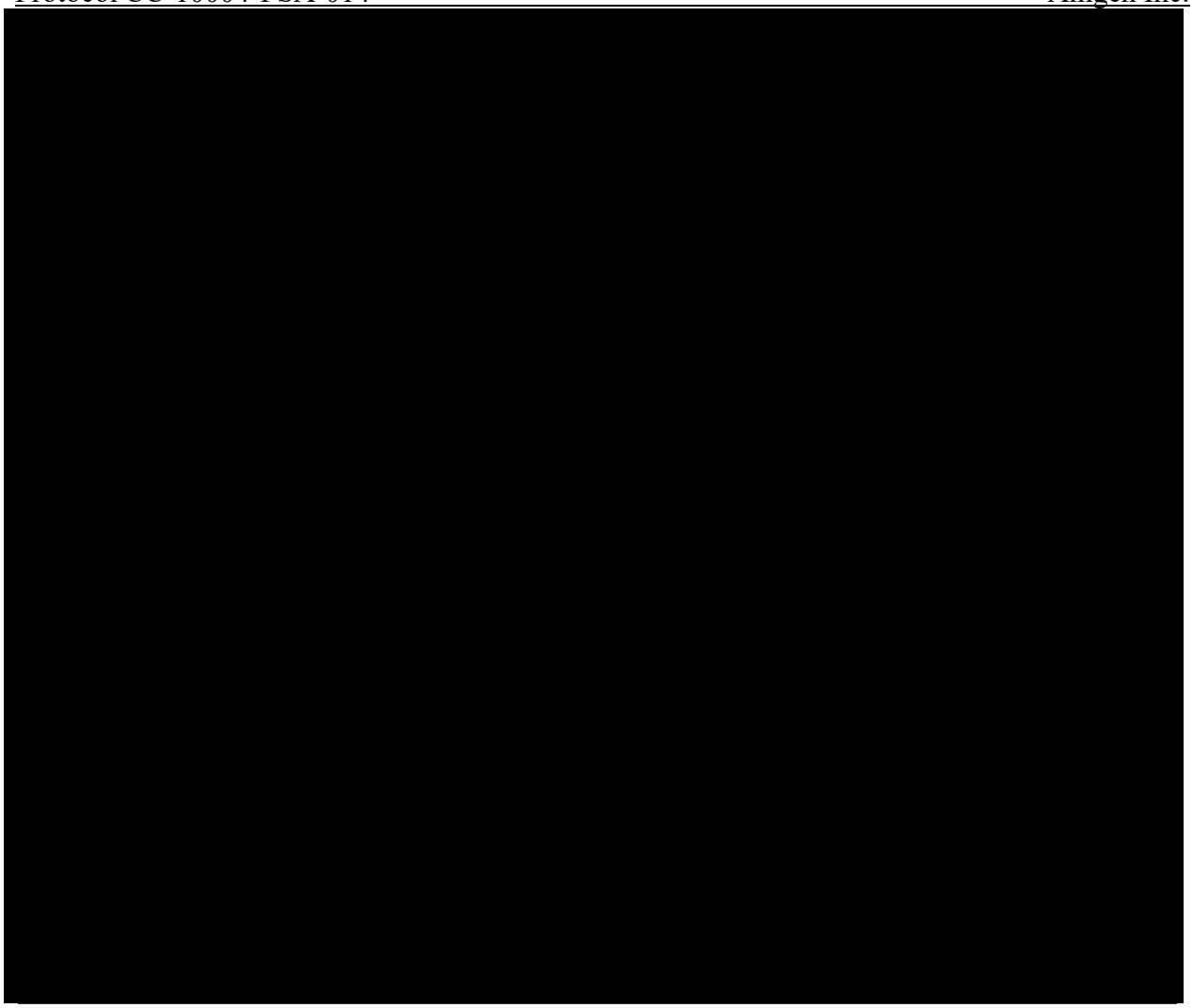
2. Missing data imputation

If one of the 12 NRS values composing the PsAID is missing, the imputation is as follows:

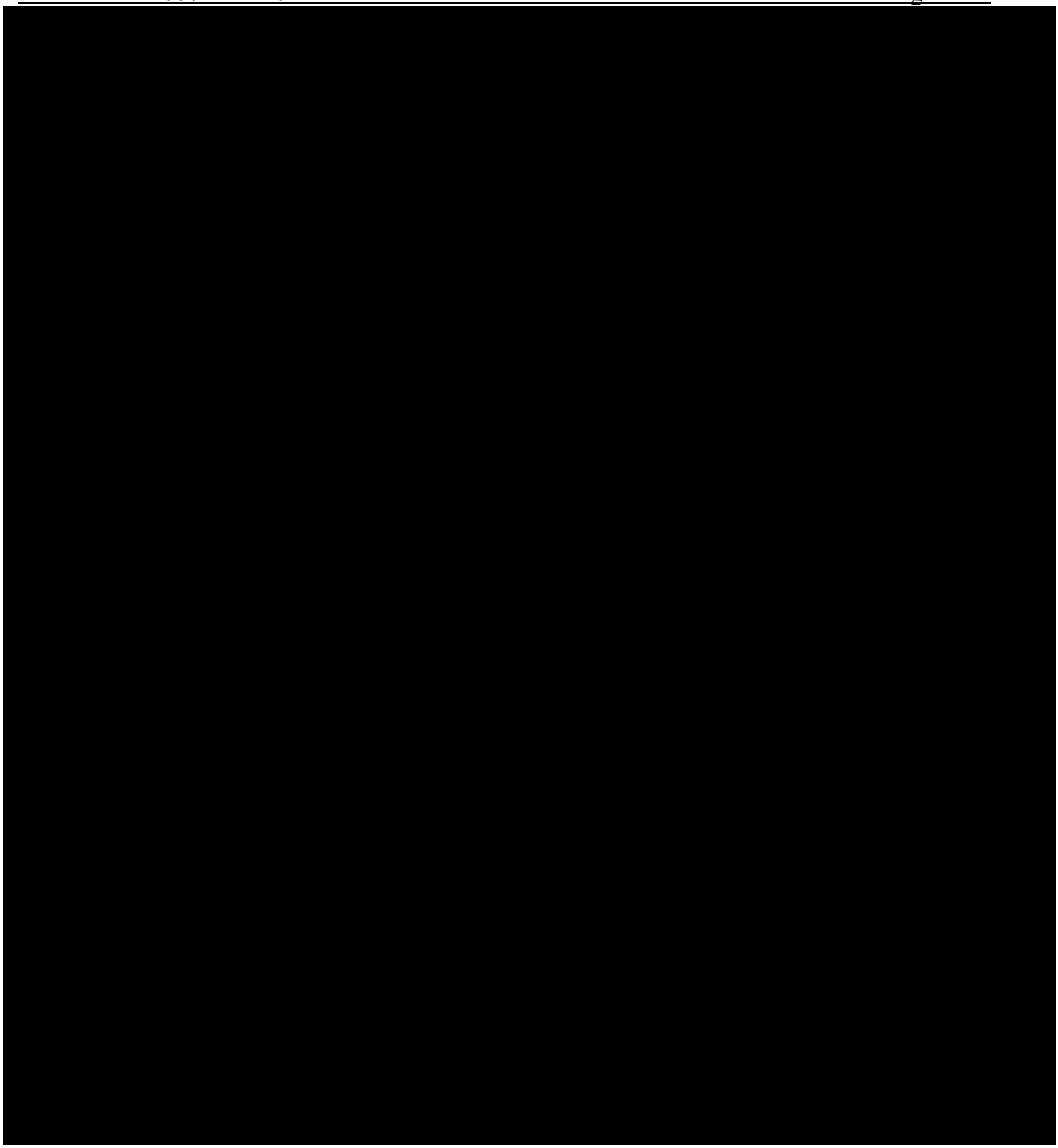
a. calculate the mean value of the 11 other (non-missing) NRS values (range, 0-10)
b. impute this value for the missing NRS value
c. then, calculate the PsAID score as explained above.

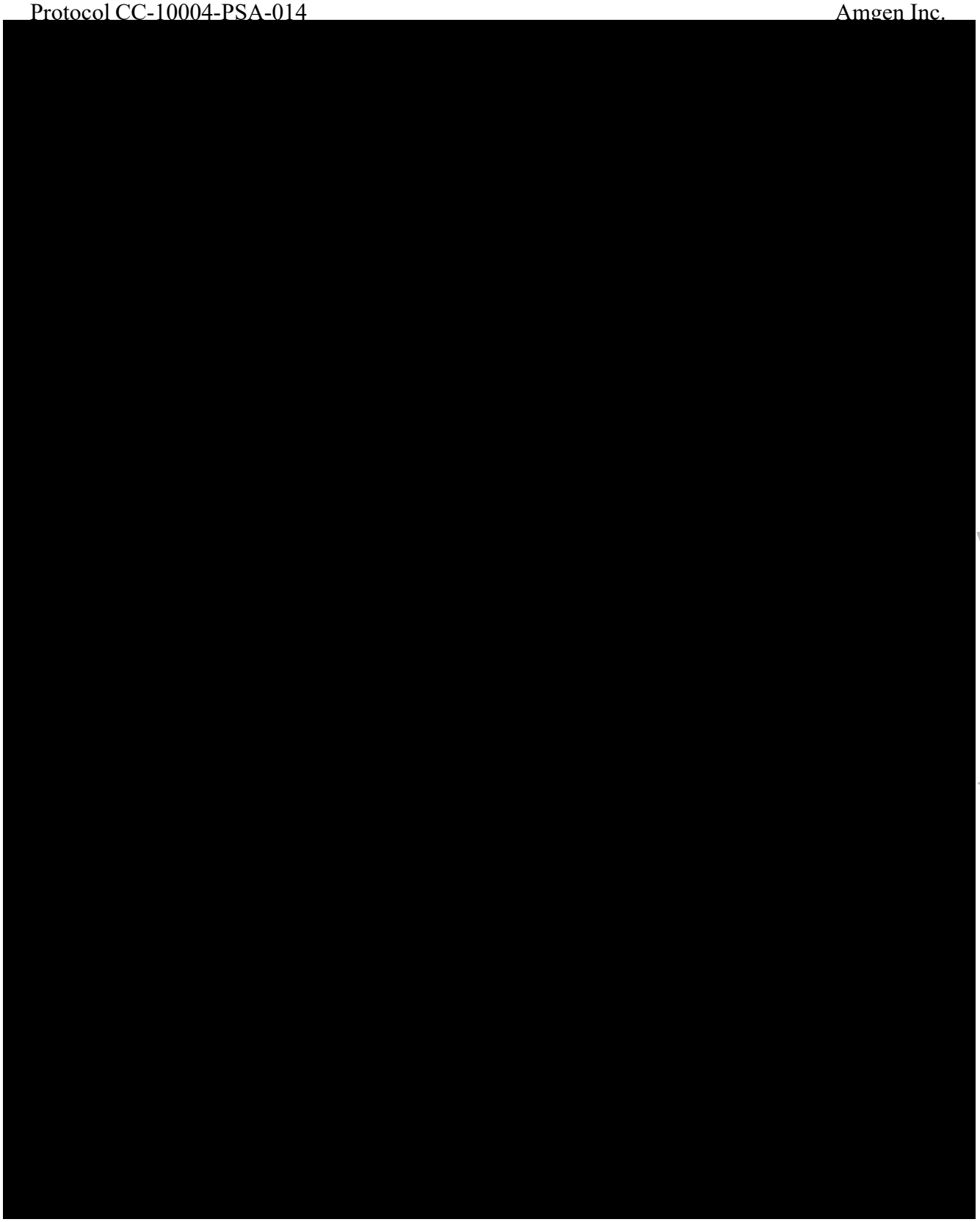
If 2 or more of the NRS values are missing, the PsAID score is considered a missing value (no imputation).

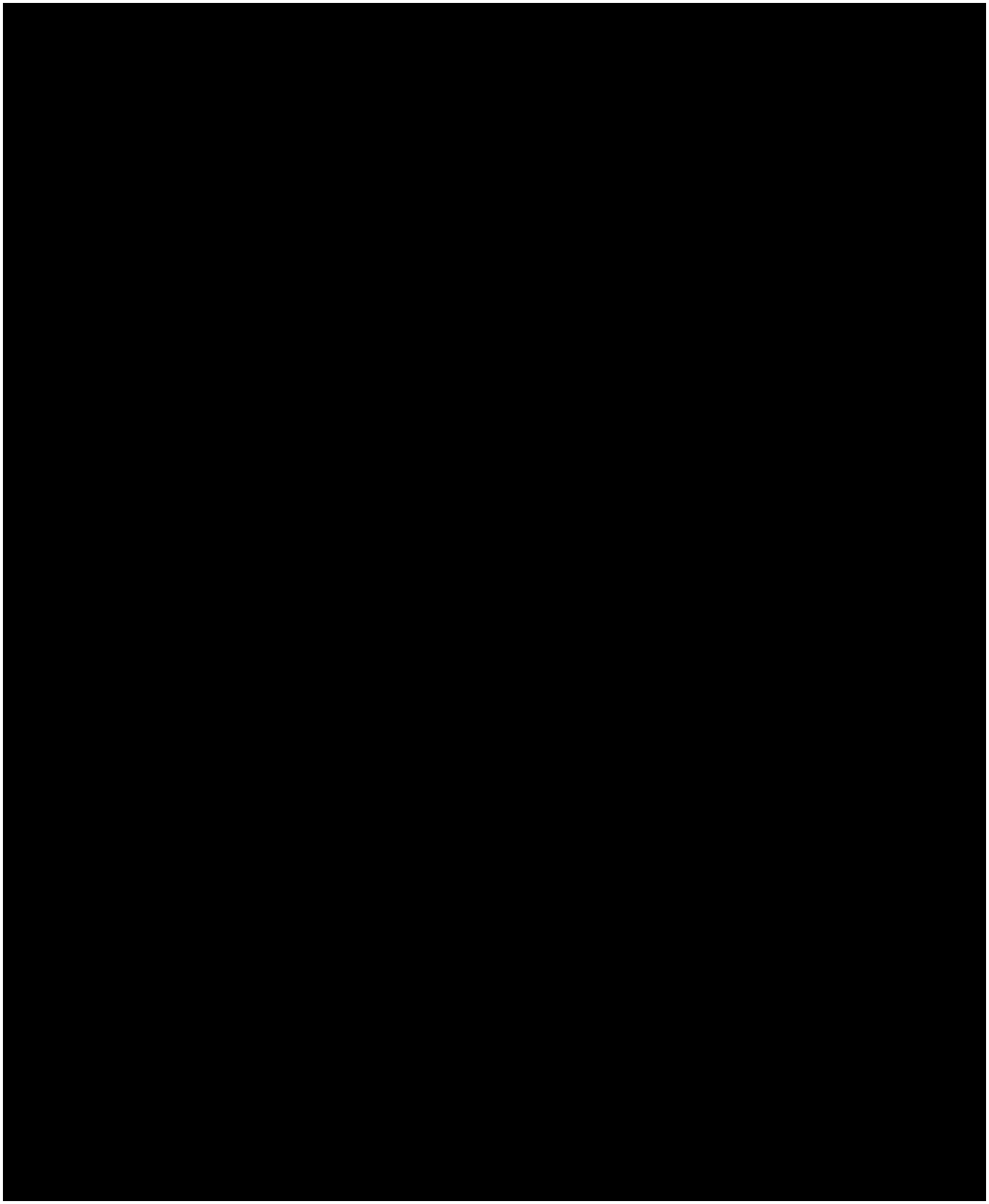
[redacted]

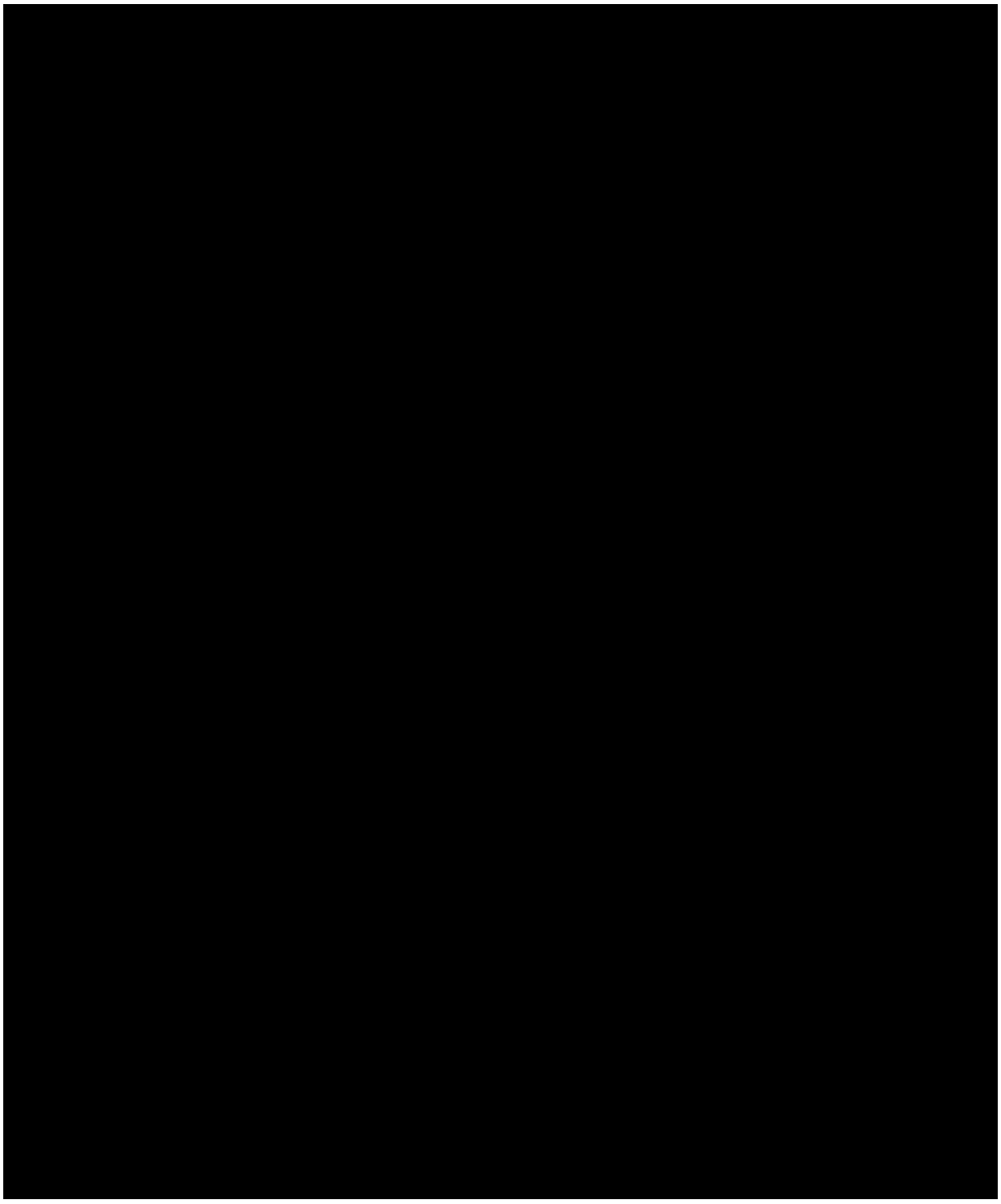


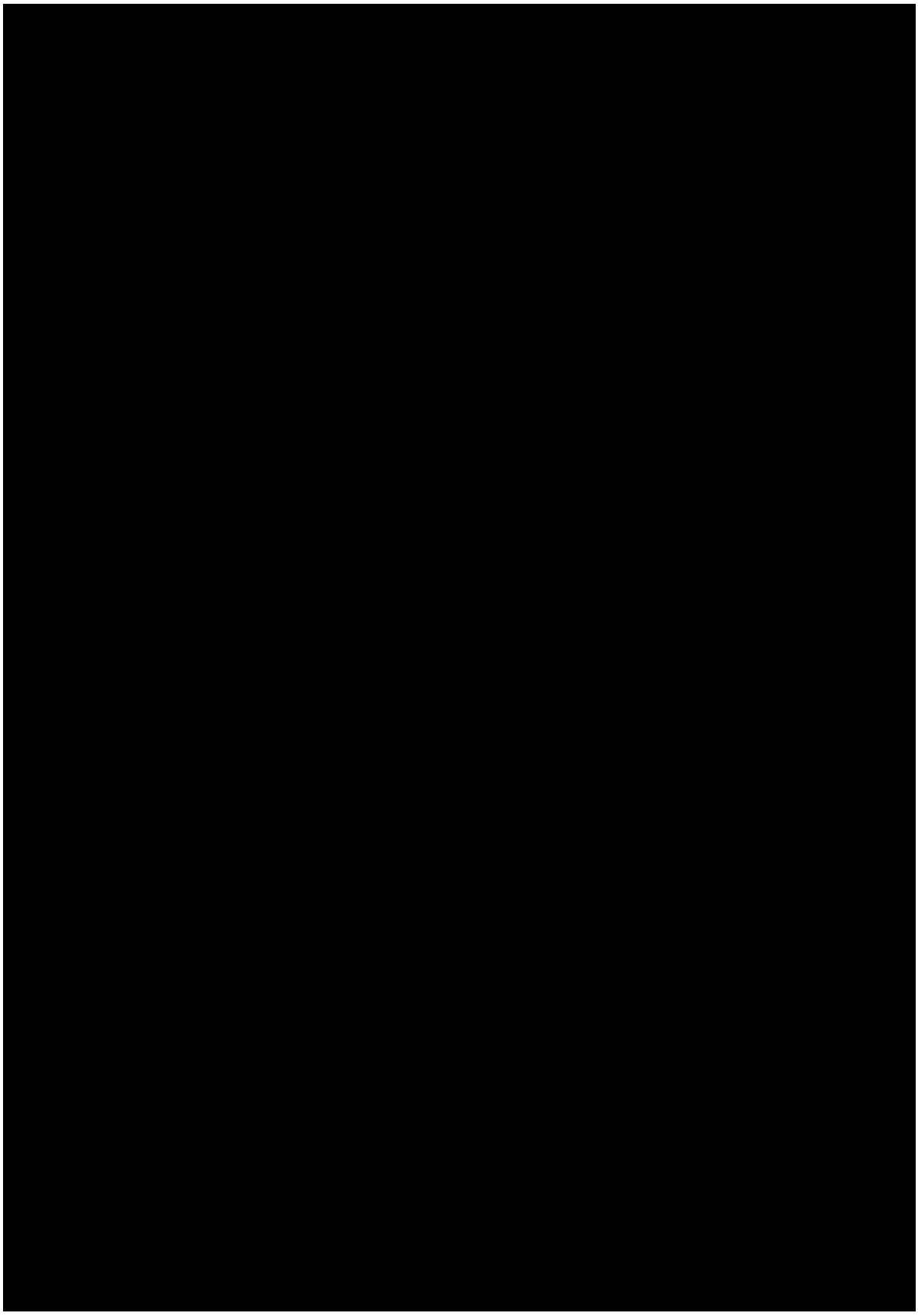
[redacted]











APPENDIX P. PSORIATIC ARTHRITIS MAGNETIC RESONANCE IMAGING SCORING SYSTEM (PSAMRIS)

Sheet for PsAMRIS scoring of MRIs of PsA hands (Version of July 24, 2008)

Patient name and ID:_____Date of MRI timepoint 1:_____ Date of MRI timepoint 2:_____

Centre where MRI was performed: _____

Scorer's name: _____ Date of scoring:_____ Centre where MRI was evaluated: _____

Sequences scored: _____

		2. finger		3. finger		4. finger		5. finger	
M. MCP JOINT REGION									
Time-point		1	2	1	2	1	2	1	2
Synovitis *(score 0-3)*									
Flexor tenosynovitis *(score 0-3)*									
Periarticular inflammation *(score 0 or 1)*	Volar								
	Dorsal								
Bone oedema *(score 0-3)*	Proximal (M1)								
	Distal (M2)								
Bone erosion *(score 0-10)*	Proximal (M1)								
	Distal (M2)								
Bone proliferation *(score 0 or1)*									
P. PIP JOINT REGION									
Time-point		1	2	1	2	1	2	1	2
Synovitis *(score 0-3)*									
Flexor tenosynovitis *(score 0-3)*									
Periarticular inflammation *(score 0 or 1)*	Palmar								
	Dorsal								
Bone oedema score *(score 0-3)*	Proximal (P1)								
	Distal (P2)								
Bone erosion *(score 0-10)*	Proximal (P1)								
	Distal (P2)								
Bone proliferation (score 0 or 1)									
D. DIP JOINT REGION									
Time-point		1	2	1	2	1	2	1	2
Synovitis *(score 0-3)*									
Flexor tenosynovitis *(score 0-3)*									
Periarticular inflammation *(score 0 or 1)*	Palmar								
	Dorsal								
Bone oedema score *(score 0-3)*	Proximal (D1)								
	Distal (D2)								
Bone erosion *(score 0-10)*	Proximal (D1)								
	Distal (D2)								
Bone proliferation *(score 0 or1)*									

Please score as described below. Write NA for not possible to assess. Feel free to give additional comments, e.g. note particular location if considered relevant.

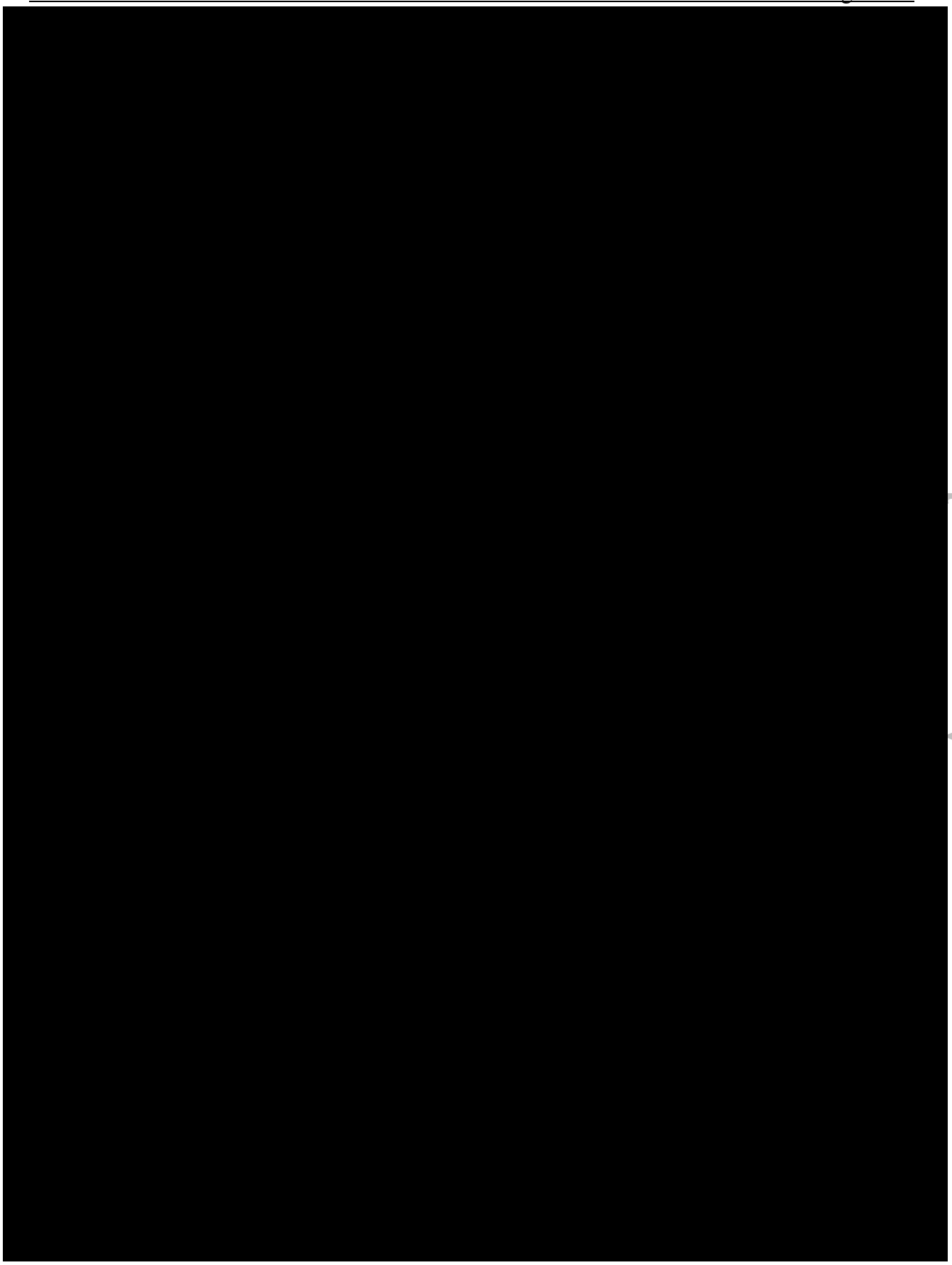
Synovitis: To be scored 0-3 per M, P, and D regions. Grading scale: Similar to RAMRIS.
Flexor tenosynovitis: To be scored 0-3 per M, P, and D regions.
Grading scale: Per maximal thickness of enhancing/bright signal on T1 weighted post-contrast /STIR or T2 weighted FS images, as follows: Grading scale: 0: none; 1: <½ tendon thickmess; 2: >= ½ and <1 tendon thickness; 3: >= 1 tendon thickness
Periarticular inflammation: To be scored 0-1 in dorsal part and 0-1 in palmar part of each M, P, and D region. Grading scale: 0: absent; 1: present.
Bone oedema: To be scored 0-3 per M1, M2, P1, P2, D1, and D2 regions. Grading scale: Similar to RAMRIS
Bone erosion: To be scored 0-10 per M1, M2, P1, P2, D1, and D2 regions. Grading scale: Similar to RAMRIS.
Bone proliferation: To be scored 0-1 in each M, P, and D regions. Grading scale: 0: absent; 1: present.

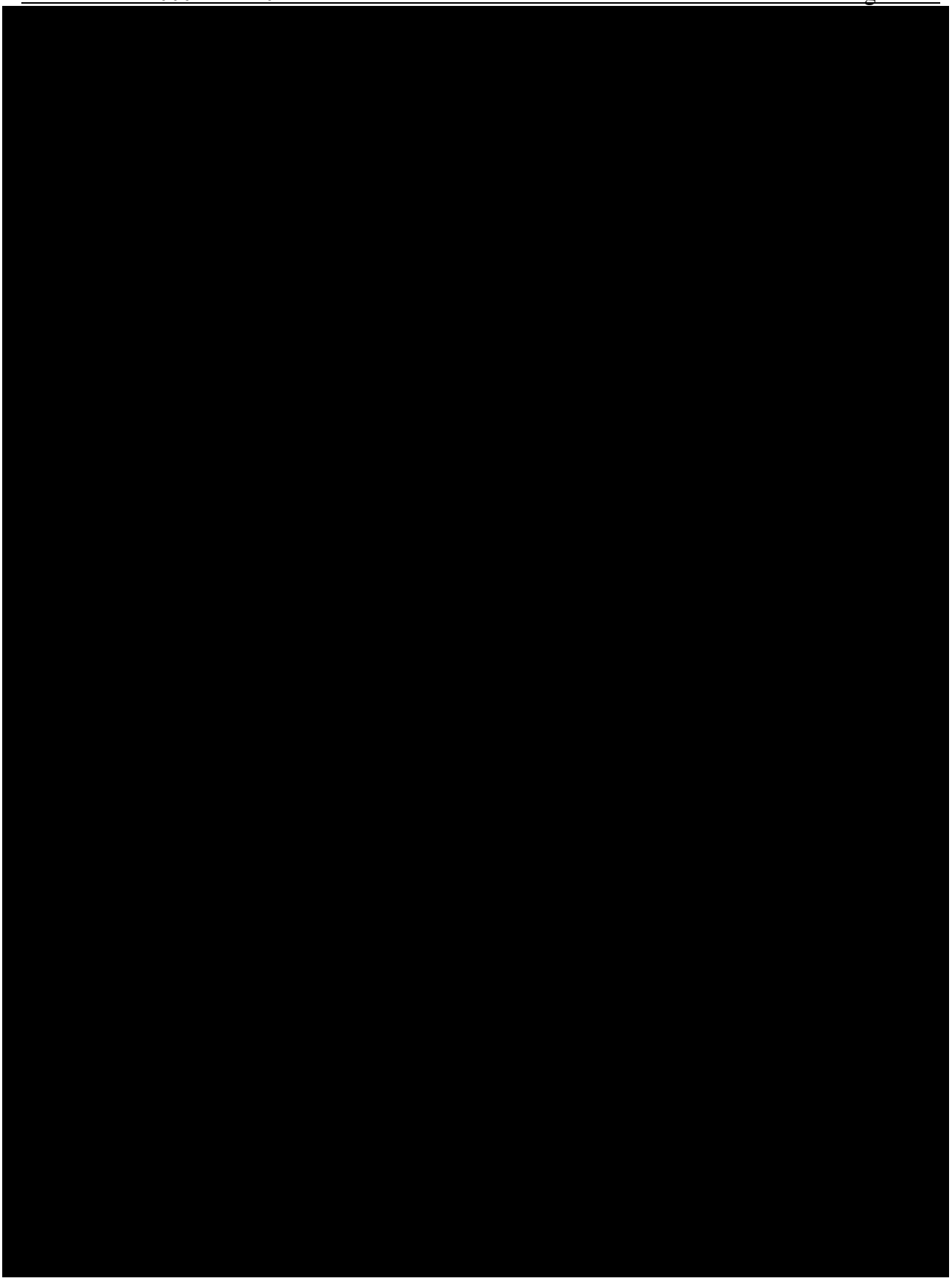
Space for Comments:_____
_____

Source: Glinatsi, 2015.

APPENDIX Q. WHOLE-BODY (WB)–MRI ASSESSMENTS

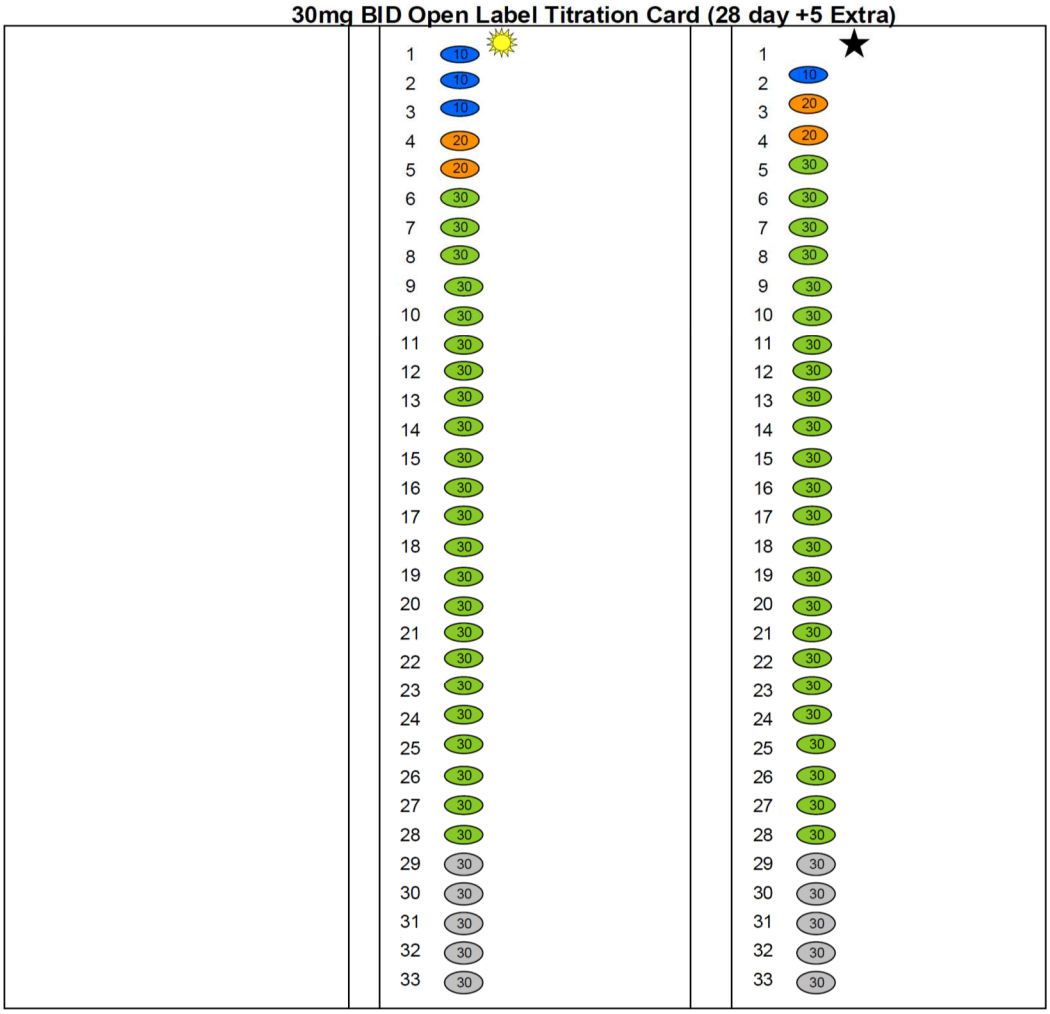
The final WB-MRI assessment protocol will be developed based on the prevalent recommendations by the OMERACT MRI in arthritis working group at the time of reading initiation. The final detailed MRI manual will be available before any reading starts.





APPENDIX S. BLISTER CARD CONFIGURATION FOR THE TITRATION PERIOD

The blister card figure displayed below is an approximate representation of the actual blister card, which may not have the exact number of extra tablets. Subjects must be instructed to use tablets from the blister card through the first 31 days and then switch to the bottle.



APPENDIX T. CONTRACEPTION EDUCATION

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

All females of childbearing potential[3] must use one of the approved contraceptive options as described in Section 4.3 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 screened for the study (for example, hormonal contraception should be initiated at least 28 days before screening).

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

[3] A female of childbearing potential 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). A tubal ligation alone is not sufficient to qualify a female as of non-childbearing potential.

APPENDIX U. SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

AMGEN CC-10004-PSA-014 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

Please refer to your site's Serious Adverse Event Report Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

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 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 **06** Persistent or significant disability /incapacity **08** Congenital anomaly / birth defect **07** Other medically important serious event

4. HOSPITALIZATION

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

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event				Action Taken with Product U1 Still being Administered U2 Permanently discontinued U3 Withheld	Lot # and Serial #
		Date of Dose Day Month Year	Dose	Route	Frequency		
Apremilast ☐ blinded ☐ open label							Lot #_____ ☐ Unknown Serial #_____ ☐ Unknown

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 02-April-2020*
Page 1 of 3

APPENDIX U: SAMPLE SERIOUS ADVERSE EVENT REPORT FORM (CONTINUED)

AMGEN CC-10004-PSA-014 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

APPENDIX U: SAMPLE SERIOUS ADVERSE EVENT REPORT FORM (CONTINUED)

AMGEN CC-10004-PSA-014 Apremilast (Otezla)	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event* *Reminder: Enter the SAE information into RAVE and then send the paper Serious Adverse Event Report*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 02-April-2020*
Page 3 of 3

APPENDIX V. PREGNANCY NOTIFICATION FORM

AMGEN® Pregnancy Notification Form

Please refer to your site's Pregnancy Notification Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. Case Administrative Information

Protocol/Study Number: CC-10004-PSA-014 (Apremilast/Ofezia)

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 W. LACTATION NOTIFICATION FORM

AMGEN Lactation Notification Form

Please refer to your site's Lactation Notification Form for Amgen Safety's Country Fax Number and if Fax is unavailable, Amgen Safety's Country email address.

1. Case Administrative Information

Protocol/Study Number: CC-10004-PSA-014 (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

– SUMMARY OF CHANGES –

A PHASE 4, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE IMPACT OF APREMILAST (CC-10004) ON MRI OUTCOMES IN SUBJECTS WITH PSORIATIC ARTHRITIS

AMENDMENT NO. 4

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSA-014**
ORIGINAL DATE:	**14 AUG 2018**
AMENDMENT No. 1 DATE:	**21 SEP 2018**
AMENDMENT No. 2 DATE:	**12 FEB 2019**
AMENDMENT No. 3 DATE:	**17 MAY 2019**
AMENDMENT No. 4 DATE:	**04 MAY 2020**
EudraCT NUMBER:	**2018-002748-10**
IND NUMBER:	**101761**
NCT NUMBER	**NCT03783026**

Contact Information:

Name: [redacted], MD

Title: Medical Director Global Development
Amgen Inc.

Address: Amgen Inc,
Amgen Center Dr, Thousand Oaks, CA 91320
USA

Phone: [redacted]

E-mail: [redacted]

Note: Only call Amgen Medical Information, if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Amgen Medical Information: 1- 800-77-AMGEN (1 800-772-6436)

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
[redacted], Vice President and Head of Immunology &Fibrosis Clinical Development **Printed Name of CelgeneTherapeutic Area Head and Title** By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable. **NOTE: Signed by Celgene based on Approval from Amgen Therapeutic Head** [redacted]	

1. JUSTIFICATION FOR AMENDMENT

The purpose of this amendment is to update the change in Sponsor, as well as key contact and emergency information, and to update safety reporting and product complaints to align with Amgen processes.

- All references to "Celgene Corporation" were removed and replaced with "Amgen Inc" and "Celgene" changed to "Amgen" throughout the protocol.
- Cover Pages were updated with Amgen contact information
- Section 10 Monitoring and Reporting of Adverse Events was updated to align with Amgen Global Drug Safety processes.
- Section 10.4 Pregnancy was modified according to the Amgen Global Drug Safety process:
    - Collection of Pregnancy Information and Infant Health Information
    - Collection of information: Male Subjects with Partners Who Become Pregnant
    - Collection of Lactation Information
- Section 10.5 Reporting of Serious Adverse Events was updated to include instructions for paper reporting of SAEs
- Section 12.1 Emergency Contact was updated with Amgen emergency contact information.
- Section 15.3 Product Complaint Section added

The amendment also includes minor clarifications and corrections to align with Amgen process:

- Section 7.5-Investigational Product Accountability
- Section 15.2Audits and Compliance
- Section 16 Publications.

– SUMMARY OF CHANGES –

AMENDMENT NO. 3

A PHASE 4, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE IMPACT OF APREMILAST (CC-10004) ON MRI OUTCOMES IN SUBJECTS WITH PSORIATIC ARTHRITIS

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSA-014**
ORIGINAL DATE:	**14 AUG 2018**
AMENDMENT No. 1 DATE:	**21 SEP 2018**
AMENDMENT No. 2 DATE:	**12 FEB 2019**
AMENDMENT No. 3 DATE:	**17 MAY 2019**
EudraCT NUMBER:	**2018-002748-10**
IND NUMBER:	**101761**

Contact Information:

Name:	[redacted]
Title:	Medical Director
Address:	PPDI 900 Perimeter Park Drive Morrisville, NC 27560
Phone:	[redacted]
E-mail:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted], Executive Director, Inflammation and Immunology Global Medical Affairs Rheumatology
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:

- All references to "approved product labeling" and "prescribing information" were removed.

  Based on comments from Health Authorities, there should be one reference safety information (RSI) for a trial. Therefore, Celgene clarifies that the investigator brochure (IB) is the identified RSI for this trial. The IB will be submitted to all sites and clearly identified as the RSI in the clinical trial application (CTA) package.

  Revised sections:

  – Section 1.2.2.2.2;

  – Section 7.1.

- Exclusion criteria #22 updated to include prior exposure to a tyk2 inhibitor, as prohibited medication.

The amendment also includes several other minor clarifications and corrections:

- References to the [redacted] were corrected to reflect the appropriate nomenclature of such subject-reported outcome questionnaire.

  Revised sections:

  – Protocol Summary;

  – Table of Contents;

  – Table 12;

  – Section 5 (Table 13);

  – Section 6.7.4;

  – Appendix A;

  – [redacted]

- The BASDAI questionnaire will be performed for all subjects, at the timepoints specified as per the Table of Events.

  Revised sections:

  – Section 5 (Table 13, footnote h).

- Quality of Life abbreviature (QoL) was removed from the text in all the instances it was placed together with "subject-reported outcomes", for clarity and consistency across different sections of the protocol.

  Revised sections:

  – Section 6.2;

  - Section 6.2.1;
  - Section 6.7.

- The word "electronic" was deleted in all the instances it was displayed right before the word CRF.

  Revised sections:

  - Section 7.2.1;
  - Section 8;
  - Section 8.1;
  - Section 10.1;
  - Section 10.2.1;
  - Section 14.2.

- The following abbreviations were inserted: EDC, LOCF, NRI, SRO, vs.

  Revised section:

  - Appendix A.

- CASPAR Criteria replaced with a corrected version that includes an additional footnote.

  Revised section:

  - Appendix B.

- Protocol number updated from CC-10004-PsA-014 to CC-10004-PSA-014 for consistency purposes.

  Revised sections:

  - Headers and footers throughout the document and the protocol title on Title Page.

– SUMMARY OF CHANGES –

AMENDMENT NO. 2

A PHASE 4, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE IMPACT OF APREMILAST (CC-10004) ON MRI OUTCOMES IN SUBJECTS WITH PSORIATIC ARTHRITIS

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PsA-014**
ORIGINAL DATE:	**14 AUG 2018**
AMENDMENT No. 1 DATE:	**21 SEP 2018**
AMENDMENT No. 2 DATE:	**12 FEB 2019**
EudraCT NUMBER:	**2018-002748-10**
IND NUMBER:	**101761**

Contact Information:

Name:	[redacted]
Title:	Medical Director
Address:	PPDI 900 Perimeter Park Drive Morrisville, NC 27560
Phone:	[redacted]
E-mail:	[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted], Executive Director, Inflammation and Immunology Global Medical Affairs Rheumatology
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:

- Medical Monitor/Emergency Contact Information text was modified.

  Change made to reflect PPD's (clinical research organization) responsible personnel.

  Revised section: Medical Monitor/Emergency Contact Information

- Deleted text: "Detailed information can be found in the Investigator's Brochure (IB)"

  As this is a Phase 4 study, approved product labeling or the IB (depending on regional regulations) should be used as the reference for additional information on apremilast in this approved indication. Since selected countries, as per local regulations, will have the product label as the main document for additional information on apremilast, the reference to IB in isolation was deleted.

  Revised sections:

  - 1.2.2.1.1, Efficacy Data From Phase 3 Studies CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2), and CC-10004-PSA-004 (Palace 3) Through Week 24 in Subjects With Prior csDMARDs and/or Biologic DMARDs
  - 1.2.2.1.2, Efficacy Data From Phase 3 Study CC-10004-PSA-005 (Palace 4) Through Week 24 in Subjects Naïve to csDMARDs and Biologic DMARDs
  - 1.2.2.1.3, Efficacy Data From Phase 3 CC–10004-PSA-006 (ACTIVE) Through Week 24 in Subjects With an Inadequate Response to ≤1 csDMARDs and Who Received Apremilast Monotherapy

- Added text: "/approved product labeling"

  As this is a Phase 4 study, approved product labeling or the IB (depending on regional regulations) should be used as the reference for additional information on apremilast in this approved indication.

  Revised sections:

  - Section 1.2.2.2.2, Long-term Safety Data From CC-10004-PSA-006 (ACTIVE), CC-10004-PSA-002 (Palace 1), CC-10004-PSA-003 (Palace 2) and CC-10004-PSA-004 (Palace 3)
  - Appendix T, Contraception Education

- A note was added to inclusion criterion #17.

  Addition to highlight that option 2 may not be considered as highly effective contraceptive measures in all countries.

  Revised section: Section 4.3 Inclusion Criteria

- In exclusion criterion #1, "history of hypersensitivity to gadolinium contrast agent" was added. In exclusion criterion #8, the word "hypersensitivity" was added.

Exclusion criterion #9 was added: "History of rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption".

Additions made to comply with requests from European Health Authorities.

Revised section: Section 4.4 Exclusion Criteria

- The Table of Events was updated to reflect: Weight will be captured at every visit; [redacted].

  Weight will now be captured at every visit to comply with the request~~ed~~ from European Health Authorities. Other changes made for consistency with other sections of the protocol.

  Revised section: Section 5, Table of Events (Table 13)

- Demographics: "initials" deleted; "date" substituted by "year" of birth, for consistency with CRF; Contraception Education: reference to Section 4.3 and Appendix T were added; Urinalysis: "a urine dipstick may be used" deleted; 4) Chemistry panel: "creatinine clearance added. Changes made for consistency with other sections of the protocol.

  Revised section: Section 6.1, Screening Period

- Weight: reference to Section 6.5.2 was added; Assessment of diarrhea: reference to Section 6.5.5 was added; Contraception Education: reference to Section 4.3 and Appendix T were added; Urinalysis: "a urine dipstick may be used" deleted; Chemistry panel: "creatinine clearance added; "MRI assessments" moved to same bullet point as "Efficacy assessments" for consistency with protocol sections.

  Revised section: Section 6.2, Treatment Period

- Added "End of Treatment" for compliance with protocol template; Urinalysis: "a urine dipstick may be used" deleted; "MRI assessments" moved to same bullet point as "Efficacy assessments" for consistency with protocol sections.

  Revised section: Section 6.2.1 Early termination/End of Treatment

- Cut-offs for cDAPSA put in bullet points for clarity.

  Revised section: Section 6.4.5.9, Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA)

- Text was revised to delete reference to SMT, for consistency with wording in Phase 4 protocols across Rheumatology and Dermatology, as approved by Safety team.

  Revised section: Section 6.5, Safety Assessments

- A paragraph was added to reference country guidelines for pregnancy testing.

  Revised section: Section 6.5.1, Serum and Urine Pregnancy Tests for FCBP

- Weight will now be captured at every visit. A paragraph was added for consideration of study treatment discontinuation ~~of study treatment~~ in the event of unexplained and clinically significant weight loss.

  Revised section: Section 6.5.2, Vital Signs, Height and Weight

- A paragraph was added as a recommendation for study treatment discontinuation in the event of new/worsening psychiatric symptoms or suicidal ideation/attempt.

  Addition made to comply with European Health Authorities' requests.

  Revised section: Section 6.5.4, Psychiatric Evaluation

- A section dedicated to "Diarrhea, Nausea and Vomiting" was added, including a statement that "discontinuation of study treatment may be necessary if severe diarrhea, nausea and vomiting occur".

  Addition made to comply with European Health Authorities requests.

  Revised section: Section 6.5.5, Diarrhea, Nausea and Vomiting

- Text revised to add "creatinine clearance".

  Revised section: Section 6.5.7, Clinical Laboratory Evaluations

- Text revised to reflect new safety gateway process, as agreed upon by the Safety team. Paragraphs referencing diarrhea were moved to newly created section 6.5.5 "Diarrhea, Nausea and Vomiting".

  Revised section: Section 6.5.8, Adverse Events

- "Concomitant Medications Not Recommended" section was added.

  Addition was made to comply with European Health Authorities, for consistency with apremilast's label.

  Revised section: Section 8.2, Concomitant Medications Not Recommended

- The word "violation" was substituted by "deviation" for compliance with current SOP.

  Revised section: Section 9.2, Study Population Definitions

- Text was revised to reflect new safety gateway process, as agreed upon by the Safety team.

  Revised section: Section 10, Adverse Events (10.1, 10.4, 10.5, 10.5.1)

- Text was revised to reflect subjects' right to withdraw from the study (and proper documentation), as well as the importance of early termination assessments.

  Revised section: Section 11.1, Treatment Discontinuation

- HAQ-DI questionnaire was updated to display validated version used in the eRT tablet which the subjects will be responding to.

  Revised section: Appendix E, Health Assessment Questionnaire–Disability Index (HAQ-DI)

- A paragraph was added to reference the evaluation of the number of affected digits, for completion and consistency between Phase 4 PsA protocols.

  Revised section: Appendix H, Leeds Dactylitis Index (LDI)

- The BASDAI questionnaire was updated to display validated version used in the eRT tablet subjects will be responding to.

  Revised section: Appendix J, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

- Questions 9, 10 and 11 had the text near the NRS extremes revised, to display the exact language in the validated version of the questionnaire, which is used in the eRT tablet subjects will be responding to. Also, Scoring and Calculation Rules were updated to display PsAID-12 accurate multiplying factors for each domain, as agreed upon by Biostats team.

  Revised section: Appendix K, Psoriatic Arthritis Impact of Disease 12-domain questionnaire (PsAID-12)

- A paragraph was added to clarify that the figure displayed is an approximate representation of the actual blister card and to better explain the transition from blister card to bottle.

  Revised section: Appendix S, Blister Card Configuration for the Titration Period

– SUMMARY OF CHANGES –

AMENDMENT NO. 1

A PHASE 4, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE IMPACT OF APREMILAST (CC-10004) ON MRI OUTCOMES IN SUBJECTS WITH PSORIATIC ARTHRITIS

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PsA-014-MOSAIC™**
ORIGINAL DATE:	**14 AUG 2018**
AMENDMENT No. 1 DATE:	**21 SEP 2018**
EudraCT NUMBER:	**2018-002748-10**
IND NUMBER:	**101761**

Contact Information:

Name: [redacted], MD

Title: Medical Director

Address: Celgene Corporation
86 Morris Avenue
Summit, NJ `07901 USA

Phone: [redacted]

E-mail:

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head dd mmm yyyy
[redacted], Executive Director, Inflammation and Immunology Global Medical Affairs Rheumatology
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:

- 14-3-3 eta biomarker was deleted from the protocol since it will no longer be part of the study, due to feasibility issues. Revised Sections: Section 2, Section 5, Section 6.2 and Section 6.6.
- Section 6.4.1 was revised to specify the timeframes within which the Magnetic Resonance Imaging (MRI) assessments should be performed.
- Section 10.5.1 was revised to reflect the current safety language.
- Appendix S was revised to better represent this study's design (open label, single-arm trial). The blister card configuration for the titration period was replaced by a card with no placebo.