A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH EARLY, OLIGOARTICULAR PSORIATIC ARTHRITIS DESPITE INITIAL STABLE TREATMENT WITH EITHER NSAIDS AND/OR ≤ 1 CONVENTIONAL SYNTHETIC DMARD

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Printed Name of Site Principal Investigator **Institution Name:**_____	

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Amgen representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH), Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

PROTOCOL SUMMARY

Study Title

A phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of apremilast (CC-10004) in subjects with early, oligoarticular psoriatic arthritis despite initial stable treatment with either non-steroidal anti-inflammatory drugs (NSAIDs) and/or ≤1 conventional synthetic disease-modifying antirheumatic drugs (DMARD).

Indication

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatologic disorder characterized by inflammatory 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 up to 50% of patients with PsA. In addition, PsA is associated with enthesitis and dactylitis, which are common to SpA. Finally, the majority of patients with PsA are negative for rheumatoid factor (RF) (Gladman, 2005; Kruithof, 2005; Roberts, 1976).

Asymmetrical oligoarthritis sometimes involving distal interphalangeal (DIP) joints, is a frequent form of PsA (Ritchlin, 2017). Despite this, very little is known with respect to the burden of disease and the appropriate management of patients with asymmetrical oligoarthritis. Indeed, there is a paucity of data on the treatment of patients with oligoarthritis since published clinical trials focus on polyarticular forms of the disease. Likewise, treatment recommendations tend to also focus on polyarticular forms (Gossec, 2016). Knowledge regarding the efficacy of drugs in oligoarticular forms would be of great value to clinicians.

Standard classification criteria of 'oligoarticular PsA' for use in clinical studies remain to be established. In recent studies, patients with $\leq$ 4 active joint counts (tender and/or swollen) at baseline were classified as oligoarticular (Coates, 2013; Helliwell, 2007; Jones, 1994; Kane, 2003). Using this definition, the proportion of subjects with oligoarthritis appears to range from 14% to 63%, the higher values being observed in patients with shorter disease duration. It is believed that the evolution of the disease, from oligoarthritis to polyarthritis, accounts for the lower proportion of patients with oligoarthritis in populations with longer disease duration. Indeed, results from the long-term follow-up of PsA cohorts, including subjects with short articular symptoms duration (< 24 months), showed that about two third of subjects presenting with an oligoarthritic disease at baseline evolved into the polyarticular sub-type over time (Jones, 1994). In addition, treatments with conventional synthetic DMARDs (csDMARDs) were associated with the reclassification of subjects, from polyarthritic at the initial clinical presentation into oligoarthritic at follow-up (Kane, 2003). Such oligoarticular patients may be associated with residual joints that are less responsive to treatment when compared to patients with recent onset of oligoarthritis. Taken together, these observations suggest that patients with oligoarticular form of PsA but with long standing disease duration and previous response to anti-rheumatic treatments may be less sensitive to further improvement after additional therapies than earlier populations who are mainly csDMARDs-naive. Therefore, the current study will enroll subjects with short disease duration and limited exposure to prior NSAIDs and/or csDMARDs.

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 (cAMP) 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 TNF-α, IL-17, IL-23, IL-6, IL-8, MIP-1β, and MCP-1, as well as increases in anti-inflammatory mediators, including IL-10 and the IL-1 receptor antagonist. It is believed, therefore, that apremilast exerts its therapeutic benefits through the modulation of multiple inflammatory pathways (Schafer, 2015).

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.

Apremilast has been shown to be safe and efficacious in reducing signs and symptoms of PsA, as well as improving physical function (Cutolo, 2016; Edwards, 2016; Kavanaugh, 2014; Nash, 2018). Like most agents, the clinical development program of apremilast was restricted to subjects with ≥ 3 swollen and ≥ 3 tender joints at baseline. This allowed for a limited proportion of subjects with asymmetric oligoarthritis at study entry. Consequently, the safety and efficacy of apremilast in patients with oligoarthritis remains to be further investigated.

The current study is designed to evaluate the benefit:risk profile of apremilast in subjects with an early diagnosis of PsA (≤ 5 years since **signs and symptoms began**), presenting with oligoarthritis, despite initial stable treatments with either NSAIDs and/or ≤ 1 csDMARD (methotrexate [MTX] or sulfasalazine [SSZ]).

Objectives

Primary Objective

- To evaluate the efficacy of apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs in subjects with early oligoarticular PsA, assessed by modified MDA (MDA-Joints).

Secondary Objectives

- To evaluate the impact of treatment with apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs on disease activity in subjects with early oligoarticular PsA,
- To evaluate the impact of apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs on patient reported outcomes (PROs) in subjects with early oligoarticular PsA,
- To evaluate the safety and tolerability of apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs in subjects with early oligoarticular PsA.

Exploratory Objectives

Study Design

This is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of apremilast (CC-10004) in subjects with early (≤ 5 years since **signs and symptoms began**) oligoarticular PsA **(according to Classification Criteria for Psoriatic Arthritis [CASPAR] criteria)**, despite treatment with either NSAIDs and/or ≤ **2** csDMARD. Approximately **285** subjects will be randomized (2:1) to apremilast 30 mg BID or placebo. Treatment assignment will be stratified via an Interactive Web Response System (IWRS) based on concomitant use of glucocorticosteroids at baseline (yes/no) and prior/concomitant use of a csDMARD, either MTX or SSZ, (ie, csDMARD-naïve; csDMARD use prior to baseline [treatment not continued]; or csDMARD use prior to and concomitant at baseline). The number of subjects who are csDMARD-naïve is targeted to comprise up to 50 % of the subjects enrolled in the study. Given that this is a phase 4 study, all subjects are required to meet the existing apremilast regulatory labeling conditions specific to the countries where enrollment will take place (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada). There is no planned protocol extension following the end of the study.

Subjects will be enrolled in this study if they received ≤ **2** prior csDMARD for the treatment of PsA. All subjects will be permitted to take NSAIDs and/or low-dose oral glucocorticosteroids (prednisone ≤ 10 mg/day or equivalent) throughout the study. The NSAIDs and low-dose oral glucocorticosteroids must be administered as a stable regimen for at least 2 weeks and 4 weeks prior to the Baseline Visit, respectively. A maximum of 1 concomitant use of csDMARD will be permitted if the subject is on a stable regimen for at least 3 months prior to the Baseline Visit. Stable doses of glucocorticosteroids, NSAIDs, and a csDMARD must be continued from the Baseline Visit through the Week 24 Visit. During this phase of the study, any change in dose, 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 glucocorticosteroids, NSAIDs, or csDMARDs may be adjusted as clinically required.

Subjects with prior exposure to biologic DMARD (bDMARD) and/or JAK-inhibitors will not be allowed in the study.

This is a 56-week study. Subjects will have up to 4 weeks in the Screening Phase, followed by 24 weeks in the Double-blind, Placebo-controlled Treatment Phase, which provides an

opportunity for "early escape" at Week 16. At the Week 24 Visit, subjects will be offered to enter the Active-treatment Extension Phase. All subjects enrolled in the Extension Phase will receive treatment with apremilast (30 mg BID) until the end of the study (ie, up to the Week 48 Visit) or until early discontinuation.

Beginning at the Week 28 Visit, all subjects in the Extension Phase will be dispensed open-label apremilast (30 mg BID) in high-density polyethylene (HDPE) bottles. The original treatment assignments (apremilast 30 mg BID or placebo) will remain blinded until the end of the study (Section 3.1). Subjects may also discontinue at any time during the study.

The study will consist of 4 phases:

- Screening Phase – up to 4 weeks
- Randomized, Double-blind, Placebo-controlled Treatment Phase – Weeks 0 to 24. Henceforth, this will be referred to as the Placebo-controlled Phase.
  - Subjects will be randomly assigned in a 2:1 ratio to either apremilast 30 mg BID or placebo. Subjects randomized to apremilast will be dose-titrated in a blinded fashion.
  - Dose titration is described in Study Treatments, Section 7.2 and Section 7.3.
  - Early Escape: Subjects with no improvement in SJC (sentinel joints) at Week 16 are eligible for early escape, at the discretion of the Investigator and will receive apremilast 30 mg BID. The joints monitored for early escape must be the "sentinel joints" (ie, the joints affected at baseline).
  - Placebo-treated subjects who escape early will be transitioned to apremilast 30 mg BID in a blinded fashion via an Interactive Web Response System (IWRS), while apremilast-treated subjects will remain on their original treatment assignment. Placebo-treated subjects will be dose-titrated in a blinded fashion.
  - All subjects who complete this 24-week treatment phase will have the option to enter the Active-treatment Extension Phase.
- Active-treatment Extension Phase – Week 24 to Week 48. Henceforth, this will be referred to as the Extension Phase.
  - All subjects will receive apremilast 30 mg BID until the completion of the study (ie, up to the Week 48 Visit). The remaining placebo-treated subjects will be dose-titrated in a blinded fashion.
  - Beginning at the Week 28 Visit, all subjects in the Extension Phase will be dispensed open-label apremilast (30 mg BID) as described in Study Treatments and Section 7.3.
- Post-treatment Observational Follow-up Phase – up to 4 weeks. Henceforth this will be referred to as the Observational Follow-up Phase.
  - All subjects who complete the Placebo-controlled Phase, the Extension Phase or prematurely discontinued from the study will participate in the 4-week Observational Follow-up Phase.

- The Observational Follow-up Visit should be performed 4 weeks after the last dose of investigational product (IP) **(± 7 days)**.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP).

Study Population

The study population will consist of male or female subjects, ≥ 18 years of age at the time of signing the informed consent form (ICF), with early (≤ 5 years since **signs and symptoms began**) oligoarthritis (> 1 swollen joint [SJ] but ≤ 4 SJs, and > 1 tender joint [TJ] but ≤ 4 TJs at the Screening Visit and confirmed prior to randomization at the Baseline Visit), despite prior treatment with either NSAIDs (stable ≥ 2 weeks prior to the Baseline Visit) and/or ≤ **2** csDMARD (stable regimen for ≥ 3 months prior to the Baseline Visit) for the treatment of PsA. See Inclusion Criteria, Section 4.2 and Permitted Concomitant Medications, Section 8.1 for details describing allowed PsA medications and dosing regimens. At Screening, subjects must have a documented diagnosis of PsA, based on the CASPAR, with a disease duration since diagnosis ≥ 3 months and ≤ 5 years. Subjects with prior exposure to biologic DMARD (bDMARD) and/or JAK-inhibitors will not be allowed in the study.

No adjustment to NSAIDs or csDMARD dosing regimens will be allowed until Week 24. Between Week 24 and Week 48, dosing of concomitant medications may be adjusted as clinically required. The complete list of Inclusion and Exclusion criteria can be found in Section 4.2 and Section 4.3, respectively. Additional allowed PsA medications (including glucocorticosteroids, MTX and SSZ) and dosing regimens are described in Section 8.1.

Length of Study

Subjects will spend up to a total of 56 weeks in this study, up to 28 days (approximately, 4 weeks) in the Screening Phase, 24 weeks in the Placebo-controlled Phase, 24 weeks in the Extension 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

Eligible subjects will enter the Placebo-controlled Phase at the Baseline Visit. Subjects will be assigned randomly to apremilast 30 mg twice daily (BID) or placebo BID. Subjects are to take investigational product (IP), as designated in the treatment card, twice daily (morning and evening, approximately 12 hours apart, with or without food).

With the aim to mitigate potential dose-related side effects associated with apremilast, such as headache and gastrointestinal (GI) disturbances, apremilast-treated subjects will be dose-titrated from 10 mg BID to 20 mg BID to 30 mg BID over the first 5 days of treatment (Table 14). Subjects assigned to placebo will receive 10-, 20-, and 30-mg placebo tablets in blister cards (treatment cards) which are identical in appearance to the corresponding strength apremilast tablets. Apremilast will be provided in blister cards as either 10 mg, 20 mg or 30 mg tablets. The

5-day titration period will also be initiated for the placebo arm after the following visits: the Baseline, Week 16 (early escape), and Week 24. The original treatment assignments (apremilast 30 mg BID or placebo) will remain blinded throughout the study.

At the Week 16 Visit, subjects with no improvement in SJC (sentinel joints) at Week 16 are eligible for early escape, at the discretion of the Investigator and will receive early escape treatment with apremilast 30 mg BID. The joints monitored for early escape must correspond to those affected at the Baseline Visit (sentinel joints). Refer to Section 4.2; Inclusion #6. Subjects will receive the following treatment:

- Subjects who were randomized to apremilast (30 mg BID) at the Baseline Visit will continue to take apremilast 30 mg BID.
- Subjects who were randomized to placebo at the Baseline Visit will be switched to receive apremilast (30 mg BID) and will be dose-titrated as described above.

After the Week 24 Visit, subjects will be offered to enter the Active treatment Extension Phase. All subjects enrolled in the Extension Phase will receive treatment with apremilast (30 mg BID) until the end of the study (ie, up to the Week 48 Visit) or until early discontinuation. Placebo subjects will be dose titrated. All subjects will receive treatment cards of identical appearance to maintain the blinding of the original treatment assignments (apremilast 30 mg BID or placebo).

Beginning at the Week 28 Visit, after placebo-treated subjects have completed the blinded titration period, all subjects in the Extension Phase will be dispensed open-label apremilast (BID) in high-density polyethylene (HDPE) bottles. Subjects must be clearly instructed to follow dosing instructions. The original treatment assignments (apremilast 30 mg BID or placebo) will remain blinded until the end of the study (Section 3.1). Subjects may also discontinue at any time during the study.

Overview of Key Efficacy Assessments

The following will be used for assessing efficacy:

- Modified Minimal Disease Activity (MDA-Joints)
  - Based on achieving ≤ 1 swollen joint count (SJC) and ≤ 1 tender joint count (TJC; 66/68 SJ/TJ counts), plus 3 out of 5 of the following cut-off values: Body Surface Area (BSA) ≤ 3%, Patient pain assessment (Visual analog scale [VAS]) ≤ 15, Patient global assessment of disease activity (VAS) ≤ 20, HAQ ≤ 0.5, Tender entheseal points ≤ 1 (Based on the Leeds Enthesitis Index - LEI).
- Swollen and Tender Joint Counts
- Evaluator's (Physician's) Global Assessments of Disease Activity on VAS scale
- Patient's (Subject's) Global Assessments of Disease Activity on VAS
- Patient's (Subject's) Pain Assessment on VAS
- Health Assessment Questionnaire – Disability Index (HAQ-DI)
- The Leeds Enthesitis Index (LEI)

[redacted]

[redacted]

- Number of digits affected by dactylitis
- Clinical Disease Activity in Psoriatic Arthritis (cDAPSA) remission score (cDAPSA≤4) or low disease activity score (4<cDAPSA≤13). cDAPSA calculation based on SJC, TJC (66/68 SJ/TJ counts), Patient pain assessment (VAS) and Patient global assessment of disease activity (VAS).
- Measure of Very Low Disease Activity (VLDA) defined as achieving ≤1 SJC and ≤1 TJC (66/68 SJ/TJ counts), plus all 5 of the following cut-off values: BSA ≤ 3%, Patient pain assessment (VAS) ≤ 15, Patient global assessment of disease activity (VAS) ≤ 20, HAQ ≤ 0.5, Tender entheseal points ≤ 1 (based on the Leeds Enthesitis index - LEI)
- Psoriatic Arthritis Disease Activity Score (PASDAS) to assess good or moderate response.
- Plaque psoriasis assessment by Body Surface Area (BSA)

[redacted]

Overview of Patients' Reported Outcomes

The following will be used for assessing health-related quality of life:

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

[redacted]

The following will be used for assessing safety:

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

Statistical Methods

Assuming a 15% dropout rate during the Randomized, Placebo-controlled, Double-blind Treatment Phase, a sample size of **approximately** [redacted] for the active and placebo groups, respectively, will have 80% power to detect a true 15% difference (30% versus 15%) in the proportions of subjects achieving the modified MDA between the treatment groups, using a chi-square test with a two-sided significance level of 0.05. The primary efficacy endpoint, proportion of subjects who achieve the modified MDA at Week 16, between the treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test, controlling for concomitant use of glucocorticosteroids at baseline (yes/no) and use of a csDMARD (csDMARD-naïve; csDMARD use prior to baseline; or csDMARD use prior to and concomitant at baseline).

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Psoriatic Arthritis

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatologic disorder characterized by inflammatory 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 up to 50% of patients with PsA. In addition, PsA is associated with enthesitis and dactylitis, which are features common to SpA. Finally, the majority of patients with PsA are negative for rheumatoid factor (RF) (Gladman, 2005; Kruithof, 2005; Roberts, 1976). Moll and Wright described five subgroups of PsA (Moll, 1973). These include distal interphalangeal (DIP) joint only, asymmetrical oligoarthritis, polyarthritis, spondylitis and arthritis mutilans. Among these five subtypes, asymmetrical oligoarthritis sometimes involving distal interphalangeal (DIP) joints, is a frequent form of PsA (Ritchlin, 2017). Very little is known with respect to the burden of disease, the performance of different measurement tools and the appropriate management of patients with oligoarthritis. Indeed, there is a paucity data on the treatment of patients with oligoarthritis, one reason being that published clinical trials focus on polyarticular forms of the disease. In addition, treatment recommendations tend to focus on polyarticular forms (Gossec, 2016). Knowledge regarding the efficacy of drugs in oligoarticular forms would be of great value to clinicians.

Standard classification criteria for use in clinical studies remain to be established. In recent studies, patients with $\leq$ 4 active joint counts (tender and/or swollen) at baseline were classified as oligoarthritic (Coates, 2013; Helliwell, 2007; Jones, 1994; Kane, 2003). Use of this definition in different studies, indicated that the proportion of subjects with oligoarthritis ranges from 14% to 63%, the higher values being observed in patients with shorter disease duration. It is believed that the evolution of the disease, from oligoarthritis to polyarthritis, accounts for the lower proportion of patients with oligoarthritis in populations with longer disease duration. Indeed, results from the long-term follow-up of PsA cohorts, including subjects with short articular symptoms duration (< 24 months), showed that about two-thirds of subjects presenting with an oligoarthritic disease at baseline evolved into the polyarticular sub-type over time (Jones, 1994). In addition, treatments with conventional synthetic DMARDs (csDMARDs) were associated with the reclassification of subjects, from polyarthritic at the initial clinical presentation into oligoarthritic at follow-up (Kane, 2003). Such oligoarticular patients may be associated with residual joints that are less responsive to treatment when compared to patients with recent onset of oligoarthritis. Taken together, these observations suggest that patients with oligoarticular form of PsA but with long standing disease duration and previous response to anti-rheumatic treatments may be less sensitive to further improvement after additional therapies than earlier populations who are mainly csDMARDs-naive. As a result, the current study will enroll subjects with short disease duration and limited exposure to prior nonsteroidal anti-inflammatory drugs (NSAIDs) and/or csDMARDs.

Results from the GRACE cohort (GRAPPA Composite Exercise) highlight the burden of disease of patients with oligoarthritis. The GRACE cohort enrolled 503 PsA patients, out of which 266

(53%) were classified with oligoarthritis. This subpopulation of patients reported other aspects of the disease, such as enthesitis (34% of the patients) and dactylitis (12% of patients). Limited skin involvement was observed in these patients, as shown by a median Psoriasis Area and Severity Index (PASI) score of 1.2 points. Noteworthy, when comparing subjects with mono/oligoarthritis to polyarthritis, subjects with mono/oligoarthritis were associated with lower levels of inflammation and lower proportions of subjects with erosive disease at follow-up (Lindqvist, 2008).

The results from the Tight Control of Psoriatic Arthritis (TICOPA) trial in patients with early and treatment-naive PsA allowed for the comparison of outcomes measures between subjects with oligoarthritis and polyarthritis. Patients with oligoarthritis were more likely to achieve minimal disease activity (MDA) as defined by Coates, et al (Coates, 2010) than those with polyarticular disease. Conversely, a significantly greater proportion of subjects with polyarthritis achieved 20% improvement in the American College of Rheumatology ACR criteria (ACR 20) when compared with those with oligoarthritis (Coates, 2016). Further analyses of the TICOPA trial has shown that both Psoriatic Arthritis Disease Activity Score (PASDAS) and Composite Psoriatic Disease Activity Index have limited ability to distinguish effects of therapy in the subgroup of study patients with oligoarthritis (Coates, 2017). The value of the Clinical Disease Activity in Psoriatic Arthritis score (cDAPSA) [without measuring C-reactive protein], alone or in comparison to the MDA, has not been extensively studied in this subset of PsA patients.

The limited performance of ACR20 response criteria reported in the TICOPA trial are inherent to the baseline level of disease activity associated with patients with oligoarthritis. This is partially explained by the limited discriminative ability of the ACR20 response criteria to report 20% changes in populations with limited number of joint counts at baseline. For example, for a subject with 1 SJ and 1 TJ at baseline, a 20% improvement would correspond to a 0.2 reduction in 1 swollen joint (SJ) and 1 tender joint (TJ). This is not assessable by clinical palpation, making this endpoint less desirable for the studied population. As a result, the primary endpoint of the current study will be based on a modification of the MDA.

1.2. Compound Background

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 (cAMP) 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 TNF-α, IL-17, IL-23, IL-6, IL-8, MIP-1β, and MCP-1, as well as increases in anti-inflammatory mediators, including IL-10 and the IL-1 receptor antagonist. It is believed, therefore, that apremilast exerts its therapeutic benefits through the modulation of multiple inflammatory pathways (Schafer, 2015).

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.

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

1.2.1. 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 DMARD-naive, DMARDs-experienced, biologic-naive, and biologic-experienced subjects (Table 1). The results from these studies indicated that apremilast is safe and effective, both as monotherapy and in combination with 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-naive and biologic-naive	Apremilast monotherapy vs. PBO	527
ACTIVE/ CC-10004-PSA -006	Maximum 1 prior csDMARD, biologic-naive	Apremilast monotherapy vs. PBO	219

1.2.1.1. Efficacy

1.2.1.1.1. 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]; (Kavanaugh, 2014; Cutolo, 2016; Edwards, 2016). The studies were similarly designed. Adult patients with active PsA (≥ 3 swollen and ≥ 3 tender joints) despite prior csDMARD and/or biologic tumor necrosis factor (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 concomitant methotrexate (MTX) (≤ 25 mg/week), sulfasalazine (SSZ [≤ 2 g/day]), leflunomide (LEF [≤ 20 mg/day]), low-dose oral corticosteroids (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 patients were randomized equally to placebo (N = 496), apremilast (APR) 20 twice daily (BID (N = 500), or APR 30 BID (N = 497). Placebo patients whose tender and swollen joints counts 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 patients 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 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 Week 16 and 24 among subjects with body surface area (BSA) for psoriasis ≥ 3 % at baseline.

Detailed information can be found in the Investigator's Brochure (IB).

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)*
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) **

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	
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; HAQ-DI = Health Assessment Questionnaire Disability Index; PASI 50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index; LOCF = last observation carried forward; NRI = nonresponder imputation; PASI 50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index; SE = standard error.

[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.

Note: ***$p < 0.001$ for apremilast versus placebo. **$p < 0.01$ for apremilast versus placebo. *$p < 0.05$ for apremilast versus placebo.

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 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.

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

The efficacy of apremilast in subjects naive to csDMARDs therapy was investigated in a multicenter, randomized, double-blinded, placebo-controlled Phase 3 study (CC-10004-PSA-005 [Palace 4]; Wells, 2018). 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 tender and swollen joint counts 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 Week 16 and 24 among subjects with BSA for psoriasis ≥ 3% at baseline.

Detailed information can be found in the IB.

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)***
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; HAQ-DI = Health Assessment Questionnaire Disability Index; PASI 50/75 = 50%/75% or greater improvement in the Psoriasis Area and Severity Index; LOCF = last observation carried forward; NRI = nonresponder imputation; SE = standard error.

[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.

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

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 Weeks 16 (FAS; LOCF), Study CC 10004 PSA-005

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

APR = apremilast; BID = twice daily; FAS = Full Analysis Set; LOCF = last observation carried forward; LS = least **squares**; 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.

1.2.1.1.3. 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-naive patients 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; 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 vs PBO was noted at Week 2 (16.4% vs 6.4%; $P = 0.0252$), the first post-baseline visit. Early onset of response to APR was observed across clinical assessments, with improvements in DAS-28 (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 reductions in PsA disease activity/manifestations vs placebo were also demonstrated by changes in DAS-28 (CRP) ($P < 0.0001$), SJC ($P \leq 0.0001$), and HAQ-DI (Table 6).

Detailed information can be found in the IB.

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

	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)**
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 = nonresponder 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. n with non-missing values were 103 and 91 for Placebo and APR 30 BID at Week 16, and 63 and 76 at Week 24, respectively.

[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 corticosteroids (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 patients with enthesitis at Baseline, significant improvements from Baseline in Gladman Enthesitis Index (GEI) score were observed with APR 30 mg (-1.1) vs 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)

Visit Treatment Group	n[a]	Change From Baseline	
		Week 16 LS Mean (SE)[b]	Week 24 LS Mean (SE)[b]
Placebo	51	-0.4 (0.26)	-0.5 (0.27)
APR 30 BID	56	-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**.** n with non-missing values were 48 and 49 for Placebo and APR 30 BID at Week 16, and 29 and 41 at Week 24, respectively.

[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 corticosteroids (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 unassessable 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.

1.2.1.1.4. 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.

1.2.1.1.5. Long-term Efficacy Data From Phase 3 Study CC-10004-PSA-005 (Palace 4) in csDMARD-naive patients

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.

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

In biologic-naive PsA patients 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 67.1%, 36.7%, and 21.3.0% respectively; also, 45.6% achieved HAQ-DI improvements ≥ 0.35, which corresponded to the MCID. 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 (Nash, 2018).

1.2.1.2. Safety

1.2.1.2.1. 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 patients 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.

1.2.1.2.2. 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 patients who had received ≤ 1 csDMARD was assessed in the ACTIVE study over a period of 52 weeks (Nash, 2018). The overall incidence of AEs in the placebo-controlled period was generally similar for APR monotherapy and placebo. The most commonly reported AEs (≥ 5% of patients) with APR vs placebo were nasopharyngitis (8.3% vs 6.4%, respectively), nausea (8.3% vs 1.8%), headache (7.3% vs 3.7%), hypertension (6.4% vs 6.4%), and diarrhea (patient- or investigator-reported) (14.7% vs 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% vs 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 patients treated with apremilast discontinued treatment due to depression or depressed mood vs 0 placebo-treated patients (0/495). Depression was reported as serious in 0.2% (3/1441) of patients exposed to apremilast vs 0 placebo-treated patients (0/495). Two patients who received placebo committed suicide vs 0 apremilast-treated patients. Importantly, the rates of depression remained low over time.

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

APR-Exposure Period*	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)
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)

APR30 = apremilast 30 mg BID; AE = adverse event; n/m = number of subjects with ≥1 occurrence of the abnormality at any time point/number of subjects with ≥1 post-baseline value; ULN = upper limit of normal.
Note: *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 > 53% 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 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

Apremilast has been shown to be safe and efficacious in reducing signs and symptoms of PsA, as well as improving physical function (Cutolo, 2016; Edwards, 2016; Kavanaugh, 2014; Nash, 2018). Like most agents, the clinical development program of apremilast was restricted to subjects with ≥3 swollen and tender joints at baseline. This allowed for a limited proportion of subjects with asymmetric oligoarthritis at study entry. Consequently, the safety and efficacy of apremilast in patients with oligoarthritis remains to be further investigated.

The current study is designed to evaluate the benefit: risk profile of apremilast in subjects with **an early diagnosis** of PsA (≤ 5 years since **signs and symptoms began**), presenting with oligoarthritis despite concurrent stable treatments with either NSAIDs and/or ≤ 1 csDMARD.

1.3.1.2. Rationale for the Study Design

Analyses in PsA subjects with oligoarthritis (defined by different combinations of limited numbers of swollen and tender joints) in five Phase 3 PsA studies (PSA-002, PSA-003, PSA-004, PSA-005 and PSA-006) indicated that in patients with oligoarticular PsA, apremilast 30 mg BID was associated with a numerically greater proportion of subjects achieving the modified MDA (MDA-joint) at week 16 compared with placebo. In addition, results from the apremilast development program demonstrated that responses to apremilast improve over a period of up to 24 weeks when compared to placebo. Therefore, the 24-week, double-blind, placebo-controlled treatment period with frequent visits and assessments will provide adequate time to reasonably assess the onset of action of, and durability of, response to apremilast in achieving the modified MDA (MDA-Joints). The joints monitored for early escape must correspond to those affected at the Baseline Visit (sentinel joints).

The Active-treatment Extension Phase (24 weeks) will allow for the investigation of the long-term efficacy, safety and tolerability of apremilast ± concomitant therapies for the treatment of patients with oligoarthritis. In addition, this period will allow for the investigation of the impact of apremilast ± concomitant therapies after a course of placebo ± NSAIDs and/or ≤ 1 csDMARDs.

1.3.1.3. Rationale for Dose, Schedule, and Regimen Selection

The dosing regimen and dose of apremilast is based on the approved dosing regimen and dose of apremilast for the treatment of PsA.

After a dose titration over a 5-day period, an oral dose of apremilast 30 mg BID will be given to all subjects randomized or enrolled to receive apremilast.

1.3.1.4. Rationale for Choice of Comparator Compounds

The comparator of this study is Placebo. This will allow for the assessment of the risk / benefit of apremilast.

To allow for the treatment of oligoarticular PsA, apremilast $\pm$ NSAIDs and/or $\leq$ 1csDMARDs will be compared to placebo $\pm$ NSAIDs and/or $\leq$ 1 csDMARDs. Stable low doses of glucocorticoids (prednisone $\leq$ 10 mg/day or equivalent) will be allowed. Indeed, it is understood that several patients with oligoarthritis are managed with NSAIDs and/or csDMARDs.

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 BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs in subjects with early oligoarticular psoriatic arthritis (PsA), assessed by modified MDA (MDA-Joints).
Secondary Objective(s)
• To evaluate the impact of treatment with apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs on disease activity in subjects with early oligoarticular PsA. • To evaluate the impact of apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs on patient-reported outcomes (PROs) in subjects with early oligoarticular PsA. • To evaluate the safety and tolerability of apremilast 30 mg BID ± NSAIDs and/or csDMARDs vs. Placebo ± NSAIDs and/or csDMARDs in subjects with early oligoarticular PsA.
Exploratory Objective(s)
The exploratory objectives are: [redacted]

[redacted] csDMARDs = Conventional synthetic disease-modifying antirheumatic drugs; cDAPSA = Clinical disease activity in psoriatic arthritis (without measuring C-reactive protein); [redacted] NSAIDs = Nonsteroidal anti-inflammatory drugs; MDA = Minimal disease activity; HAQ-DI = Health Assessment Questionnaire Disability Index; PGA = Physician's Global Assessment of Disease activity; PRO = Patient-reported outcome; PsAID = Psoriatic Arthritis Impact of Disease (questionnaire).

Table 12: Study Endpoints

Endpoint	Name	Description	Timeframe
Efficacy Endpoints at Week 16: Double-Blind Placebo-Controlled Treatment Phase			
Primary	MDA-Joints	Proportion of subjects who achieve a clinical state of minimal disease activity defined MDA-Joints. Subjects must achieve ≤ 1 SJC and TJC, plus 3 out of 5 of the remaining cut-off values (BSA ≤ 3%; Patient pain (VAS) ≤ 15; Patient global disease activity (VAS) ≤ 20; HAQ≤0.5; Tender entheseal points ≤ 1 (based on Leeds Enthesitis Index - LEI).	Week 16
Secondary	cDAPSA remission or low disease activity	Proportion of subjects who achieve remission (defined by clinical disease activity in psoriatic arthritis [DAPSA] ≤ 4 score) or low disease activity (defined by cDAPSA > 4 but ≤ 13 score).	Week 16
	Swollen Joint Count (SJC) ≤ 1	Proportion of subjects with SJC ≤ 1.	Week 16
	Tender Joint Count (TJC) ≤ 1	Proportion of subjects with TJC ≤ 1.	Week 16
	Patient's global assessment of disease activity	Proportion of subjects whose global assessment of disease activity score ≤ 20 in the visual analogue scale (VAS).	Week 16
	Patient's assessment of pain	Proportion of subjects whose assessment of pain score ≤ 15 in VAS.	Week 16
	PsAID-12	Change from Baseline in the Psoriatic Arthritis Impact of Disease 12-item for clinical trials (PsAID-12) questionnaire.	Week 16
	PASDAS good and moderate response	Proportion of patients achieving a good or moderate response in PASDAS score.	Week 16

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory Efficacy Endpoints: Evaluated for the Duration of the Study: (Double-Blind Placebo-Controlled Treatment Phase and/or the Active-treatment Phase)			
Exploratory	[redacted]		

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory Efficacy Endpoints: Evaluated for the Duration of the Study: (Double-Blind Placebo-Controlled Treatment Phase and/or the Active-treatment Phase)			
Exploratory (Continued)	[redacted]		

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory Efficacy Endpoints: Evaluated for the Duration of the Study: (Double-Blind Placebo-Controlled Treatment Phase and/or the Active-treatment Phase)			
Exploratory (Continued)	[redacted]		

Table 12: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory (Continued)	[redacted]		
Safety Endpoints	**Safety Endpoints: Evaluated throughout the duration of the study:**		
	Adverse events	Type, frequency, severity, and relationship of adverse events (AEs) to investigational product (IP).	Throughout the duration of the study
	Discontinuation due to AEs	Number of subjects who discontinue IP due to any AE.	Throughout the duration of the study
	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.	Throughout the duration of the study

3. OVERALL STUDY DESIGN

3.1. Study Design

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.

This is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of apremilast (CC-10004) in subjects with early (≤ 5 years since **signs and symptoms began**) oligoarticular PsA **(according to Classification Criteria for Psoriatic Arthritis [CASPAR] criteria)** despite treatment with either NSAIDs and/or ≤ **2** csDMARD. Subjects must also meet the following criteria: > 1 SJ but ≤ 4 SJ, and > 1 TJ but ≤ 4 TJ at the Screening Visit and confirmed prior to randomization at the Baseline Visit.

Given that this is a phase 4 study, all subjects are required to meet the existing apremilast regulatory labeling conditions specific to the countries where enrollment will take place (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada]. There is no planned protocol extension following the end of the study.

Approximately **285** subjects will be randomized in a 2:1 ratio to either apremilast 30 mg BID or identically appearing placebo, with approximately [redacted] subjects assigned to the active treatment group and approximately [redacted] subjects assigned to receive placebo. Treatment assignment will be stratified via an Interactive Web Response System (IWRS) based on concomitant use of glucocorticosteroids at baseline (yes/no) and prior/concomitant use of a csDMARD, either MTX or SSZ (ie, csDMARD-naïve; csDMARD use prior to baseline [treatment not continued]; or csDMARD use prior to and concomitant at baseline). The number of subjects who are csDMARD-naïve is targeted to comprise up to 50 % of the subjects enrolled in the study.

This is a 56-week study. Subjects will have up to 4 weeks in the Screening Phase, followed by 24 weeks in the Double-blind, Placebo-controlled Treatment Phase, which provides an opportunity for "early escape" at Week 16, allowing subjects to receive treatment with apremilast 30 mg BID beginning at Week 16. At the Week 24 Visit, all subjects will be offered entry into the Active-treatment Extension Phase. Subjects enrolled in the Extension Phase will receive treatment with apremilast (30 mg BID) until the end of the study (ie, up to the Week 48 Visit) or until early discontinuation.

Beginning at the Week 28 Visit, all subjects in the Extension Phase will be dispensed open-label apremilast (30 mg BID) in high-density polyethylene (HDPE) bottles (Section 7.3). Subjects, Investigators and persons responsible for the ongoing conduct of the study will continue to be blinded to the original treatment assignment. Subjects must be clearly instructed to follow dosing instructions. Subjects may discontinue at any time during the study.

After all subjects complete the Week 24 Visit (or discontinue prematurely from the study), selected members of the Amgen study team who do not have direct interaction with subjects will be unblinded for the analysis of the Week 24 data. These persons may include but are not limited

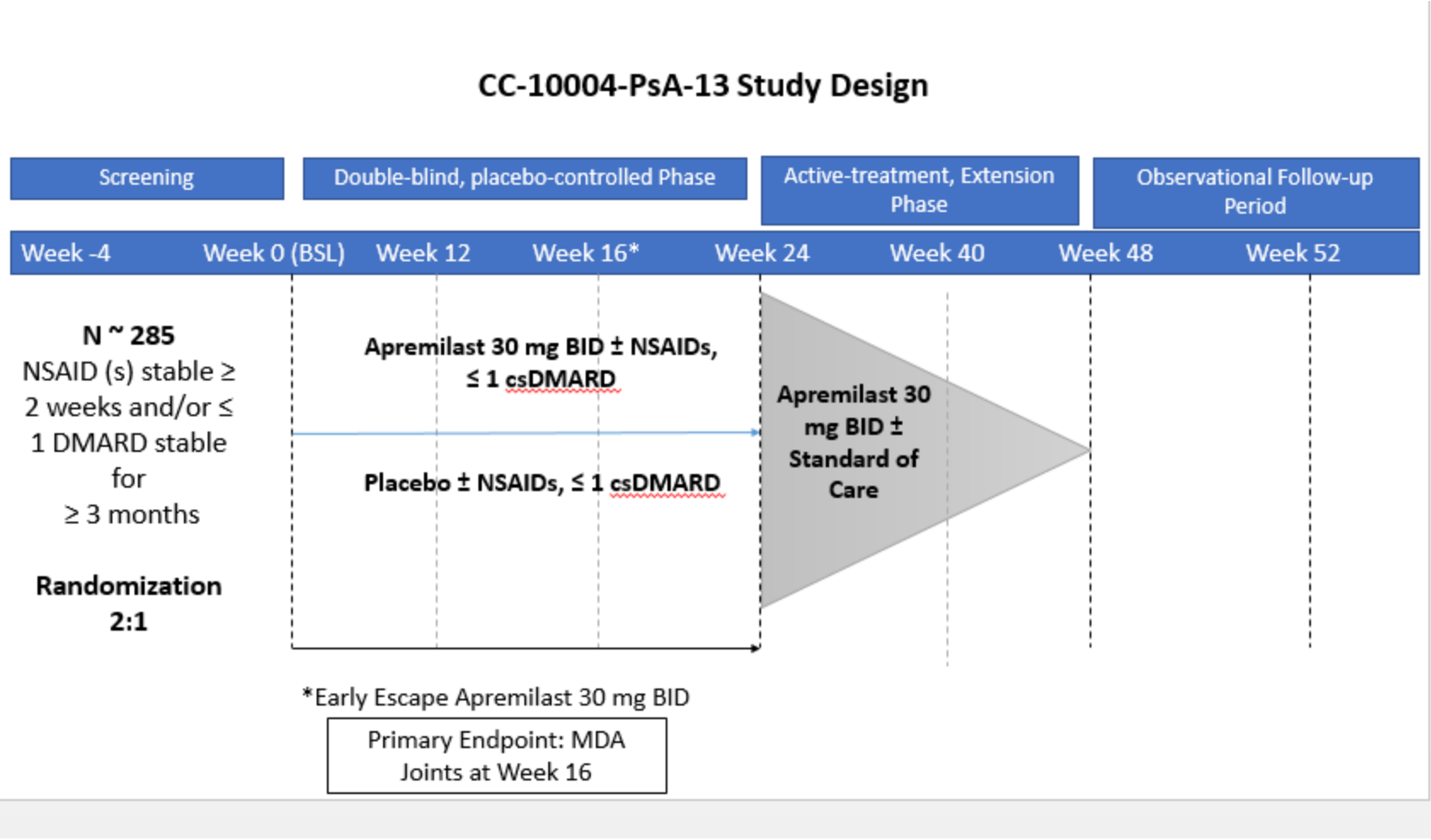
to the following: Therapeutic Area Head, Study Lead, Medical Director and the Statistician. The results from these analyses may be published prior to the end of the study.

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

This is a 56-week study which will consist of 4 phases:

- Screening Phase – up to 4 weeks
- Randomized, Double-blind, Placebo-controlled Treatment Phase – Weeks 0 to 24. Henceforth, this will be referred to as the Placebo-controlled Phase.
    - Subjects will be randomly assigned in a 2:1 ratio to either apremilast 30 mg BID or placebo. Subjects randomized to apremilast will be dose-titrated in a blinded fashion.
    - Dose titration is described in Study Treatments, Section 7.2. and Section 7.3.
    - Subjects with no improvement in SJC (sentinel joints) at Week 16 are eligible for early escape, at the discretion of the Investigator and will receive apremilast 30 mg BID. The joints monitored for early escape must be the "sentinel joints" (ie, the joints affected at baseline).
    - Placebo-treated subjects who escape early will be transitioned to apremilast 30 mg BID in a blinded fashion via an Interactive Web Response System (IWRS), while apremilast-treated subjects will remain on the original treatment assigned at baseline. Placebo-treated subjects will be dose-titrated in a blinded fashion.
    - All subjects who complete this 24-week treatment phase will have the option to enter the Active-treatment Extension Phase.
- Active-treatment Extension Phase – Week 24 to Week 48. Henceforth, this will be referred to as the Extension Phase.
    - All subjects will receive apremilast 30 mg BID until the completion of the study (ie, up to the Week 48 Visit). All remaining placebo-treated subjects will be dose-titrated in a blinded fashion.
    - Beginning at the Week 28 Visit, all subjects in the Extension Phase will be dispensed open-label apremilast (30 mg BID) as described in Study Treatments and Section 7.3.
- Post-treatment Observational Follow-up Phase – up to 4 weeks. Henceforth this will be referred to as the Observational Follow-up Phase.
    - All subjects who complete the Placebo-controlled Phase or the Extension Phase or discontinue early will participate in the 4-week Observational Follow-up Phase.
    - The Observational Follow-up visit should be performed 4 weeks after the last dose of IP **(± 7 days)**.

Figure 1: Overall Study Design



*– Subjects with no improvement in SJC (sentinel joints) at Week 16 are eligible for early escape, at the discretion of the Investigator.

Abbreviations: BID = twice daily; csDMARD = conventional synthetic disease-modifying antirheumatic drug; MDA = Minimal Disease Activity; NSAIDs = non-steroidal anti-inflammatory drug.

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 24 (ie, 24 weeks) in the Placebo-controlled Phase
- Weeks 24 to 48 (ie, 24 weeks) in the Extension Phase
- Weeks 48 to 52 (ie, 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 48 weeks of treatment and completion of the Observational Follow-up Visit (Week 52), 4 weeks after the last dose of IP **(± 7 days)**. A subject not meeting this definition is considered an early discontinuation subject (Section 6.2.1). For the purpose of analysis, study completion for an individual subject is defined as reaching the Week 48 Visit.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately **285** subjects will be enrolled worldwide.

4.2. Inclusion Criteria

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

1. Subject is a male or female, ≥ 18 years at time of consent.
2. Subjects must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have **signs and symptoms** of PsA ≤ 5 years duration at the time of the Screening Visit.
5. Subject meets the CASPAR (Appendix B) criteria for PsA at the Screening Visit.
6. Subject must have a total number of swollen joints greater than 1 and equal or less than 4 (> 1 but ≤ 4 swollen joints) at the Screening Visit and confirmed prior to randomization at the Baseline Visit.
7. Subject must have a total number of tender joints greater than 1 and equal or less than 4 (> 1 but ≤ 4 tender joints) at Screening and confirmed prior to randomization at the Baseline Visit.
8. Subjects taking oral glucocorticosteroids must be on a stable dose of prednisone ≤ 10 mg/day or equivalent for at least 4 weeks prior to the Baseline Visit (Section 8.1).
9. 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.
10. Subjects taking 1 protocol-allowed csDMARD (methotrexate [MTX] or sulfasalazine [SSZ]) to treat PsA may enter the study provided that the treatment is taken at a stable dose for at least 3 months prior to the Baseline Visit. See Permitted Medications (Section 8.1) for details describing dose criteria.
11. Subjects exposed to MTX or SSZ and stopped treatment due to intolerance or due to safety reasons may enter the study provided that treatment was stopped within at least 4 days of the Baseline Visit.
12. Subjects taking NSAIDs may enter the study provided that the dose is stable for at least 2 weeks prior to the Baseline Visit. Subjects may discontinue NSAIDs at any time up to and including the Baseline Visit, prior to study randomization.
13. Females of childbearing potential (FCBP)[†] must have a negative pregnancy test at Screening and the Baseline Visit. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive[§] options described below:

Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); 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/regulations.

† A female of childbearing potential is defined as a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

§ The female subject's chosen form of contraception must be effective by the time the female subject is screened into the study (for example, hormonal contraception should be initiated at least 28 days before screening).

14. Must be in general good health (except for psoriatic arthritis) 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).

4.3. Exclusion Criteria

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

1. Prior use of > **2** csDMARD to treat PsA.
2. Prior exposure to a JAK-inhibitor, including tyk2 inhibitors and/or a biologic DMARD.
3. Use of intra-articular (IA) or intra-muscular (IM) glucocorticoid injection within 8 weeks before the Baseline Visit.
4. Use of leflunomide within 12 weeks of randomization. Subjects who stopped leflunomide and completed 11 days of treatment with cholestyramine (8 g, 3 x daily) prior to the Baseline Visit may enter the study.
5. Prior use of cyclosporine.
6. Prior treatment with apremilast, or participation in a clinical study, involving apremilast.
7. Use of any investigational drug within 4 weeks of the Baseline Visit, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
8. History of clinically significant or uncontrolled disease (as determined by the Investigator), which places the subject at unacceptable risk if he/she were to participate in the study.

9. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study. Subjects with a creatinine clearance level less than 30 mL/min (estimated by the Cockcroft–Gault equation) will be considered to have severe renal impairment and will be excluded from the study.
10. 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.
11. Pregnant or breast feeding.
12. Active substance abuse or a history of substance abuse within 6 months prior to Screening.
13. History of allergy or hypersensitivity to any component of the investigational product.
14. History of positive human immunodeficiency virus (HIV), or congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease).
15. Active tuberculosis or a history of incompletely treated tuberculosis.
16. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within **1** week of Screening. Any treatment for such infections must have been completed and the infection cured, at least **1** week prior to Screening and no new or recurrent infections prior to the Baseline Visit.
17. 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.
18. Major surgery (including joint surgery) within 8 weeks prior to the Screening Visit or planned major surgery within 6 months following the Baseline Visit.
19. Rheumatic autoimmune disease other than PsA, including, but not limited to: systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, polymyositis, or fibromyalgia.
20. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, rheumatoid arthritis [RA], ankylosing spondylitis, Lyme disease), which confounds the ability to interpret data from the study.
21. Erythrodermic, guttate, or generalized pustular psoriasis at randomization.

5. TABLE OF EVENTS

Table 13: Table of Events

	Screening	Placebo-controlled Phase					Extension Phase			Early Termination Visit	Observational Follow-up-Phase
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early Termination**	**10**
Week (Visit Window)	**-28 Days**	**Week 0**	**4 (±3 days)**	**12 (± 3 days)**	**16[a] (±3 days)**	**24[b] (±3 days)**	**28[c] (±3 days)**	**40 (± 1 week)**	**48 (±1 week))**	**ET[d]**	**Obs. Follow-up Visit[e] 4 wks after the last dose of IP (± 7 days)**
Informed consent	X	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Medical History/PsA History	X	-	-	-	-	-	-	-	-	-	-
Smoking and alcohol intake history	X	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-	-	-	-
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X
Safety and Laboratory Assessments											
Vital Signs [f]	X	X	X	X	X	X	X	X	X	X	
Height	X	-	-	-	-	-	-	-	-	-	
Weight [g]	X	X	X	X	X	X	X	X	X	X	
Diarrhea assessment	X	X	X	X	X	X	X	X	X	X	-

Table 13: Table of Events (Continued)

	Screening	Placebo-controlled Phase					Extension Phase			Early Termination Visit	Observational Follow-up-Phase
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early Termination**	**10**
Week (Visit Window)	**-28 Days**	**Week 0**	**4 (±3 days)**	**12 (± 3 days)**	**16[a] (±3 days)**	**24[b] (±3 days)**	**28[c] (±3 days)**	**40 (± 1 week)**	**48 (±1 week))**	**ET[d]**	**Obs. Follow-up Visit[e] 4 wks after the last dose of IP (± 7 days)**
Complete Physical Examination	X	-	-	-	-	X	-	-	X	X	-
Limited Physical Examination	-	X	X	X	X	-	X	X	-	-	-
Laboratory Evaluations (including high sensitivity C-reactive protein and urinalysis)	X	X	X	X	X	X	X	X	X	X	-
Rheumatoid Factor	X	-	-	-	-	-	-	-	-	-	-
Pregnancy Test for Females of Child Bearing Potential (FCBP) and Contraception Education [h]	X	X	-	-	-	-	-	-	X	X	-
Adverse Events [i]	X	X	X	X	X	X	X	X	X	X	X
Clinical Efficacy Assessment											
Tender Joint Count (0-68)	X	X	X	X	X	X	X	X	X	X	-
Swollen Joint Count (0-66)	X	X	X	X	X	X	X	X	X	X	-
Physician's Global Assessment of Disease Activity (VAS)	-	X	X	X	X	X	X	X	X	X	-
Patient's Global Assessment of Disease Activity (VAS)	-	X	X	X	X	X	X	X	X	X	-

Table 13: Table of Events (Continued)

	Screening	Placebo-controlled Phase					Extension Phase			Early Termination Visit	Observational Follow-up-Phase
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early Termination**	**10**
Week (Visit Window)	**-28 Days**	**Week 0**	**4 (±3 days)**	**12 (± 3 days)**	**16[a] (±3 days)**	**24[b] (±3 days)**	**28[c] (±3 days)**	**40 (± 1 week)**	**48 (±1 week))**	**ET[d]**	**Obs. Follow-up Visit[e] 4 wks after the last dose of IP (± 7 days)**
Patient's Assessment of Pain (VAS)	-	X	X	X	X	X	X	X	X	X	-
Dactylitis [redacted] [j]	X	[redacted]									
Enthesitis assessment- [redacted] LEI	-	X	X	X	X	X	X	X	X	X	-
HAQ-DI	-	X	X	X	X	X	X	X	X	X	-
BSA	-	X	X	X	X	X	X	X	X	X	-
[redacted]											
PROs/QOLs											
PsAID-12	[redacted]				X	[redacted]					
[redacted]											

Table 13: Table of Events (Continued)

	Screening	Placebo-controlled Phase					Extension Phase			Early Termination Visit	Observational Follow-up-Phase
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early Termination**	**10**
Week (Visit Window)	**-28 Days**	**Week 0**	**4 (±3 days)**	**12 (± 3 days)**	**16[a] (±3 days)**	**24[b] (±3 days)**	**28[c] (±3 days)**	**40 (± 1 week)**	**48 (±1 week))**	**ET[d]**	**Obs. Follow-up Visit[e] 4 wks after the last dose of IP (± 7 days)**
Health Economics Assessment											
[redacted]											
Dosing											
Dispense Study Drug	-	X	X	X	X	X	X	X	-	-	-
Return/Count Study Drug	-	-	X	X	X	X	X	X	X	X	-

BID = twice daily; BSA = Body Surface Area; [redacted] FCBP = Females of Child Bearing Potential; HAQ-DI = Health Assessment Questionnaire – Disability Index; IP = Investigational Product; [redacted] LEI = Leeds Enthesitis Index; [redacted] Obs. Follow-up Visit = Observational Follow-up Visit; PROs = Patient Reported Outcomes; PsAID = PsA Impact of Disease; [redacted] QOL = Quality of Life; [redacted] VAS = Visual Analog Scale; [redacted]

[a] At the Week 16 Visit, subjects with no improvement in SJC (sentinel joints) at Week 16 are eligible for early escape, at the discretion of the Investigator and will receive treatment with apremilast 30 mg BID. The joints monitored for early escape must correspond to those affected at the Baseline Visit (sentinel joints).

[b] All subjects who complete the Week 24 Visit will enter Extension Phase and receive apremilast 30 mg BID. The original treatment assignments (apremilast 30 mg BID or placebo) will remain blinded until the end of the study.

[c] Beginning at the Week 28 Visit, all subjects in the Extension Phase will be dispensed open-label apremilast (30 mg BID) in high-density polyethylene (HDPE) bottles. Subjects must be clearly instructed to follow dosing instructions.

[d] Subjects who discontinue the study prior to the Week 48 Visit, will have an Early Termination (ET). [redacted]

[e] The Observational Follow-up Visit will be conducted 4 weeks after the last dose of IP **(± 7 days)**.

[f] If an on site study visit is replaced with a telemedicine assessment, vital signs will not be measured.

[g] If an on site study visit is replaced with a telemedicine assessment, the subject's weight will not be measured.

[h] Females of childbearing potential (FCBP) will have a serum pregnancy test done at the Screening Visit and at the Week 48 Visit (or Early Termination Visit). The urine pregnancy test collected at the Baseline Visit must be assessed prior to study randomization. The Investigator must educate all FCBP about the options for and correct use of contraceptive methods at the Screening and Baseline Visits and at any time when a subject's contraceptive measures or ability to become pregnant change. An unscheduled pregnancy test should be administered if the subject has missed a menstrual period or at the discretion of the Investigator per country specific guidelines.

[i] Details pertaining to the monitoring and collection of adverse events are included in Section 10. Information about specific safety assessments are provided in Section 6.5.
[j] For the dactylitis assessment at Screening, only a binary evaluation is needed (yes/no). [redacted]

[redacted]

6. PROCEDURES

The following procedures will be conducted as outlined in Table 13, the Table of Events.

6.1. Screening Period

Following the signing of the informed consent form (ICF), 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.

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

- Demographics include year of birth, sex, race, and ethnicity-if allowed by local regulations, will be collected.
- Smoking and alcohol intake history
- Complete medical history including all relevant medical conditions diagnosed, and occurring prior to the Screening Visit, should also be recorded.
- PsA history will be collected.
- Prior and concomitant medication evaluation including all medications (prescription and nonprescription, including vitamins) taken by the subject up to ≤ 28 days prior to the Screening Visit should be recorded. All medications taken by the subject at any time during the study must also be recorded. Other key medications and therapies, such as previous treatment for tuberculosis or relevant diseases, should also be recorded.
- Prior and concomitant PsA-related medications:
    - All medications for PsA and oligoarthritis taken by the subject are to be recorded in the subject's source document prior to study randomization.
    - Careful attention must be taken when randomizing a subject in IWRS regarding a subject's use of glucocorticosteroids and DMARDs. This includes use prior to study randomization and at the time of study randomization at the Baseline Visit.
    - PsA medications and all other medications must also be recorded in the eCRF according to the CRF guidelines.
    - Contraindicated PsA medications:
        - For this protocol, contraindication to PsA medications will refer to those subjects who have a pre-existing medical condition where administration of the medication is not possible since the treatment could cause harm to

the subject, resulting in the subject NOT TAKING the medication. For subjects who meet this criterion, this information must be recorded in the source document along with the pre-existing medical condition that prevented the subject from receiving the treatment. The pre-existing medical condition must also be reported the eCRF.

- Prior and concomitant procedures including all procedures occurring ≤ 28 days before the Screening Visit must be collected.
- Vital signs
- Height and weight
- Chest X-ray is not required per protocol but may be done at the discretion of the Investigator or according to local regulations and guidelines.
- Diarrhea assessment (Section 6.5.5)
- Complete physical examination (recorded in the source document)
- Laboratory evaluations will be performed by a central laboratory and are described in Section 6.5.7 and are listed below:
    - Hematology panel
    - Chemistry panel
    - Urinalysis
        - Microscopic urinalysis (epithelial cells, red blood cells [RBCs], white blood cells [WBCs], crystals, bacteria, and casts) will be performed only if the urinalysis is abnormal.
    - High sensitivity C-reactive Protein (hsCRP)
    - Rheumatoid factor
- Adverse event evaluation (continuously)
- SJC and TJC assessment
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin β-hCG pregnancy test will be performed at the Screening Visit. 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 will be performed by the Investigator at screening for all FCBP about the options for and correct use of contraceptive methods at the Screening and Baseline Visits and at any time when a FCBP's contraceptive measures or ability to become pregnant changes.
    - A pregnancy test should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed
    - Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.

6.2. Treatment Period

The Treatment Period includes the Placebo-controlled Phase and the Extensions Phase.

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 28 days of signing the ICF. The following evaluations will be performed at the frequency specified in Table 13. In addition, at the discretion of the investigator, an Unscheduled Visit may be performed to evaluate subject safety and efficacy as needed.

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Limited or complete physical examination (source documented only) as described in Table 13. During the Extension Phase, limited physical exam may be done at the discretion of the Investigator.
- Vital signs
- Diarrhea assessment (Section 6.5.5)
- Weight (Section 6.5.2)
- [redacted]
- Hematology panel
- Chemistry panel
- [redacted]
- hsCRP
- Urinalysis
  - Microscopic urinalysis (epithelial cells, RBCs, WBCs, crystals, bacteria, and casts) will be performed only if the urinalysis is abnormal.
- Adverse event evaluation (continuously)
- Efficacy assessments (see Section 6.4)
- Patient reported outcomes (PROs), Quality of Life (QOL) assessments and Health Economics (Section 6.6)
- Urine pregnancy testing will be done for FCBP prior to dosing at the Baseline Visit. Serum beta human chorionic gonadotropin β-hCG pregnancy test will be performed at the Week 48 Visit
- IP dispensing and accountability

6.2.1. End of Treatment

An end of treatment (EOT) evaluation 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 evaluations will be performed as specified in Table 13, Table of Events:

- Complete physical examination (source documented only)
- Vital signs
- Weight
- [redacted]
- Diarrhea assessment (Section 6.5.5)
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Subject reported outcomes or quality of life
- Adverse event evaluation
- Hematology panel
- Chemistry panel
- [redacted]
- hsCRP
- Urinalysis
  - Microscopic urinalysis (epithelial cells RBCs, WBCs, crystals, bacteria, and casts) will be performed only if the urinalysis is abnormal.
- Serum beta human chorionic gonadotropin β-hCG pregnancy test will be performed for FCBP.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.
- Efficacy Assessments (Section 6.4)
- PROs (Quality of Life (QOL) assessments and Health Economics (Section 6.6)
- Return/count of study drug

6.3. Observational Follow-up

6.3.1. Safety Follow-up

All subjects will be followed for 28 days after the last dose of apremilast for AE reporting, as well as SAEs made known to the Investigator at any time following the protocol-required reporting period or after end of study , as described in Section 10.

The following evaluations will be performed at the Observational Follow-up Visit, or if necessary via telephone contact, as specified in Table 13, Table of Events:

- Concomitant medications evaluation
- Concomitant procedures evaluation

- Adverse event (non-serious and serious) evaluation

6.4. Efficacy Assessments

The following assessments will be conducted as outlined in Table 13, Table of Events. Subject questionnaires and clinician assessments will be reported using electronic data capture. These data will be entered directly into the ERT tablet.

6.4.1. Modified Minimal Disease Activity–Joints (MDA-Joints) and its Components

For this study, the MDA-Joints (Appendix C) is used as the primary endpoint and is defined as Tender Joint Counts (TJC) ≤ 1 and Swollen Joint Counts (SJC) ≤ 1 plus 3 of any of the 5 criteria: 1) patient's global VAS on a 100-mm scale ≤ 20, 2) patient pain VAS on a 100-mm scale ≤ 15, 3) physical function [HAQ-DI] ≤ 0.5, 4) enthesitis count ≤ 1 (based on the Leeds Enthesitis Index) and 5) psoriasis Body Surface Area (BSA) ≤ 3%. Joint assessment to be based on 66 swollen joints and 68 tender joints (see Section 6.4.1.1). Assessment of the joint counts will be performed by the evaluator, however, calculation of the MDA-Joints will be done programmatically.

6.4.1.1. Joint Assessment

A modified joint count that includes the distal interphalangeal joints of the fingers and toes (the "68 tender and 66 swollen" joint scores; (Appendix D) will be performed at every visit. 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 or intra-muscular glucocorticoid (allowed only after Week 24 assessments are completed, and up to the Week 48 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.

6.4.1.2. Patient's Global Assessments of Disease Activity

The Patient's (Subject's) Global Assessments of Disease Activity (Appendix E) is an assessment of how active a subject's psoriatic arthritis was on average during the last week. The subject will be asked to place a vertical line on a visual analogue scale (VAS) on which the left-hand boundary represents the lowest level of disease activity and the right-hand boundary represents the highest. Distance from the mark to the left-hand boundary will be recorded in millimeters, except when calculating cDAPSA score, where the distance will be calculated in centimeters.

6.4.1.3. Patient's Pain Visual Analogue Scale

The pain visual analogue scale (VAS) is the subject's assessment of how much pain he/she had, on average, last week in his/her joints due to PsA. The subject will be asked to place a vertical line on a VAS on which the left-hand boundary represents "no pain," and the right-hand boundary represents "pain as severe as can be imagined" (Appendix E). The distance from the

mark to the left-hand boundary will be recorded in millimeters, except when calculating cDAPSA score, where the distance will be calculated in centimeters.

6.4.1.4. HAQ-DI

The HAQ-DI (Appendix F; 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).

6.4.1.5. Enthesitis: Leeds Enthesitis Index

In the evaluation of MDA-Joints, enthesitis will be assessed by the Leeds Enthesitis Index (LEI) (Appendix G; Healy, 2008).

For the LEI, pain will be assessed at the following entheses (tendon insertions): Lateral epicondyle humerus (left/right (L/R)); Medial condyle femur (L/R); Achilles tendon insertion into calcaneum (L/R). The LEI ranges from 0 to 6.

6.4.1.6. BSA

BSA (Appendix H) is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint"), which equates to approximately 1% of total body surface area. All subjects will have their BSA assessed by the Evaluator.

6.4.1.7. Physician's Global Assessments of Disease Activity

The Physician's (Evaluator's) Global Assessments of Disease Activity is an assessment of how active a subject's psoriatic arthritis was on average during the last week. For the Physician's (Evaluator's) Global Assessments of Disease Activity, evaluator should mark a single vertical mark on a 100-mm VAS (see Appendix E), with zero representing the lowest level of disease activity or pain and 100 representing the highest. The distance from the mark to the left-hand boundary of the scale will be recorded in millimeters (Appendix E, Felson, 1995).

6.4.2. Enthesitis: [redacted]

In addition to assessment by the Leeds Enthesitis Index (Section 6.4.1.5), enthesitis will also be assessed using the [redacted]

6.4.3. Dactylitis

Dactylitis assessment will be done at screening, only a binary evaluation is needed (yes/no). [redacted]

[redacted]

6.4.4. Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA)

The cDAPSA score (Appendix K) is based on the numerical summation of 4 disease activity variables: tender and swollen joints, patient global and pain assessments on a 10 cm Visual Analogue Scale (VAS) (Appendix E). Proposed cut-offs for cDAPSA are a score ≤ 4 for remission, a score > 4 and ≤ 13 for low disease activity, > 13 and ≤ 27 for moderate disease activity, and > 27 for high disease activity. Evaluation of components of cDAPSA is described above. The calculation of the cDAPSA will be performed programmatically.

6.4.5. Psoriatic Arthritis Disease Activity Score (PASDAS)

The PASDAS (Helliwell, 2014; Appendix L) is a weighted index comprising assessments of joints, function, acute-phase response, quality of life (QOL), and patient and physician by VAS. The calculation of the PASDAS will be performed programmatically using the formula below:

PASDAS = **(**(0.18 x √Physician global VAS) + (0.159 x √Patient global VAS) – (0.253 x √SF36 – PCS) + (0.101 x LN (Swollen joint count + 1)**)** + (0.048 x LN (Tender joint count + 1)**)** + (0.23 x LN (Leeds Enthesitis Count + 1)) + (0.377 **x** LN (Dactylitis count + 1)**)** + (0.102 x LN (CRP + 1)**)** +2)*1.5.

Note: LN = natural logarithm, PCS = physical component summary scale of SF36, CRP = C-reactive protein in mg/l, SF36 = Medical Outcomes Study Short Form-36. 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. Definition of good or moderate response is detailed in Appendix L.

6.4.6. High sensitivity C-reactive Protein

High sensitivity C-reactive protein (hsCRP) and rheumatoid factor will be performed at a central laboratory along with the other clinical laboratory assessments described in Section 6.5.7.

[redacted]

[redacted]

6.5. Safety Assessments

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

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

The following assessments will be conducted as outlined in Table 13, Table of Events.

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

A serum pregnancy test with a sensitivity of ≤ 15 mIU/mL will be required for FCBP subjects at Screening and the Week 48 Visit (or at the Early Termination Visit for subjects who prematurely discontinue from the study). Urine pregnancy test will be performed on all FCBP subjects at the Baseline Visit, prior to randomization. A urine pregnancy test kit will be provided by the central laboratory. Pregnancy tests should be performed if the FCBP subject has missed a menstrual period or the contraception method has changed.

In addition to the assessments specified in Table 13, 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 Table 13, Table of Events. Height will be measured and recorded at Screening; weight will also be measured and recorded at every visit. [redacted]

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 (assessment of joints and spine) systems. A complete physical examination is done at Screening and other designated visits as indicated in Table 13, Table of Events. A limited physical examination includes evaluations of skin, lymph nodes, and respiratory, cardiovascular, and

musculoskeletal systems. A limited physical examination is done at the Baseline Visit and other designated visits as indicated in Table 13.

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 subject suffers from new or worsening psychiatric symptoms, or if suicidal ideation or suicidal attempt is identified, it is recommended to discontinue the subject participation to the study (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. This data will be reported via electronic data capture in the ERT tablet. If an AE is identified by the Investigator, the AE and respective attributes will be reported in the clinical database. If the AE meets serious criteria, it must be reported to Amgen Global Patient Safety (see Section 10.5).

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 subjects 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 a subject develops severe diarrhea, nausea and vomiting, discontinuation of 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 as indicated in Table 13, Table of Events. These include complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count) and serum chemistries (total protein, albumin, calcium, phosphorous, glucose, triglycerides, total cholesterol [TC], total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST; serum glutamic-oxaloacetic transaminase, SGOT], alanine aminotransferase [ALT; serum glutamic pyruvic transaminase, SGPT], sodium, potassium, chloride, bicarbonate [carbon dioxide, CO_2], blood urea nitrogen, creatinine, creatinine clearance [estimated by the Cockcroft–Gault equation], lactate dehydrogenase [LDH], and magnesium); [redacted] rheumatoid factor; high-sensitivity C-reactive protein (hsCRP), urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen. Microscopic urinalysis (epithelial cells, red blood cells [RBCs], white blood cells [WBCs], crystals, bacteria, 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 of 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. Adverse events and serious adverse events (SAEs) will be recorded on the AE page of the electronic case report form (eCRF), the paper SAE reporting form (SAEs) and in the subject's source documents. All SAEs must be reported to Amgen Global Patient Safety immediately (ie, within 24 hours of the Investigator's knowledge of the event) by recording on the CRF and completing the paper SAE Report Form which is sent directly to Amgen Global Patient Safety by facsimile or email.

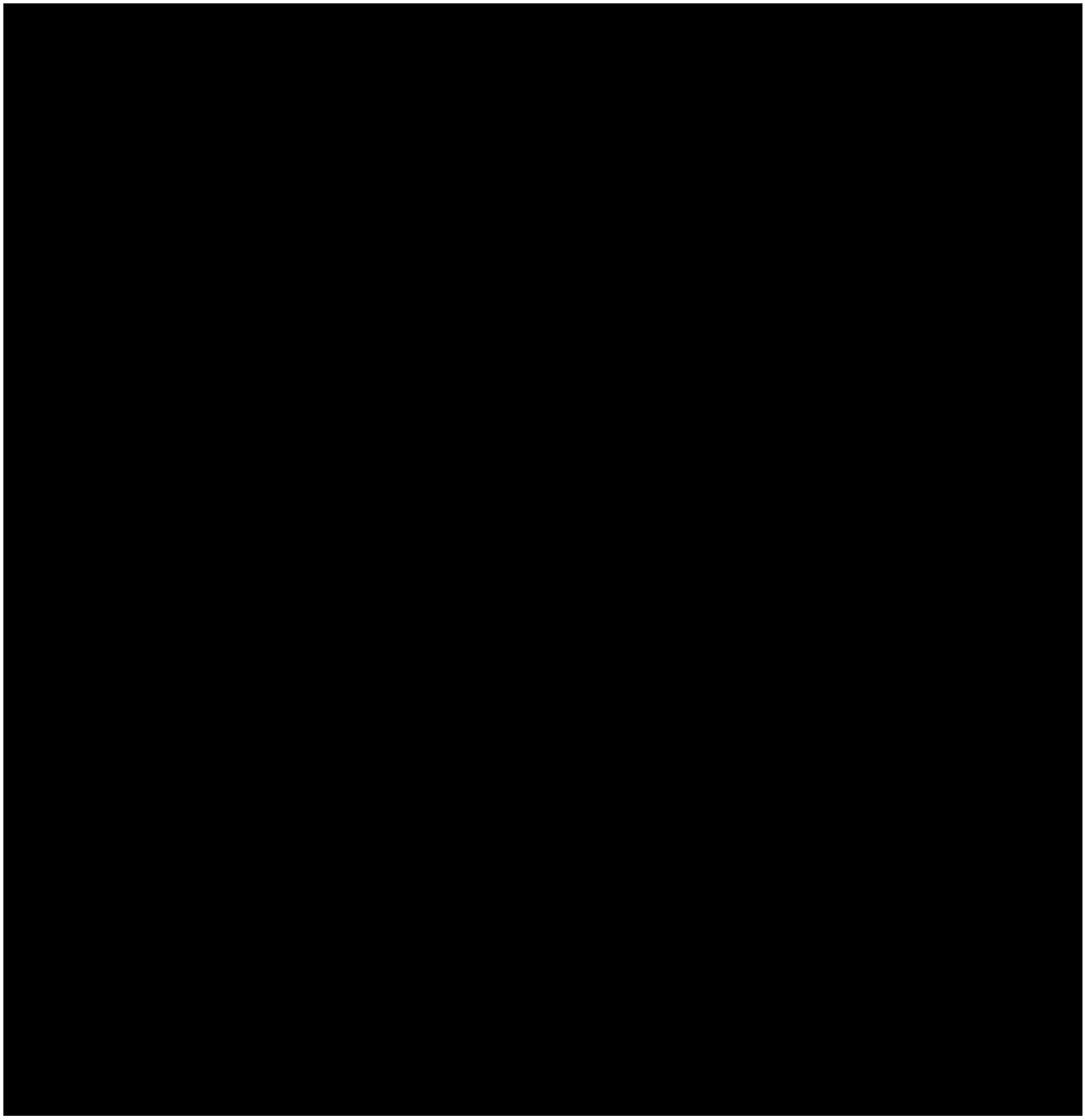
Details of AE reporting can be found in Section 10 of the protocol. It should be noted that worsening of a subject's psoriatic arthritis should be considered as worsening of disease under study and should not be captured as an adverse event.

6.6. Patient Reported Outcomes or Quality of Life or Health Economics

Questionnaires will be performed and as indicated in Table 13, Table of Events.

6.6.1. The PsA Impact of Disease 12-Item (PsAID-12) Questionnaire

The PsAID-12 Questionnaire (Appendix N; Gossec, 2014) 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 ≤ 4.



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 and placebo will be provided as identically appearing by the Sponsor and labeled appropriately as investigational product for this study. In addition, tablets (both apremilast and placebo) required for dose titration cards will also be provided.

Please refer to the IB for more details on approved indications, known precautions, warnings, and adverse reactions of apremilast.

The apremilast dosing schedule to be followed for this study is described in Section 7.2.

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 (see Table 14).

At the Week 0 (ie, initial randomization), Week 16 (ie, for Early Escape subjects), and Week 24 (ie, Active-treatment Phase) visits, subjects will be dispensed blister cards with 10, 20, and 30 mg apremilast tablets or identically appearing placebo for the dose titration. Subjects will be dispensed blister cards containing 30 mg apremilast tablets or identically appearing placebo at designated visits (Table 13). Beginning at the Week 28 Visit, subjects will be dispensed open label bottles with 30 mg apremilast tablets. Pictures of the blister card configurations are shown in Appendix T. Dose modifications are not permissible in this study. Apremilast and placebo tablets (oral IP) are identical in appearance.

Table 14: Treatment of Schema for Dose Titration at Baseline

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

Table 15: Treatment Schema for Dose Titration at Week 16 (Early Escape) or Week 24

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

7.3. Method of Treatment Assignment

After the informed consent is signed, subjects will be assigned a subject identification number using a centralized interactive web response system (IWRS). At the Baseline Visit, a centralized schema will be applied to assign subjects who meet the inclusion and none of the exclusion criteria in a 2:1 ratio to receive either apremilast 30 mg tablets or placebo. The IWRS will stratify the randomized subjects by their use of glucocorticosteroids (yes/no) and use of a csDMARD: (csDMARD-naïve; csDMARD use prior to baseline; or csDMARD use prior to and concomitant at baseline).

Subjects who are randomized to apremilast at baseline will be dose-titrated during their first week of active treatment (see Section 7.2), while subjects who are randomized to placebo will receive identically appearing placebo titration cards while continuing to receive their assigned dose of placebo BID.

Subjects with no improvement in the swollen joint count at Week 16 are eligible for early escape. The joints monitored for early escape must correspond to those affected at baseline (sentinel joints). To maintain the study blind, placebo-treated subjects who escape early will be transitioned in a blinded fashion via an IWRS to apremilast 30 mg BID and apremilast-treated subjects will remain blinded on their original treatment assignment. Placebo subjects will be dose-titrated during their first week of active treatment (see Section 7.2), while subjects who were already on apremilast 30 mg BID will receive identically appearing placebo titration cards while continuing to receive their assigned dose of apremilast 30 mg BID.

At the Week 24 Visit, subjects will be offered to enter a 24-week Active - treatment Extension Phase (Extension Phase). All subjects enrolled in the Extension Phase will receive treatment with apremilast (30 mg BID) until the completion of the study (ie, up to the Week 48 Visit) or until early discontinuation. Placebo subjects will be dose titrated (5-day titration period). All subjects will receive treatment cards of identical appearance to maintain the blinding of the original treatment assignments (apremilast 30 mg BID or placebo).

Beginning at the Week 28 Visit, the next scheduled study visit following the placebo titration period, all subjects in the Extension Phase will be dispensed open-label apremilast (30 mg BID) in high-density polyethylene (HDPE) bottles. Subjects must be clearly instructed to follow dosing instructions.

Designated study personnel at the investigational sites will be assigned password protected, coded identification numbers, which give them authorization to log into the IWRS to randomize subjects. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the IWRS will assign a randomization identification number. Confirmation of the randomization will be sent via fax to the investigational site, Amgen and/or its representative.

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

7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot

number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

All IP, including placebo and apremilast tablets, will be supplied by Amgen Inc. to the principal Investigator as blister cards during the Placebo-controlled Phase.

Starting at the Week 28 Visit, apremilast 30 mg tablets will be supplied in HDPE bottles with child-resistant caps.

7.5. Investigational Product Accountability and Disposal

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

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

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

7.6. Study Medication Dispensing and Counting

After the subject has satisfied all inclusion and exclusion criteria, study medication will be dispensed as specified in Table 13, 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.

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).

7.7. 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 Table 13, Table of Events. 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 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 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.

7.8. Overdose

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

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

Adverse Events associated with an overdose must be collected on the Adverse Events page of the eCRF (see Section 10) for all overdosed subjects, but the overdose itself is not considered an AE. If the AE associated with the overdose meets seriousness criteria, it must also be reported to Amgen Global Patient Safety using the paper SAE report form (see Section 10.5).

8. 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 eCRF. The dose, unit, frequency, route, indication, the date the medication was started and the date the medication was stopped (if not ongoing) must be recorded. Subjects may continue receiving standard of care therapy (eg, folic acid for those on MTX) if not explicitly prohibited as per protocol. Additional instructions can be found in the electronic Case Report Form (eCRF) Completion Guidelines.

8.1. Permitted Concomitant Medications and Procedures

The following concomitant medications and procedures are permitted during the study:

- Oral glucocorticosteroids are to be taken on a stable dose up to the Week 24 Visit:
    - Prednisone ≤ 10 mg/day (or prednisolone equivalent) for at least 4 weeks prior to the Baseline Visit must be continued and maintained through the Week 24 Visit (change in dose and/or discontinuation are not allowed except for safety reasons or for lack of availability).
- NSAIDs (and/or narcotic analgesics) are allowed during the study, provided that the NSAIDs are taken on a stable dose for at least 2 weeks prior to the Baseline Visit.
    - The stable dose of NSAIDs or narcotic analgesics must be continued and maintained from the Baseline Visit 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 eCRF.
- csDMARDs –
    - Only 1 csDMARD (MTX or SSZ) for the treatment of PsA is permitted during the first 24 weeks of the study, provided that the treatment is taken on a stable dose ≥ 3 months prior to the Baseline Visit.
    - Subjects exposed to MTX or SSZ and stopped treatment due to intolerance or due to safety reasons may enter the study provided that treatment was stopped within at least 4 days of the Baseline Visit
        - The allowed dose for permitted csDMARDs are: MTX (oral or parenteral) ≤ 25 mg /week; SSZ (oral) ≤ 3 gm/daily
- Low-dose aspirin (acetylsalicylic acid, up to 325 mg per day) for cardiovascular prophylaxis.
- Loperamide and antidiarrheal drugs with antisecretory effect (eg, racecadotril).

- A nonmedicated skin emollient (eg, Eucerin® cream) for body psoriasis lesions only.

After the Week 24 Visit, changes in the following therapy will be permitted as clinically required for subjects with worsening arthritic symptoms of PsA:

- Change of NSAID type and/or dose
- Parenteral glucocorticoids are allowed, provided that the following criteria are met:
  - Administration of no more than 40 mg intra-articular (IA) or intra-muscular (IM) glucocorticosteroid (triamcinolone hexacetonide or equivalent) injection at a single visit.
  - Injected joints should not be counted during the visits that will take place within 4 weeks of the intra-articular injection. Joints should be marked with an X.
  - Intra-articular injection should not be performed after week 44 visit (ie, ≤4 weeks prior to study end).
- Oral glucocorticosteroids may be adjusted as clinically required
  - Short course (≤ 2 weeks) of oral corticosteroids, including a Medrol Dosepak®, not to exceed one course in any 6-month interval
- Non-biologic DMARDs: methotrexate (≤ 25 mg/week), sulfasalazine (≤ 3 gm/day), leflunomide (≤ 20 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 600 mg/day).

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 has been tapered (not required to be zero), the dose must be stable for at least 4 weeks prior to tapering the next agent. Subjects are recommended to have a reduction of background therapy in the following order (when applicable): First csDMARD, second glucocorticosteroids 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.

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.

8.2. Concomitant Medications Not Recommended

It has been observed that coadministration with strong cytochrome P450 3A4 (CYP3A4) enzyme inducers, 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 during the study as noted below:

- Use of >1 csDMARD prior to Week 24
- Prior use of tofacitinib or any other JAK-inhibitor
- Use of any biologic DMARD.
- Use of leflunomide within 12 weeks of randomization. Subjects who stopped leflunomide and completed 11 days of treatment with cholestyramine (8 g TID) prior to the Baseline Visit may enter the study. Leflunomide may be initiated (≤ 20 mg/day) after Week 24.
- Prior use of cyclosporine
- Use of DMARDs other than MTX or SSZ for the treatment of PsA, except for MTX (≤ 25 mg/week), or SSZ (≤ 3 gm daily), prior to Week 24.
- Use of intra-articular (IA) and intra-muscular (IM) glucocorticoid injection within 8 weeks before the Baseline Visit. Use of IA and IM injections may be administered after Week 24 as discussed in Section 8.1.

8.4. Required Concomitant Medications and Procedures

There are no required concomitant medications or procedures.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

The primary efficacy analysis of the proportion of subjects achieving the modified MDA (MDA-Joints) at Week 16 and the secondary analyses will be performed after all subjects complete the placebo-controlled period (Week 0 to 24) or terminate early prior to Week 24 visit. Additional analyses will be performed after the final database lock when all subjects complete the study or terminate early. 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 unblinding of the treatment assignment for the 24-week, placebo-controlled, double-blind treatment phase of the study or any analysis procedures are conducted, whichever is earlier.

9.2. Study Population Definitions

The Full Analysis Set (FAS) will consist of all subjects who are randomized. Efficacy analyses will be primarily based on the FAS and subjects will be included in the treatment group to which they are randomized.

The Per Protocol (PP) population will consist of all subjects who receive at least one dose of study medication and have no major protocol violations during the 24-week placebo-controlled treatment period. The final determination of major protocol violations will be made prior to the unblinding of treatment assignment and will be documented. The PP analyses will be based on the PP population and subjects will be included in the treatment group for the treatment they actually receive.

The Safety population will consist of all subjects who receive at least one dose of study medication. The safety analyses will be based on the safety population and subjects will be included in the treatment group for the treatment they actually receive.

9.3. Sample Size and Power Considerations

Sample size estimation was based on the results from integrated analyses of subpopulation data from five Phase 3 studies (PSA-002, PSA-003, PSA-004, PSA-005, and PSA-006). Assuming a 15% dropout rate during the randomized, placebo-controlled, double-blind treatment phase, a sample size of **approximately** [redacted] for the Apremilast 30 mg BID and placebo groups, respectively, will have 80% power to detect a true 15% difference (30% versus 15%) in the proportions of subjects achieving the modified MDA (MDA-Joints) between the Apremilast 30 mg BID and placebo groups, using a chi-square test with a two-sided significance level of 0.05.

9.4. Background and Demographic Characteristics

Subjects' 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 summarized using frequency tabulations. Treatment

history (including oral glucocorticosteroid, NSAIDs, and csDMARD use) will be summarized using frequency distributions.

9.5. Subject Disposition

Subject disposition (counting of analysis populations; and subjects enrolled, randomized, and completing or discontinuing in 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. Efficacy Evaluation for the Placebo-Controlled, Double-Blind Treatment Phase

The analyses of efficacy endpoints will be primarily based on the FAS. In addition, supportive analyses using the Per Protocol population will also be conducted for the primary endpoint.

Efficacy results will be considered statistically significant after consideration of the control of multiplicity, as specified in Section 9.6.2. Two-sided p-values and confidence intervals (CIs) will be reported, and all statistical tests will be conducted at the significance level of 0.05.

9.6.2. Multiplicity

Statistical tests for comparing the apremilast 30 mg BID and placebo will be conducted for the primary endpoint and the secondary efficacy endpoints as listed in Section 2.

The multiplicity of the analyses performed for the primary and selected secondary efficacy endpoints will be adjusted using a sequential test procedure to preserve the family-wise type I error rate. The hierarchy order of the selected secondary endpoints to be followed in the sequential test procedure will be specified in the statistical analysis plan (SAP).

It should be noted that the above multiplicity control will only be conducted for the primary endpoint and the key secondary endpoints that are evaluated in the randomized, placebo-controlled, double-blind treatment phase.

9.6.3. Primary Efficacy Endpoint

The primary efficacy endpoint, proportion of subjects who achieve the modified MDA (MDA-Joints) at Week 16, between the Apremilast 30 mg BID and placebo groups will be compared using a Cochran-Mantel-Haenszel test, controlling for concomitant use of glucocorticosteroids at baseline (yes/no) and use of a csDMARD: (csDMARD-naïve; csDMARD use prior to baseline; or csDMARD use prior to and concomitant at baseline).

Subjects who have discontinued prior to Week 16 due to lack of efficacy or adverse event will be treated as non-responders in the analysis; and the multiple imputation methodology will be utilized to impute the data for subjects whose modified MDA at Week 16 is missing for a reason other than lack of efficacy or adverse event. Sensitivity analyses will be performed using the non-responder imputation for subjects who have discontinued prior to Week 16, or do not have sufficient information for a definitive determination of the modified MDA (MDA-Joints) status at Week 16.

9.6.4. Secondary Endpoints

For the secondary endpoints, the analyses of binary responses in the placebo-controlled phase will be similar to the analysis of the primary endpoint. That is, a Cochran-Mantel-Haenszel test adjusted for concomitant use of glucocorticosteroids at baseline (yes/no) and use of a csDMARD: (csDMARD-naïve; csDMARD use prior to baseline; or csDMARD use prior to and concomitant at baseline) will be used to compare the response rates between the apremilast 30 mg BID and the placebo groups.

A mixed-effect model of repeated measures (MMRM) will be used to analyze the continuous endpoints. The MMRM model will use change from baseline as the dependent variable and include treatment group, time, treatment-by-time interaction, use of glucocorticosteroids (yes/no) and use of a csDMARD (csDMARD-naïve; csDMARD use prior to baseline; or csDMARD use prior to and concomitant at baseline) as factors, and baseline value as a covariate. Time will be treated as a categorical variable in the MMRM model.

All analyses on endpoints including joint counts will be performed on those joints that are affected at baseline (defined as sentinel joints). [redacted]

9.6.5. Active-Treatment Phase.

Efficacy endpoints beyond Week 24 will be summarized using descriptive statistics for continuous variables and frequency tabulation for discrete variables.

9.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 9.2.

Adverse events will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. All adverse events will be summarized by system organ class and preferred term; in addition, by severity and relationship to investigational product separately. Adverse events leading to death, if any, or to discontinuation from treatment, serious adverse events, and study drug-related adverse events 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 pretreatment 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 pretreatment 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, as appropriate.

9.8. Interim Analysis

Not applicable.

9.9. Other Topics

9.9.1. Investigational Product Compliance (Tablets)

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

9.9.2. Concomitant Therapy

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

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

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

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.8 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event, should be reported as an AE on the CRF. If the sequela of an overdose meets 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 of IP 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 completing the paper SAE Report Form which is sent to Amgen Global Patient Safety by facsimile/email.

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. Please refer to Section 10.2 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 the AE page 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 the IP, action taken regarding the IP, 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 the IP 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 IP as a result of each AE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for 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 to be an AE if the abnormality:

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

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a 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 X). 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 SAEs. 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 Y) 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 subject's 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 for an SAE requires the reporting of 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 IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) 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.

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.

The SAE is recorded within the CRF and reported directly 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.

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 SAE 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 W).
- 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 SAE 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 SAE Report Form (refer to Appendix W).

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

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 (EEA), Amgen or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics

Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

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

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 SAE Report Form, paper Pregnancy Notification Form and/or paper Lactation Notification Form (Appendix W, Appendix X, Appendix Y).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

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

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

The decision to discontinue a subject from treatment 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
- Loss 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 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

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

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

Emergency unblinding should only be performed by the Investigator through the Integrated Response Technology (IRT) by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblinded dose information. Beginning at Week 24 all subjects will be dispensed apremilast with titration in blinded treatment cards (Sections 7.3 and 7.4). However, subjects will receive open-label apremilast at beginning at Week 28 until the end of the study, or until early discontinuation. Therefore, IP will be identified on the package labeling beginning at Week 28.

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 informed consent form (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 for 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 investigational product 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 SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

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

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Amgen, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

15.1. Study Monitoring and Source Data Verification

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

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

15.2. Audits and Inspections

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

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, 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

Abbreviation or Specialist Term	Explanation
ACR20/50/70	American College of Rheumatology 20%/50%/70% response improvement
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
APR	Parmalat
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
bDMARD	Biologic disease-modifying antirheumatic drug
BID	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CASPAR	Classification Criteria for Psoriatic Arthritis
CBC	Complete blood count
cDAPSA	Clinical disease activity in psoriatic arthritis (without measuring C-reactive protein [CRP])
CI	Confidence interval
CL	Clearance
Cmax	Maximum plasma concentration of drug
CNS	Central nervous system
CRO	Contract research organization
CRF	Case report form
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug: antirheumatic drugs designed in a traditional way, such as methotrexate or sulfasalazine
CT	Computed tomography

Abbreviation or Specialist Term	Explanation
DIP	Distal interphalangeal
DLT	Dose-limiting toxicity
DMARD	Disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EE	Early escape
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End of treatment
[redacted]	
FAS	Full analysis set
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEI	Gladman Enthesitis Index
HAQ-DI	Health Assessment Questionnaire Disability Index
[redacted]	
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IL	Interleukin
IM	Intra-muscular
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Integrated Response Technology

Abbreviation or Specialist Term	Explanation
IWRS	Interactive Web Response System
IV	Intravenous
[redacted]	
LEF	Leflunomide
LEI	Leeds Enthesitis Index
LVEF	Left ventricular ejection fraction
LOCF	Last observation carried forward
LS mean	Least squares mean
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	Minimal clinically important difference
MDA	Minimal disease activity
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
MMRM	Mixed-effects model for repeated measures
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MTX	Methotrexate
MUGA	Multi-gated acquisition
NCI	National Cancer Institute
NRI	Nonresponder imputation
NSAID	Nonsteroidal anti-inflammatory drug
PSAID	Psoriatic Arthritis Impact of Disease
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI 50/70	≥ 50%/75% improvement in the Psoriasis Area and Severity Index
[redacted]	
PBO	Placebo
PDE	Phosphodiesterase enzyme
PRO	Patient-reported outcome
PsA	Psoriatic arthritis
PsAID	Psoriatic arthritis impact of disease
PC	Product Complaint

Abbreviation or Specialist Term	Explanation
QOL	Quality of life
RBC	Red blood cell count
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
[redacted]	
SJC	Swollen joint count
SOP	Standard operating procedure
SpA	Seronegative spondyloarthropathy
[redacted]	
SSZ	Sulfasalazine
SUSAR	Suspected unexpected serious adverse reaction
T½	Half-life
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TB	Tuberculosis
TID	Three times daily
TJC	Tender joint count
TNF	Tumor necrosis factor
ULN	Upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
VAS	Visual analog scale
VLDA	Very low disease activity
Vss	Volume of distribution
WBC	White blood cell count
[redacted]	

Appendix B: The CASPAR Criteria

To meet the CASPAR[1] (Classification criteria for Psoriatic Arthritis) 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 juxtaarticular 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 C: Modified Minimal Disease Activity (MDA-Joints) Assessment

To meet the mMDA-Joints criteria, a patient must achieve ≤ 1 SJC and TJC, plus 3 out of 5 of the following cut-off values:

1. Patient's global disease activity (VAS, 0-100 mm) ≤ 20
2. Patient's pain (VAS, 0-100 mm) ≤ 15
3. HAQ ≤ 0.5
4. Tender entheseal points ≤ 1 (Based on the Leeds Enthesitis Index - LEI)
5. BSA ≤ 3%

Appendix D: Joint Assessment - 68 and 66 Joint Counts

68 Joint Score: Upper Extremity Joint Counts

Please write in the appropriate code for every joint using the Pain/Tenderness and Swelling Codes.

Pain/Tenderness Codes

N = No pain/tenderness
Y = Pain/tenderness
ND = Not Done

Swelling Codes

N = No swelling
Y = Swelling
ND = Not Done

Joints that are swollen and tender should be marked with a tick. If a joint is injected with intra-articular glucocorticoid, this joint should be marked by an X for the next 4 weeks

Joints	Right Side				Left Side			
	Pain/Tenderness		Swelling		Pain/Tenderness		Swelling	
	Y N ND		Y N ND		Y N ND		Y N ND	
Temporomandibular								
Sternoclavicular								
Acromioclavicular								
Shoulder								
Elbow								
Wrist								
MCP 1								
MCP 2								
MCP 3								
MCP 4								
MCP 5								
PIP 1								
PIP 2								
PIP 3								
PIP 4								
PIP 5								
DIP 2								
DIP 3								
DIP 4								
DIP 5								

Appendix D: Joint Assessment – 68 and 66 Joint Counts (Continued)

68 Joint Score: Lower Extremity Joint Counts

Please write in the appropriate code for every joint using the Pain/Tenderness and Swelling Codes.

Pain/Tenderness Codes

N = No pain/tenderness
Y = Pain/tenderness
ND = Not Done

Swelling Codes

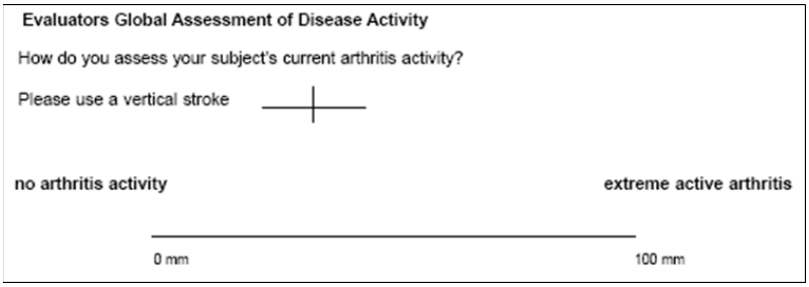
N = No swelling
Y = Swelling
ND= Not Done

Joints	Right Side		Left Side	
	Pain/Tenderness	Swelling	Pain/Tenderness	Swelling
	Y N ND	Y N ND	Y N ND	Y N ND
Hip				
Knee				
Ankle				
Mid-tarsal				
MTP 1				
MTP 2				
MTP 3				
MTP 4				
MTP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				

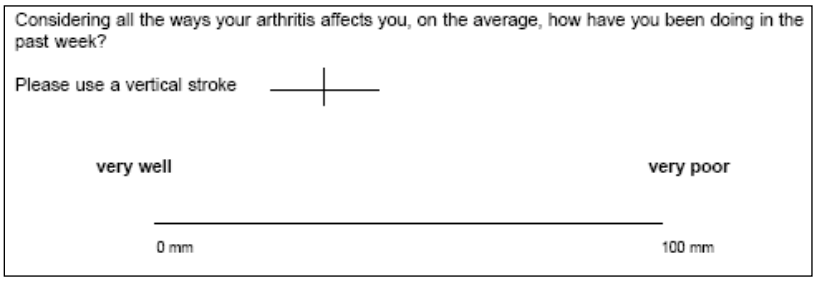
Appendix E: Visual Analog Scale

Scales depicted below are on 0-100 mm scale. Note that for the cDAPSA (Appendix K), both Subject's (Patient's) Global Assessment of Disease Activity and Subject's Assessment of Pain scales will be on 0-10 cm scale.

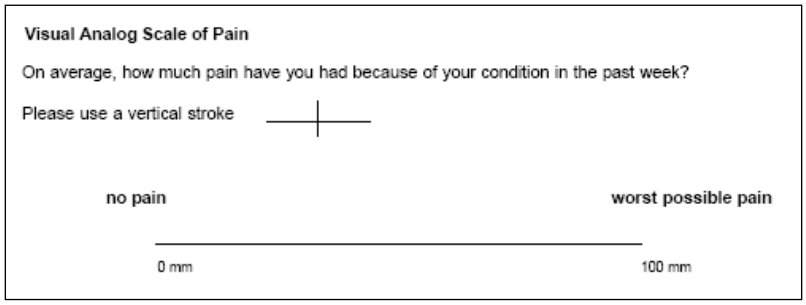
Evaluators Global Assessment of Disease Activity



Subject's (Patient's) Global Assessment of Disease Activity



Subject's Assessment of Pain



From Felson, 1995.

[redacted]

Appendix F: Disability Index of the Health Assessment Questionnaire (HAQ-DI)

When answering the questions below, it does not matter whether you actually do any of the activities mentioned, but whether you would be able to do them.

Please check the response which best describes your usual abilities over the past week:	Without ANY Difficulty 0	With SOME Difficulty 1	With MUCH Difficulty 2	UNABLE to do 3
Dressing and Grooming Are you able to: 1. Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
2. Shampoo your hair?	☐	☐	☐	☐
Arising Are you able to: 3. Stand up from a straight chair?	☐	☐	☐	☐
4. Get in and out of bed?	☐	☐	☐	☐
Eating Are you able to: 5. Cut your meat?	☐	☐	☐	☐
6. Lift a full cup or glass to your mouth?	☐	☐	☐	☐
7. Open a new carton of milk?	☐	☐	☐	☐
Walking Are you able to: 8. Walk outdoor on flat ground?	☐	☐	☐	☐
9. 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
- ☐ Rising
- ☐ Eating
- ☐ Walking

Appendix F: Disability Index of the Health Assessment Questionnaire (HAQ-DI) (Continued)

Please check the response which best describes your usual abilities over the past week:	Without ANY Difficulty 0	With SOME Difficulty 1	With MUCH Difficulty 2	UNABLE to do 3
Hygiene Are you able to: 10. Wash and dry your body?	☐	☐	☐	☐
11. Take a tub bath?	☐	☐	☐	☐
12. Get on and off the toilet?	☐	☐	☐	☐
Reach Are you able to: 13. Reach and get down a 5 -pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
14. Bend down to pick up clothing from the floor?	☐	☐	☐	☐
Grip Are you able to: 15. Open car doors?	☐	☐	☐	☐
16. Open jars which have been previously opened?	☐	☐	☐	☐
17. Turn faucets on and off?	☐	☐	☐	☐
Activities Are you able to: 18. Run errands and shop?	☐	☐	☐	☐
19. Get in and out of a car?	☐	☐	☐	☐
20. Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any *aids or devices* that you usually use for any of these activities:

- ☐ Raised toilet seat
- ☐ Bath tub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Other, specify _____
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in the bathroom
- ☐ Bath tub bar

Please check any categories for which you usually need help from another person:

- ☐ Hygiene
- ☐ Reach
- ☐ Gripping and opening things
- ☐ Errands and chores

Source: Bruce, 2003.

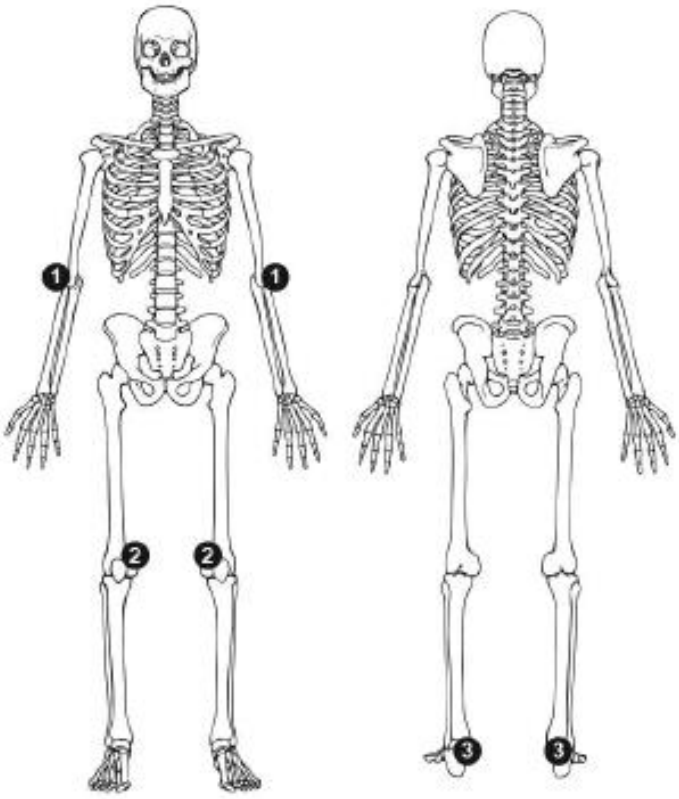
Appendix G: Leeds Enthesitis Index (LEI)

Leeds Enthesitis Index:

Enthesitis is measured by physical examination of the joints below. Tenderness will be assessed at the following entheses (tendon insertions) as depicted below:

1. Lateral epicondyle humerus, left and right
2. Medial condyle femur, left and right
3. Achilles tendon insertion into calcaneum, left and right

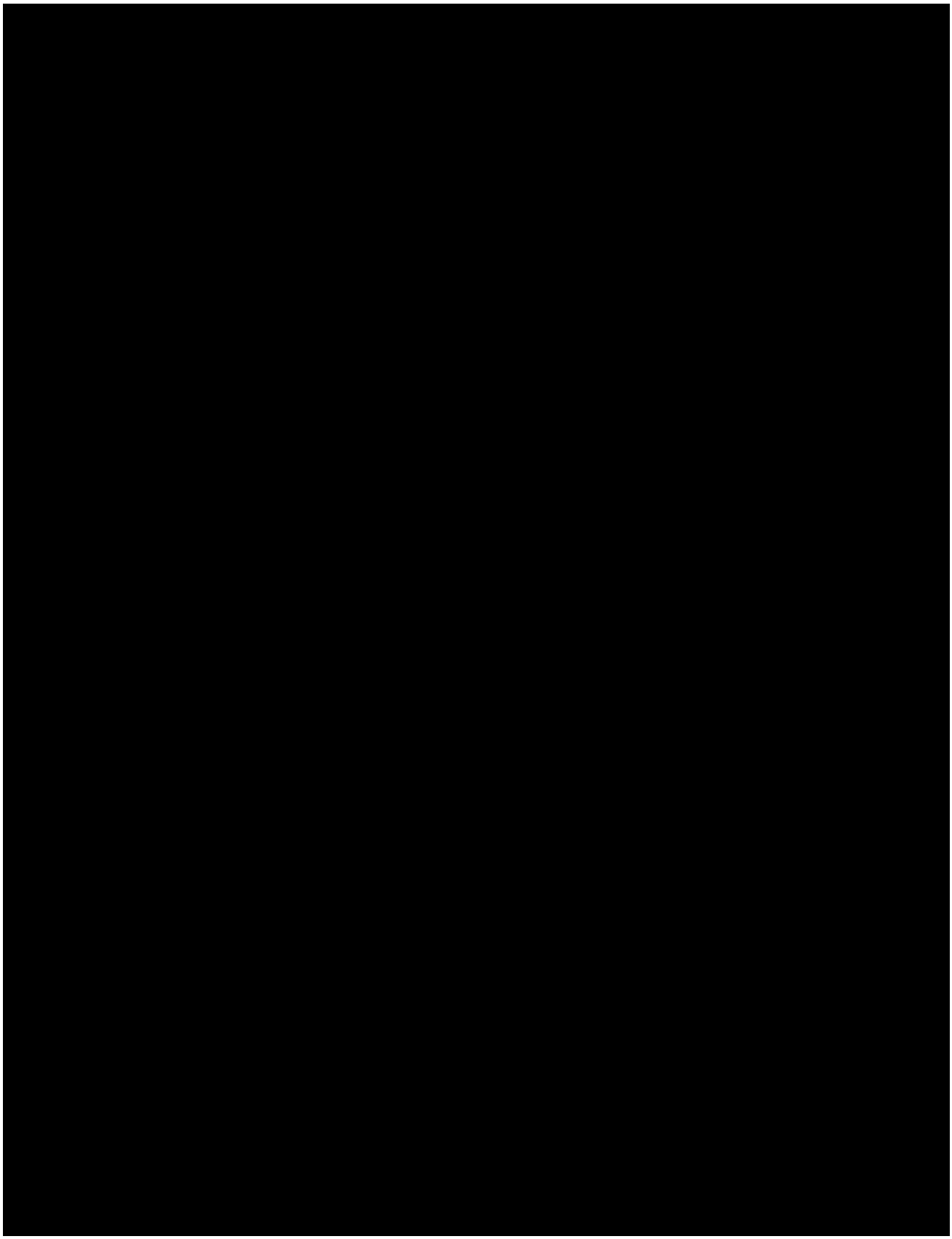
Tenderness on physical examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0 to 6. Higher count represents a greater enthesitis burden.

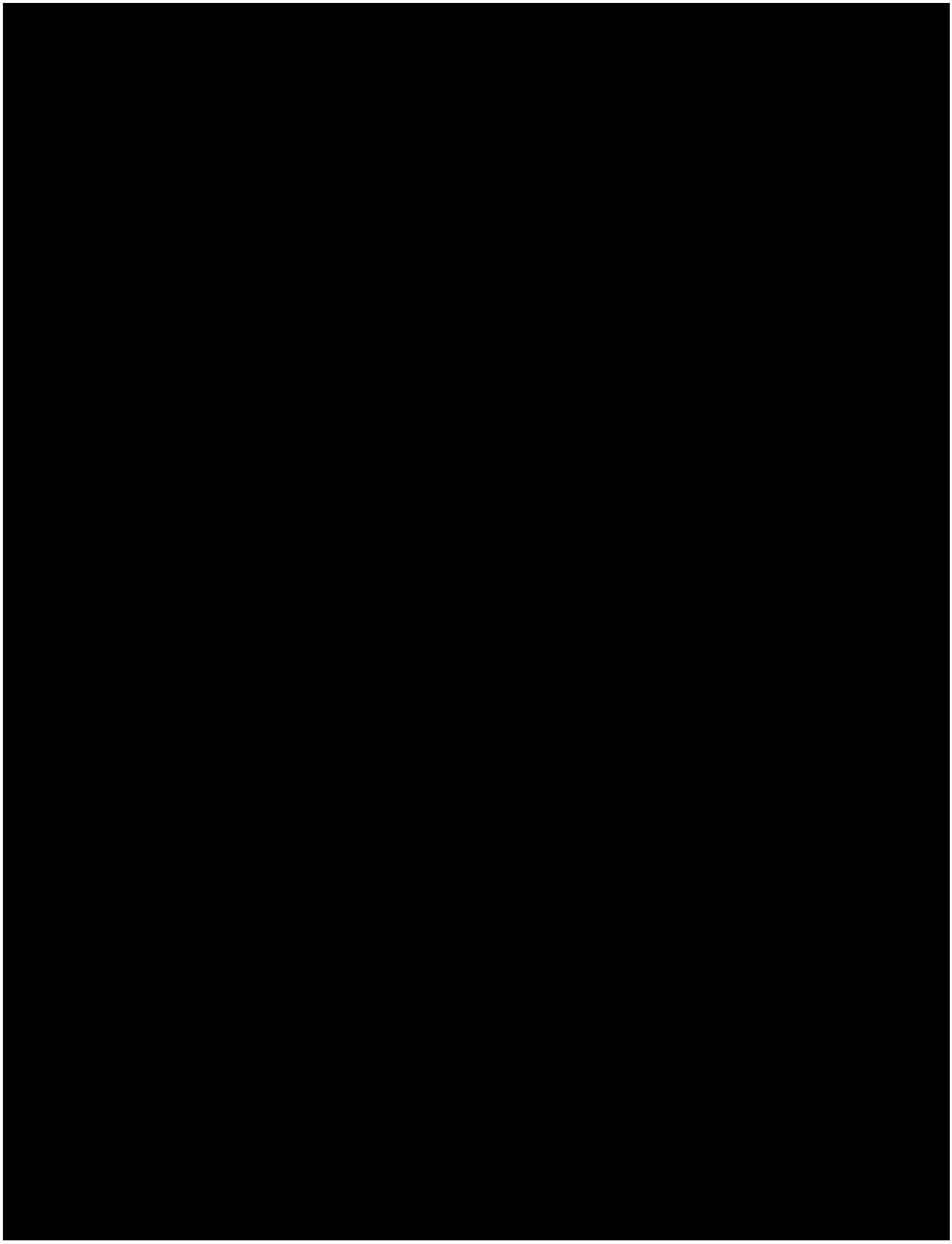


Appendix H: Body Surface Area (BSA)

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

Tutorial is available at http://www.pasitraining.com/bsa_score/





Appendix K: C-Disease Activity index for Psoriatic Arthritis (cDAPSA)

The cDAPSA score assesses four domains (Tender Joint Counts [TJC] and Swollen Joint Counts [SJC] using 66/68 joints count, patient's global VAS on a 10-cm scale, patient's pain VAS on a 10-cm scale. The cDAPSA is calculated by summing swollen + tender joint counts + patient pain + patient global assessments.

The cDAPSA score can be used to effectively separate the disease states of remission (REM), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) by specific cutpoints detailed below:

REM: cDAPSA≤4; LDA: 4>cDAPSA≤13; MDA: 13>cDAPSA≤27; HDA: cDAPSA>27.

Appendix L: Psoriatic Arthritis Disease Activity Score (PASDAS)

The PASDAS is a weighted index comprising assessments of joints, physical function, acute-phase response, patient and physician global assessment of the disease, enthesitis and dactylitis. It is represented by the formula:

PASDAS = **(**(0.18 x √Physician global VAS) + (0.159 x √Patient global VAS) – (0.253 x √SF36 – PCS) + (0.101 x LN (Swollen joint count + 1)) + (0.048 x LN (Tender joint count + 1)) + (0.23 x LN (Leeds Enthesitis Count + 1)) + (0.377 **x** LN (Dactylitis count + 1)) + (0.102 x LN (CRP + 1))+2)*1.5

CRP = C-reactive protein in mg/l, LN = natural logarithm, SF36 = Medical Outcomes Study Short Form-36, SF36-PCS = physical component summary scale of SF36. 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.

Definition of good or moderate response is detailed in the table below:

Response criteria for the Psoriatic Arthritis Disease Activity Score (PASDAS).

	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

Appendix N: The PsA Impact of Disease 12-Item (PsAID-12) Questionnaire

The PsAID-12 Questionnaire (Gossec, 2014) 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.

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

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

Appendix N: The PsA Impact of Disease 12-Item (PsAID-12) Questionnaire (Continued)

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 (ie, 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

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

Appendix N: The PsA Impact of Disease 12-Item (PsAID-12) Questionnaire (Continued)

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

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.

Appendix N: The PsA Impact of Disease 12-Item (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)

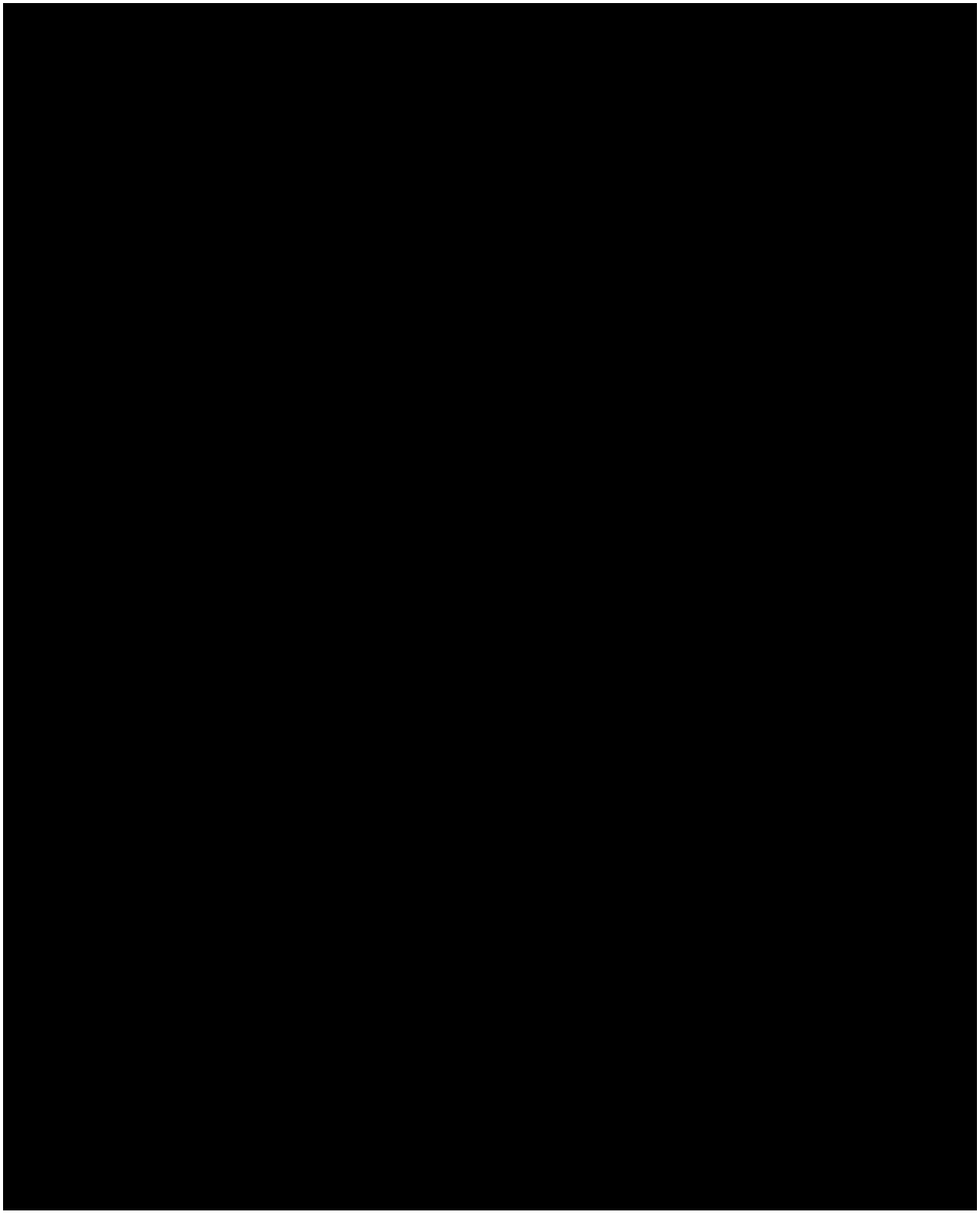
The total is divided by 20. Thus, the range of the final PsAID value is 0-10, where higher figures indicate worse status.

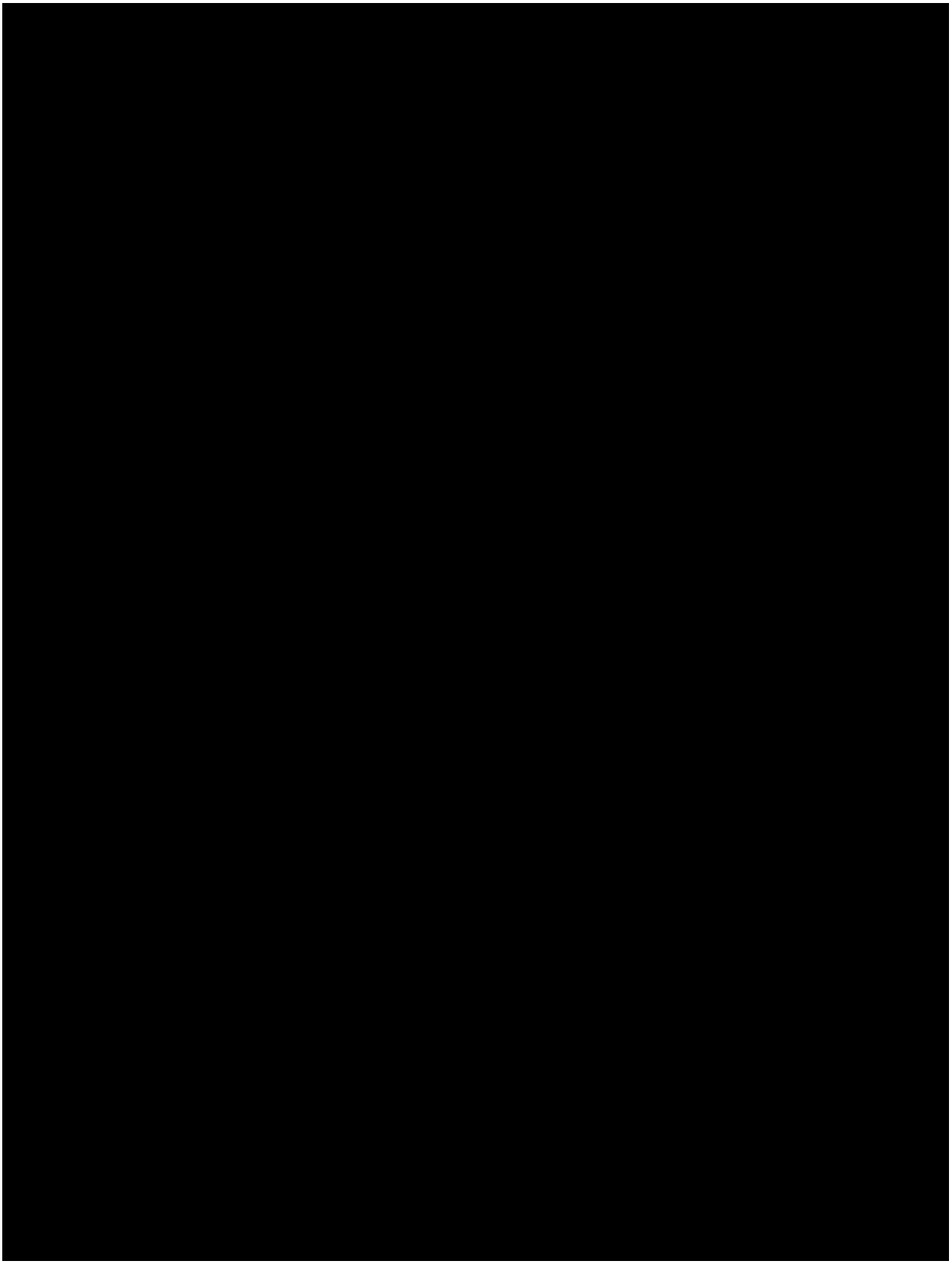
2. Missing data imputation

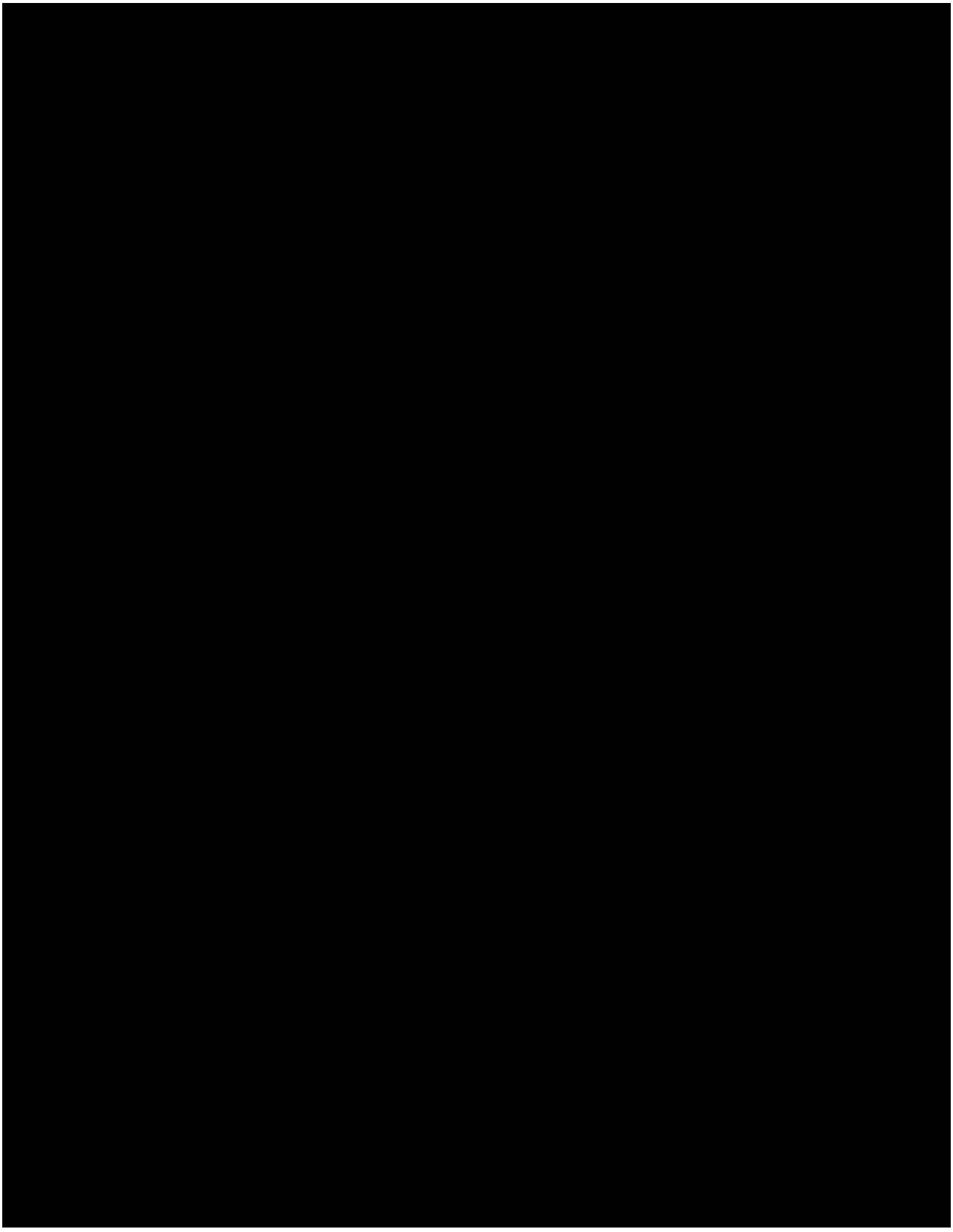
If one of the 12 NRS values composing the PsAID is missing, the imputation is as follows:

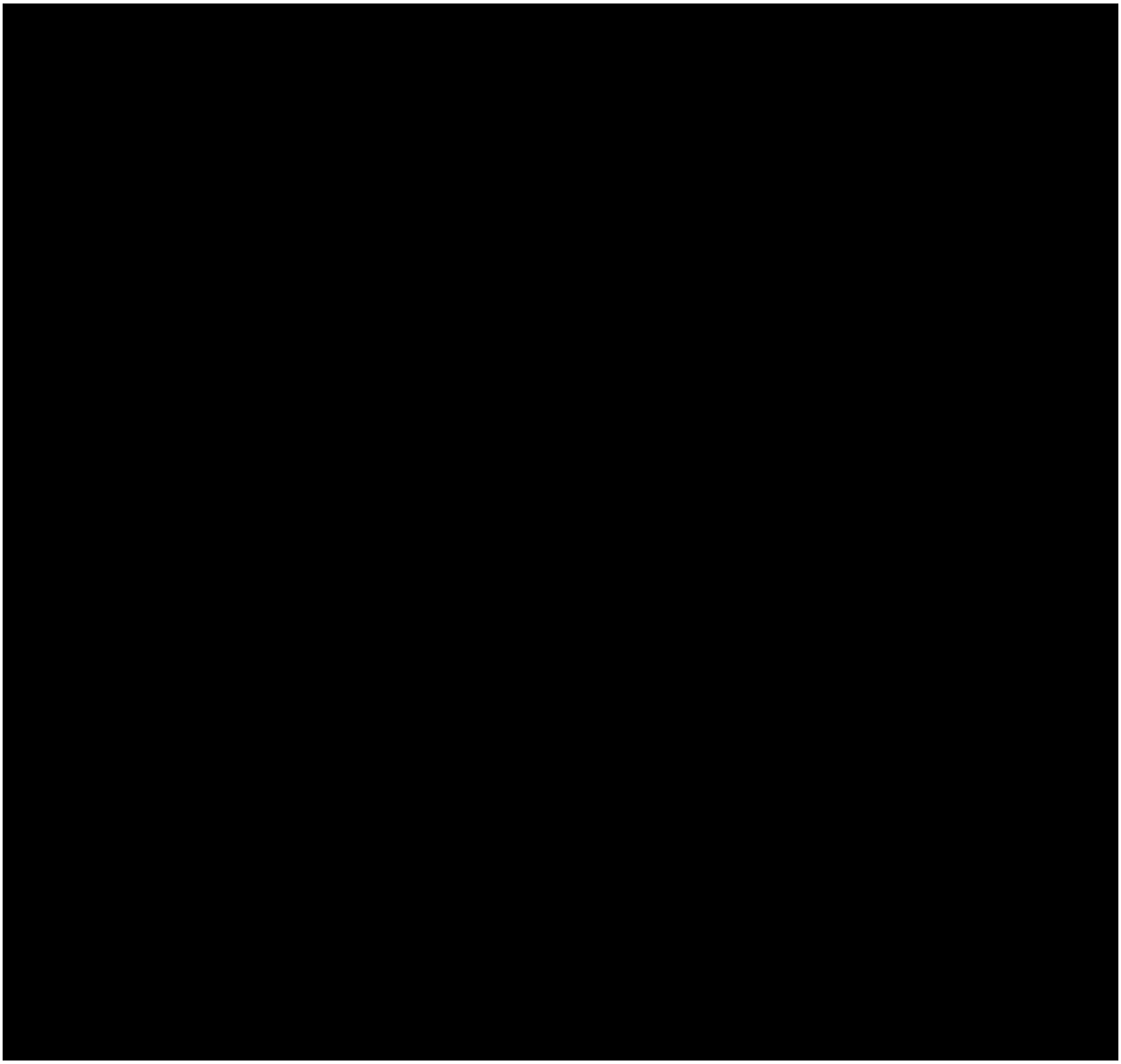
a. calculate the mean value of the 11 other (non-missing) NRS values (range, 0-10)
b. impute this value for the missing NRS value
c. then, calculate the PsAID score as explained above.

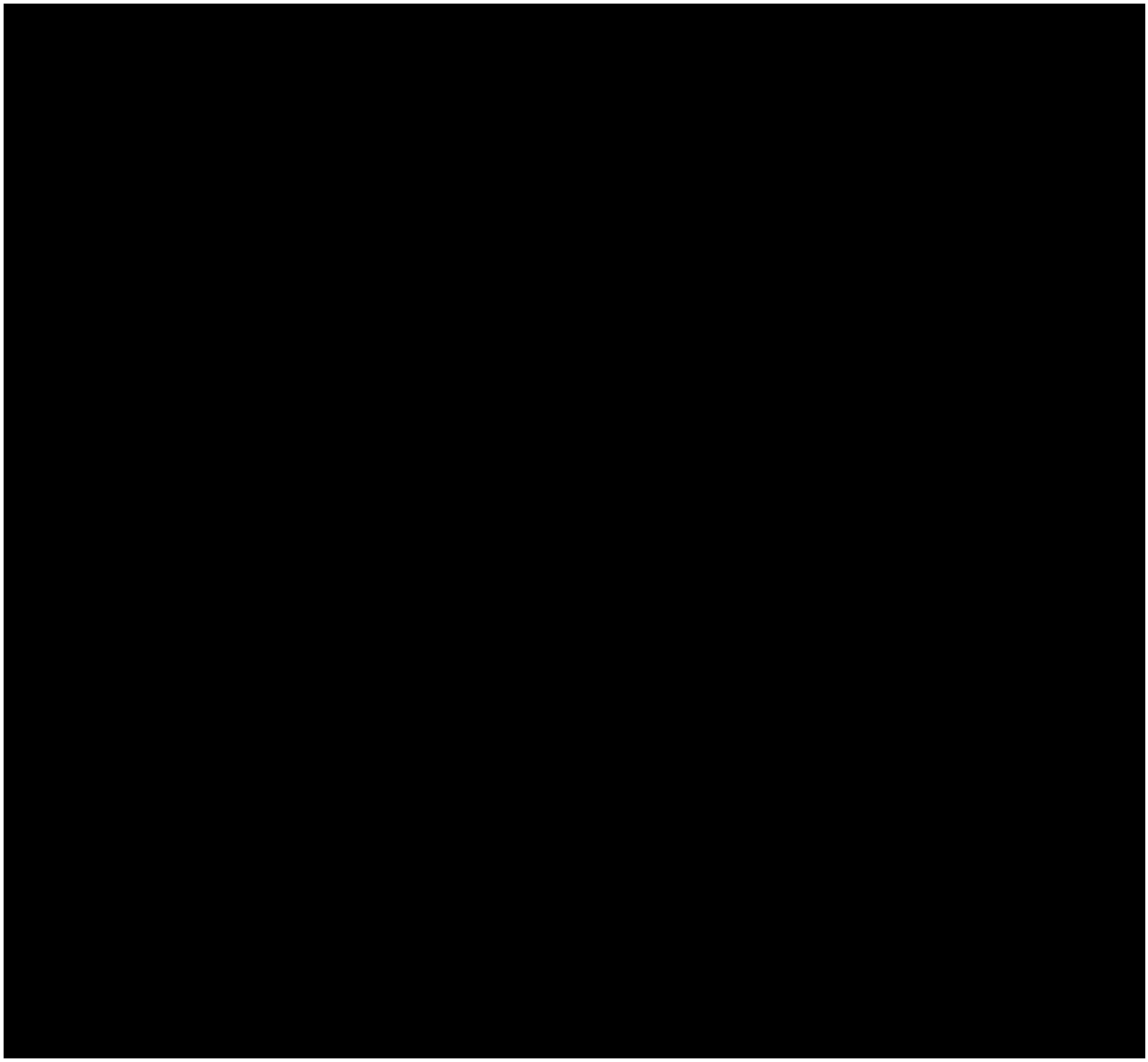
If 2 or more of the NRS values are missing, the PsAID score is considered a missing value (no imputation).

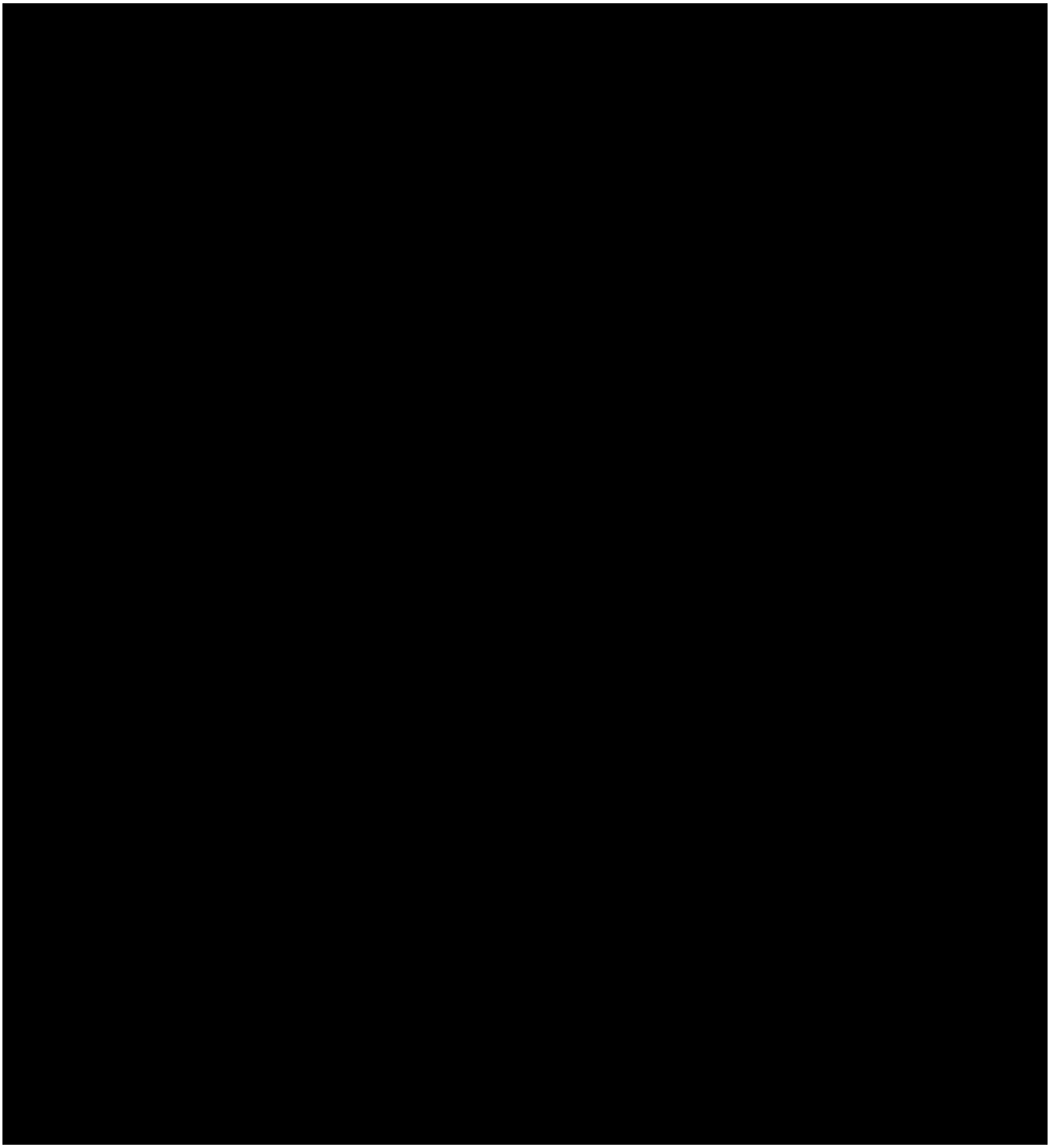


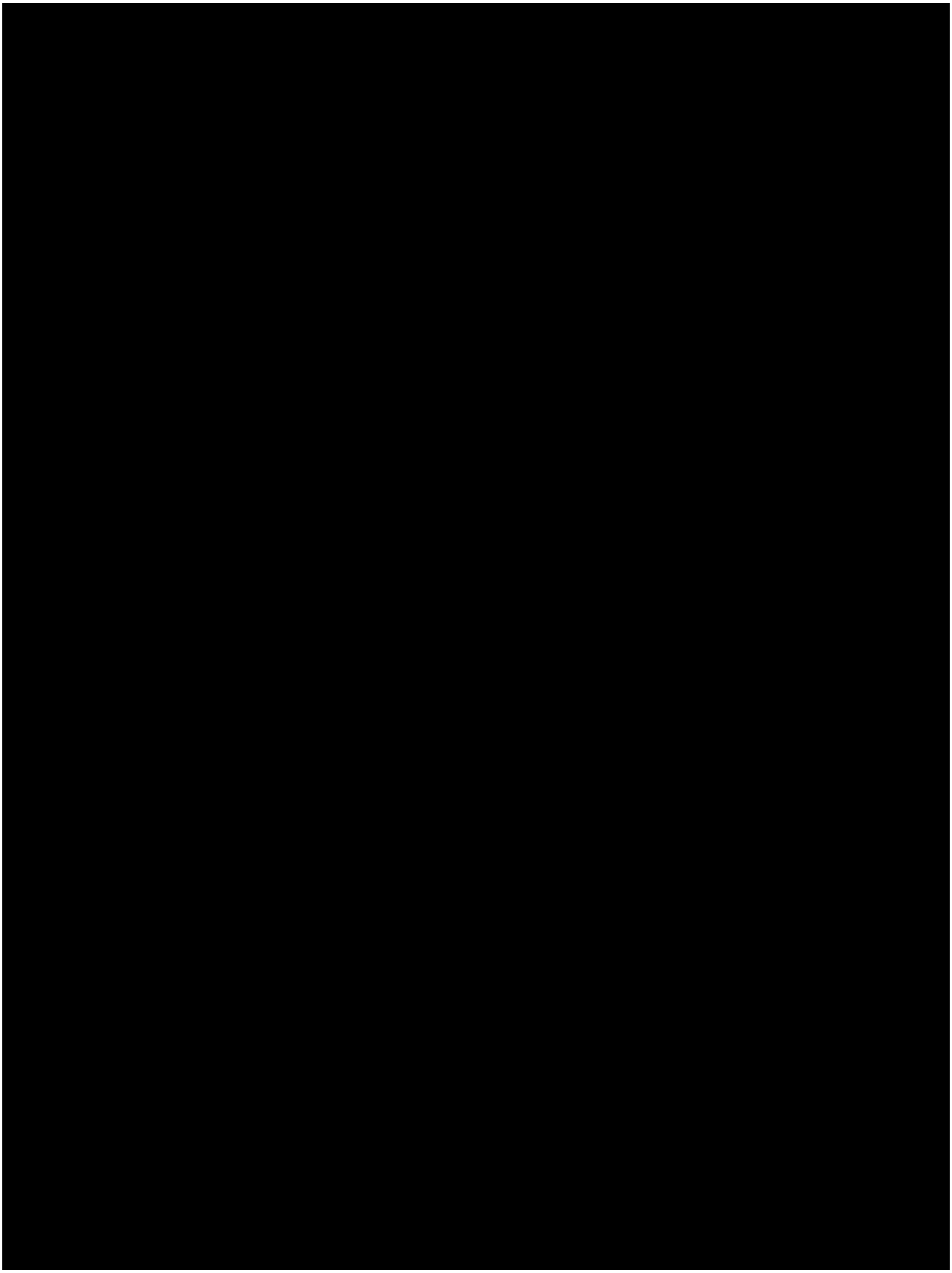


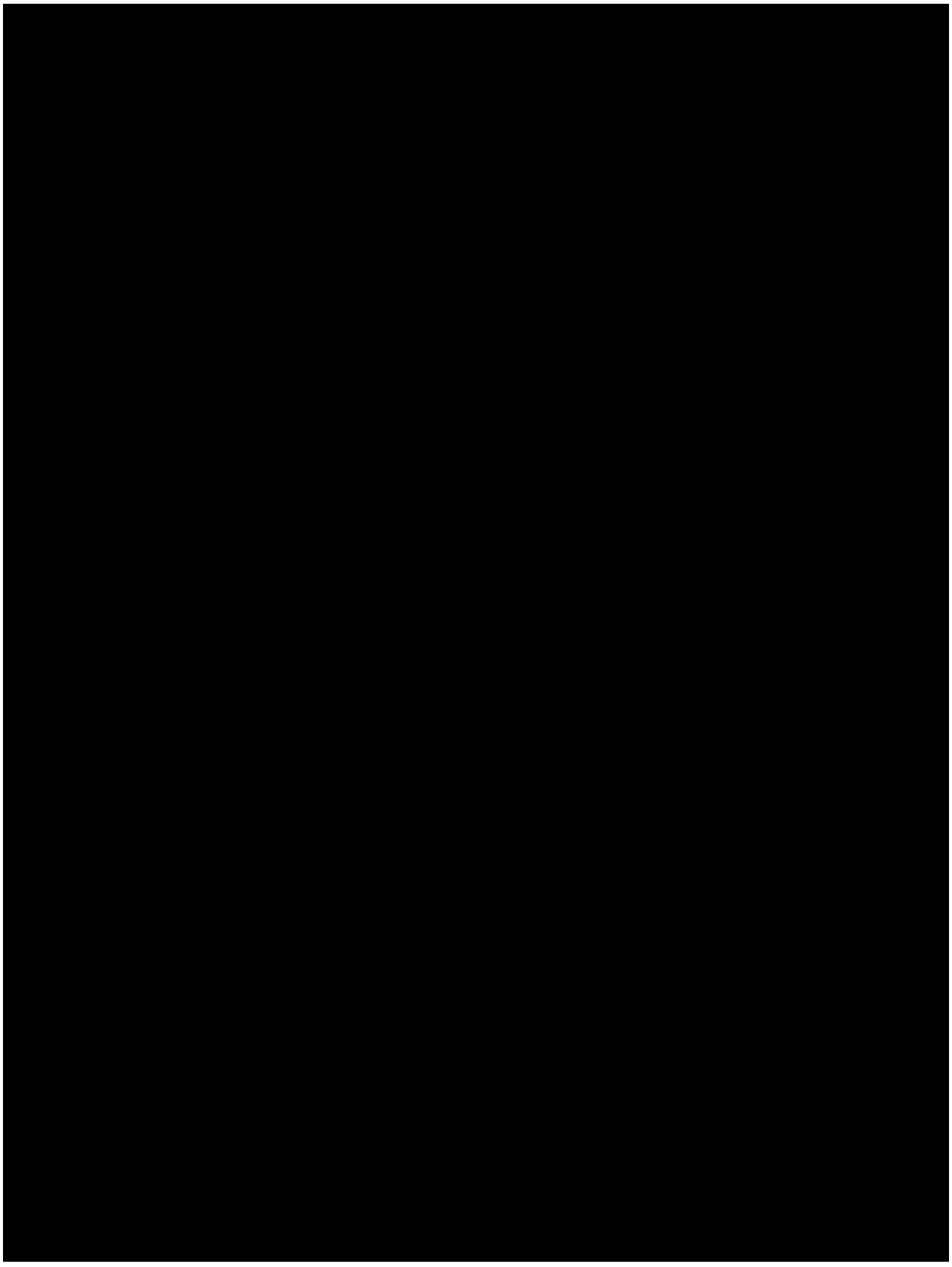




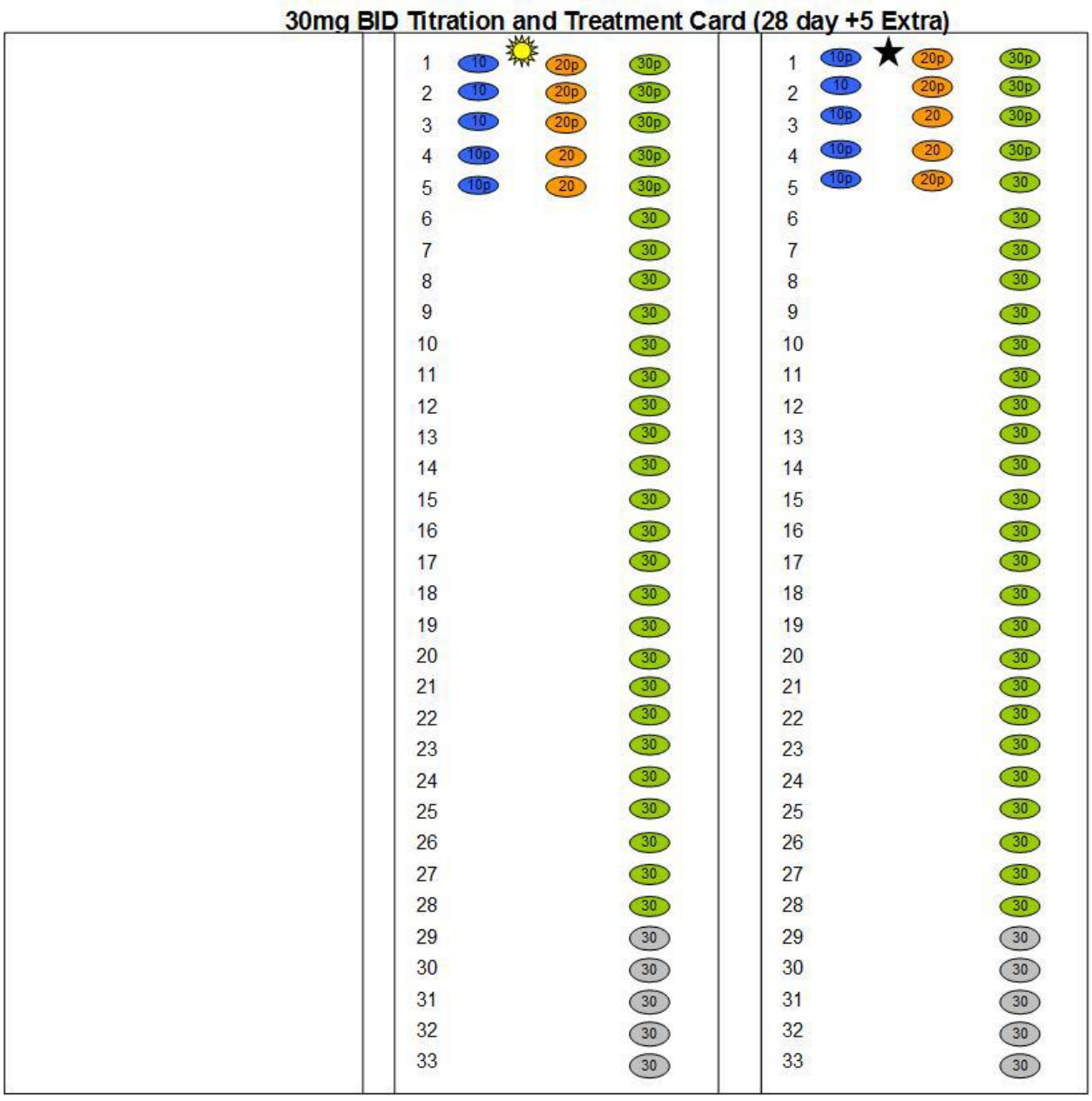






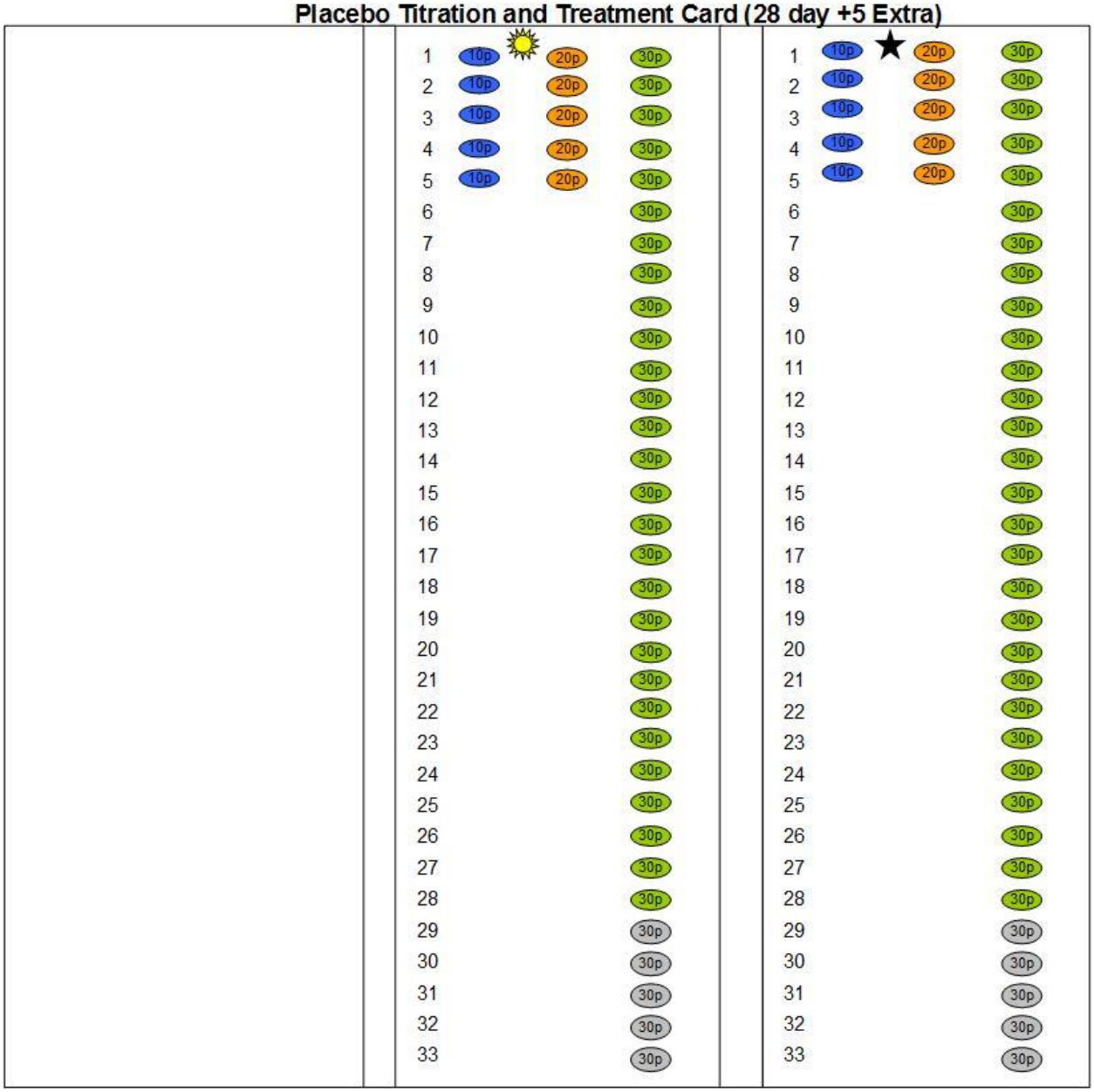


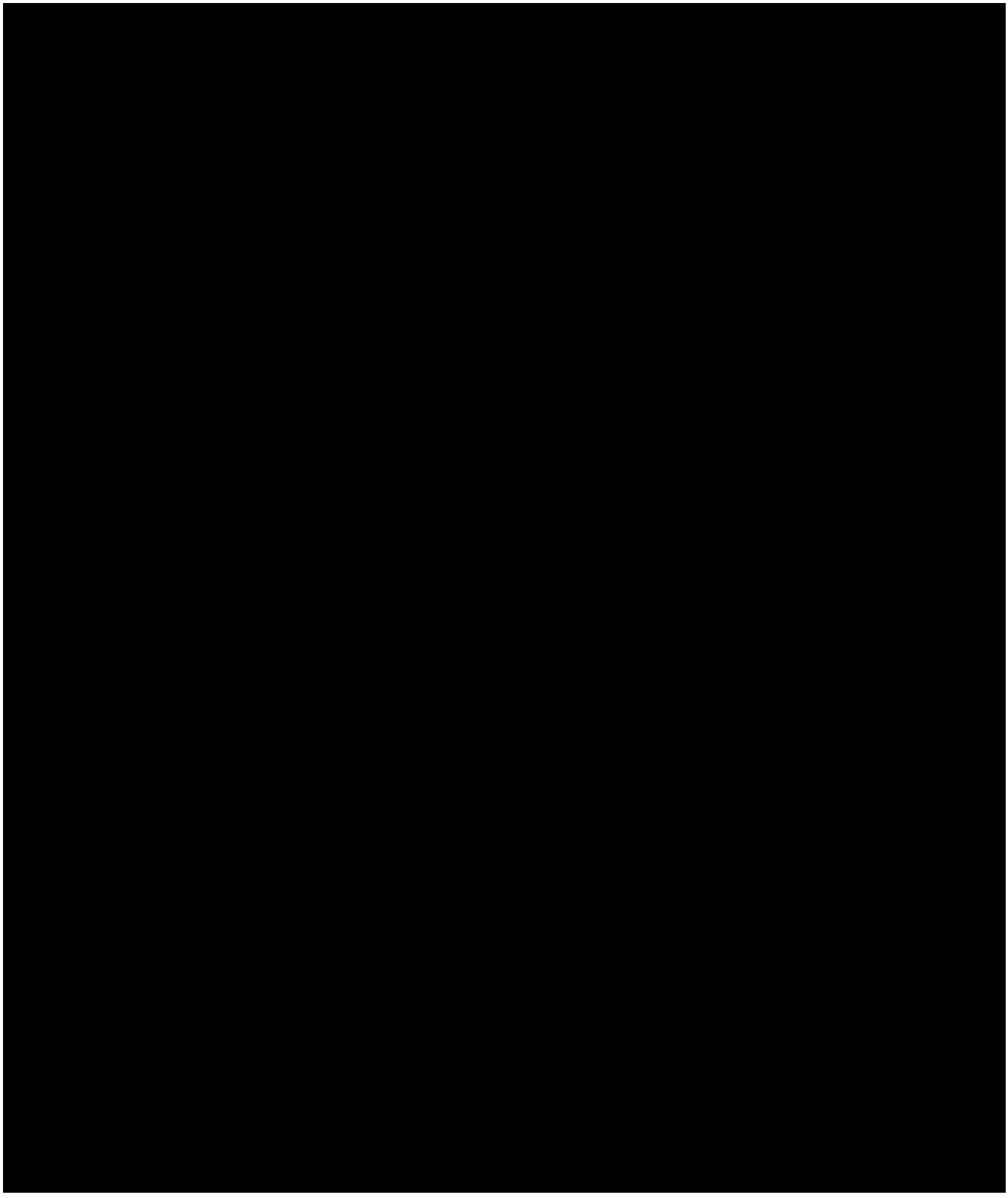
Appendix T: Blister Card Configurations



Appendix T: Blister Card Configurations (Continued)

Placebo Titration and Treatment Card (28 day +5 Extra)





Appendix W: Sample Serious Adverse Event Report Form

AMGEN CC-10004-PSA-013 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	Report Date Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____Month___Year_____

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

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

4. HOSPITALIZATION

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

5. INVESTIGATIONAL PRODUCT (IP)

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

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

Appendix W: Sample Serious Adverse Event Report Form (Continued)

AMGEN CC-10004-PSA-013 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:

	Test											
Date (Day Month Year)	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

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 02-April-2020*
Page 2 of 3

Appendix W: Sample Serious Adverse Event Report Form (Continued)

AMGEN CC-10004-PSA-013 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 X: Pregnancy Notification Form

Amgen Proprietary - Confidential

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-013 (Apremilast/Otezla)

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

Appendix Y: 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-013 (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

Amendment 5

Protocol Title: A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH EARLY, OLIGOARTICULAR PSORIATIC ARTHRITIS DESPITE INITIAL STABLE TREATMENT WITH EITHER NSAIDS AND/OR ≤ 1 CONVENTIONAL SYNTHETIC DMARD

Amgen Protocol Number Apremilast CC-1004-PSA-013 20200058

EudraCT Number: 2018-002735-26

IND Number: 101761

NCT Number: NCT03747939

Amendment Date: 12 July 2021

Rationale:

The rationale of this protocol amendment is to include following updates:

- To update the total number of subjects to be randomized in the study in all the sections wherever applicable.
- To update the inclusion criteria to update language as symptoms of psoriatic arthritis (PsA) with oligoarthritis by any criteria with no minimum time constraint.
- To update the study rationale to include subjects with early diagnosis of PsA (≤ 5 years since signs and symptoms began).
- To update the exclusion criteria for prior use of 2 conventional synthetic disease-modifying antirheumatic drugs.
- To update the exclusion criteria to change the bacterial infections requiring treatment within 1 week of Screening.
- To update the table of events table to include ± 7 days for observational follow-up visit.
- To update the statistical sample size of approximately [redacted] for the active and placebo groups.

– SUMMARY OF CHANGES –

A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH EARLY, OLIGOARTICULAR PSORIATIC ARTHRITIS DESPITE INITIAL STABLE TREATMENT WITH EITHER NSAIDS AND/OR ≤ 1 CONVENTIONAL SYNTHETIC DMARD

AMENDMENT NO. 4

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSA-013**
ORIGINAL DATE:	**09 JUL 2018**
AMENDMENT 1 DATE	**05 FEB 2019**
AMENDMENT 2 DATE:	**17 MAY 2019**
AMENDMENT 3 DATE:	**04 MAY 2020**
AMENDMENT 4 DATE:	**03 FEB 2021**
EudraCT NUMBER:	**2018-002735-26**
IND NUMBER:	**101761**
NCT NUMBER	**NCT03747939**

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:	

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)

JUSTIFICATION FOR AMENDMENT

The purpose for this amendment is to better reflect clinical practice and facilitate enrollment. The following changes were made to the protocol, dated 03 February 2021:

- Change the primary endpoint to week 16, which is closer to the timeframe in which clinicians assess efficacy in clinical practice
- Change inclusion criteria #10, a main reason for screen failure, to remove requirement that treatment with a maximum of 1 csDMARD (methotrexate or sulfasalazine) begin ≤ 6 months prior to Baseline to allow for concomitant use of 1 csDMARD if the subject is on a stable regimen for at least 3 months prior to the Baseline Visit
- Change exclusion criteria #1, another main reason for screen failure, to allow prior use of >1 csDMARD to treat other conditions like psoriasis other than the study indication (PsA)
- Change the early diagnosis period from ≥ 3 months and ≤ 24 months to ≥ 3 months and ≤ 5 years to be consistent with Study CC-10004-PSA-014, an imaging study on joint impact of PsA in the early stages of the disease. This alignment between studies will ensure a more robust clinical and imaging data set in early PsA.
- Change timepoints in secondary efficacy endpoints to include Week 16 instead of Week 24
- This amendment also includes minor clarifications and corrections to the following sections:
  - Section 1.2.1: Key Findings from Clinical Studies
  - Figure 1: Overall Study Design
  - Table 12: Study Endpoints
  - Table 13: Table of Events
  - Section 6.4: Efficacy Assessments
  - Section 6.4.3: Dactylitis
  - [redacted]
  - Section 6.5.5: Diarrhea, Nausea and Vomiting
  - Section 7.8: Overdose
  - Section 8.1: Permitted Concomitant Medications and Procedures
  - [redacted]
- Grammatical and typographical changes were made throughout the protocol.

– SUMMARY OF CHANGES –

A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH EARLY, OLIGOARTICULAR PSORIATIC ARTHRITIS DESPITE INITIAL STABLE TREATMENT WITH EITHER NSAIDS AND/OR ≤ 1 CONVENTIONAL SYNTHETIC DMARD

AMENDMENT NO. 3

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSA-013**
ORIGINAL DATE:	**09 JUL 2018**
AMENDMENT No. 2 DATE:	**17 MAY 2019**
AMENDMENT No. 3 DATE:	**04 MAY 2020**
EudraCT NUMBER:	**2018-002735-26**
IND NUMBER:	**101761**
NCT NUMBER	**NCT037479396**

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:

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 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. **NOTE: Signed by Celgene based on Approval from Amgen Therapeutic Head** [redacted]

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.

Additional updates include changes to the following sections:

- Section 8.1 Permitted Medications: Correction: "Oral glucocorticosteroids are to be taken on a stable dose: prednisone ≤ 10 mg/day (or prednisolone equivalent) for at least 4 weeks prior to the Baseline Visit". The text previous stated "at least 2 weeks prior to the Baseline Visit". This is correctly stated in Inclusion Criteria #8.

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

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

– SUMMARY OF CHANGES –

A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH EARLY, OLIGOARTICULAR PSORIATIC ARTHRITIS DESPITE INITIAL STABLE TREATMENT WITH EITHER NSAIDS AND/OR ≤ 1 CONVENTIONAL SYNTHETIC DMARD

AMENDMENT NO. 2

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSA-013**
ORIGINAL DATE:	**09 JUL 2018**
AMENDMENT No. 2 DATE:	**17 MAY 2019**
EudraCT NUMBER:	**2018-002735-26**
IND NUMBER:	**101761**

Contact Information:

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

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
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

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 the trial.

The IB will be submitted to all sites and clearly identified as the RSI in the clinical trial application (CTA) package.

All references in the protocol that include "approved product labeling" and "Prescribing Information" were removed throughout the following sections of the protocol:

- Section 1.2;
- Section 1.2.1.1.1;
- Section 1.2.1.1.2;
- Section 1.2.1.1.3;
- Section 1.2.2.2,
- Section 7.1.

Exclusion criteria #2 updated to include prior exposure to tyk2 inhibitors as a prohibited medication.

The amendment also includes several other minor clarifications and corrections:

- Section 8.1 Permitted Medications. Intramuscular glucocorticosteroids was deleted.
- Section 8.1 Permitted Medications. NSAIDs and/or narcotic analgesics text updated for clarity.
- Section 8.1 Permitted Medications. Text updated to clarify that only 1 csDMARD is allowed during the first 24 weeks of the study. The first 24 weeks of the study was added.
- Section 8.1 Permitted Medications. Text updated to clarify that after the Week 24 Visit, changes in therapy will be permitted as clinically required for subjects with worsening arthritic symptoms of PsA. The word required was added.
- References. Citation for Kruithof was updated with the abbreviated version.
- Appendix B CASPAR Criteria. Appendix was replaced with a corrected version of the criteria that includes an additional footnote.

– SUMMARY OF CHANGES –

A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH EARLY, OLIGOARTICULAR PSORIATIC ARTHRITIS DESPITE INITIAL STABLE TREATMENT WITH EITHER NSAIDS AND/OR ≤ 1 CONVENTIONAL SYNTHETIC DMARD

AMENDMENT NO. 1

INVESTIGATIONAL PRODUCT (IP):	**Apremilast**
PROTOCOL NUMBER:	**CC-10004-PSA-013**
ORIGINAL DATE:	**09 JUL 2018**
AMENDMENT No. 1 DATE:	**05 FEB 2019**
EudraCT NUMBER:	**2018-002735-26**
IND NUMBER:	**101761**

Contact Information:

Name: [redacted]

Title: Medical Director

Address: PPDI
900 Perimeter Park Drive
Morrisville, NC 27560

Phone: [redacted]

E-mail:

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
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 noted below were made based on Health Authority comments and to align with the approved label for apremilast:

- Section 4.3 Exclusion Criteria; Clarification of Exclusion #8 and addition of Exclusion #9 (laboratory abnormalities) modified to add severe renal disease as a significant laboratory abnormality.
- Section 6.5.7 Clinical Laboratory Evaluations; Creatinine clearance added to support Exclusion Criteria #9.
- Section 6.5.2: Vital Signs, Height and Weight; Section modified to clarify treatment discontinuation for severe weight loss. Weight will be added to every visit. The following sections were also revised:
    - Section 5 Table of Events; Weight assessment increased to be done at every visit to support modification of Section 6.5.2.
    - Section 6.3.1 Safety Follow-up Period; Weight added.
- Section 6.5.4: Psychiatric Evaluation; Section was modified to clarify study discontinuation for psychiatric symptoms.
- Section 6.5.5: Diarrhea, Nausea and Vomiting; Section was added to clarify treatment discontinuation for severe symptoms of diarrhea, nausea and vomiting.
- Section 8.2 Concomitant Medications Not Recommended; Section added to align with guidance provided in the label regarding co-administration of strong cytochrome P450 3A4 enzyme inducers with apremilast.

Significant changes noted below were made based on Health Authority comments:

- Section 4.2 Inclusion Criteria #13; Updated to clarify that contraception, Option 2, may not be acceptable as a highly effective contraception option in all countries per local guidelines/regulations.
- Section 6.5.1 Serum and Urine Pregnancy Tests for Females of Childbearing Potential; Section modified to clarify that additional visits (unscheduled visits) may be done to monitor pregnancy testing.

The amendment also includes several other minor clarifications and corrections:

- Medical Monitor / Emergency Contact Information; Updated with the PPD Medical Monitor names.
- The protocol was modified to update the International Conference on Harmonization with International Council for Harmonisation.
- Section 1.2 Compound Background; As this is a Phase 4 study, approved product labeling or the Investigator brochure (depending on regional regulations) should be used as the reference for additional information on apremilast in this approved indication.

- Section 4.2 Inclusion Criteria #11; Clarification to the wording of discontinuation criteria for sulfasalazine and methotrexate. Also, update was made in Section 8.1 Permitted Concomitant Medications and Procedures.
- Section 4.3 Exclusion Criteria #3; Intra-muscular glucocorticosteroids added. Also, updates were made in Section 8.1 Permitted Concomitant Medications and Section 8.3 Prohibited Concomitant Medications and Procedures.
- Section 6.5.7 Clinical Laboratory Evaluations; "dipstick urinalysis" was deleted to align with the Laboratory Manual. The updates were also made in Section 6 Procedures: (Sections 6.1, 6.2, 6.2.1) and Table 13.
- Section 6.1 Screening Period Demographics; Date of birth deleted to align with current clinical database.
- Section 10 Adverse Events; Updated with the revised language for electronic data capture of safety data ("Safety Gateway").
- Appendix N PSA Impact of Disease 12-Item (PsAID-12) Questionnaire; Calculations and Section 9 updated per statistician's request.
- Appendix T Blister Card Configuration; Treatment cards replaced with the corrected image.