2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Apremilast		
Name of Active Ingredient: CC-10004		

Title of Study:

A Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis

Principal Investigator:

Investigators: A list of investigators is provided in

Study center(s): 84 centers in Belgium; Bulgaria; Canada; Czech Republic; Estonia; France; Germany; Hungary; Italy; Poland; Russian Federation; South Africa; Spain; Taiwan, Province of China; the United Kingdom; and the United States.

Publications (reference): Not applicable

Studied period (years):		**Phase of development:** 3
Date first subject enrolled:	27 Sep 2010	
Date last subject completed last visit:	26 Jan 2017	

Objectives:

Primary:

The primary objective of this study was to evaluate the clinical efficacy of 2 doses of apremilast (APR) (20 mg or 30 mg orally twice daily [BID]), compared with placebo (PBO), on the signs and symptoms of psoriatic arthritis (PsA) after 16 weeks' administration.

Secondary:

The secondary objectives of the study were:

- To evaluate the following in subjects with active PsA who are treated with 2 doses of APR or PBO for up to 24 weeks:
  - Safety and tolerability
  - Efficacy
  - Physical function
  - Fatigue
  - Clinical disease activity
- To evaluate the following in subjects with active PsA who are treated with 2 doses of apremilast for up to 52 weeks:
  - Safety and tolerability

Name of Sponsor/Company: Celgene Corporation **Name of Finished Product:** Apremilast **Name of Active Ingredient:** CC-10004	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

- Efficacy
- Physical function
- Fatigue
- Clinical disease activity

- To evaluate the efficacy, safety, and tolerability of 2 doses of apremilast during up to 5 years of administration to subjects with active PsA.

The exploratory objectives of this study were to evaluate the effect of 2 doses of apremilast on the following disease manifestations for up to 52 weeks' treatment:

- Psoriatic skin lesions
- Axial disease

The health-related quality of life objectives of the study were to evaluate the impact of up to 5 years' treatment with 2 doses of apremilast on:

- General health state
- Worker productivity
- Sleep

Methodology:

This phase 3 parallel-group study with 2 active treatment groups consisted of 2 treatment phases: a 24-week, randomized, double-blind, placebo-controlled phase, and a 236-week active treatment/long-term safety phase consisting of 2 parts (a randomized, double-blind active treatment phase of at least 28 weeks' duration, and an open-label, long-term safety phase of up to 4 years' duration), for an overall study duration of 5 years (260 weeks).

Approximately 495 subjects were to be randomized 1:1:1 to receive PBO (PBO treatment group), APR 20 mg BID (APR 20 BID treatment group), or APR 30 mg BID (APR 30 BID treatment group) during the 24-week, placebo-controlled phase. Apremilast was to be dose-titrated in 10-mg daily increments over the first week of treatment; blinding was maintained by the use of identical blister cards for all subjects.

At Week 16 (the primary endpoint), all subjects whose swollen or tender joint count (SJC or TJC, respectively) had not improved by ≥ 20% were required to enter early escape (EE) to blinded active treatment. Subjects in the PBO group who met EE criteria were to be re randomized 1:1, in a blinded fashion, to receive either APR 20 mg BID (PBO/20 EE treatment group) or APR 30 mg BID (PBO/30 EE treatment group) and dose-titrated during the first week of active treatment. Subjects on active treatment who met EE criteria were to continue to receive, in a blinded fashion, the same dosage of apremilast to which they were originally assigned (APR 20 BID EE and APR 30 BID EE). All subjects who entered EE received blister cards of identical appearance at Week 16.

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

At Week 24, all remaining subjects in the PBO group were to be re-randomized 1:1 in a blinded fashion to receive APR 20 mg BID (PBO/20 crossover [XO] treatment group) or APR 30 mg BID (PBO/30 XO treatment group), and dose-titrated during the first week of active treatment. Subjects who were receiving apremilast at Week 24 (ie, those originally assigned to apremilast or those who entered EE at Week 16) were to remain in their assigned dose groups in a blinded fashion. All subjects received blister cards of identical appearance at Week 24.

Clinical efficacy for amelioration of signs and symptoms of PsA response (ie, 20% improvement per the American College of Rheumatology response criteria [ACR 20]) and physical function (ie, Health Assessment Questionnaire – Disability Index [HAQ-DI]) were to be assessed at Weeks 16, 24, 40, and 52.

To maintain the blind at the site and subject levels, individual subject treatment assignments were not to be revealed to the investigators until after the Week 52 database lock at Year 1, after all analyses were completed and the final results were released. At that time, open-label investigational product (IP) was to be provided at the apremilast dose the subject was receiving at the end of the 52-week phase of the study.

Number of subjects (planned and analyzed):

Planned: 495 subjects

Analyzed: 484 subjects randomized receiving at least 1 dose of IP

Diagnosis and main criteria for inclusion:

Subjects must have satisfied the following criteria in order to be enrolled in the study:

1. Males or females, aged ≥ 18 years at time of consent.
2. Understood and voluntarily signed an informed consent document prior to any study-related assessments/procedures being conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Had a documented diagnosis of PsA (by any criteria) of ≥ 6 months' duration.
5. Met the Classification Criteria for Psoriatic Arthritis at time of screening.
6. Had ≥ 3 swollen AND ≥ 3 tender joints, despite prior or current treatment with disease-modifying antirheumatic drugs (DMARDs) (inadequate control by DMARDs applies to therapeutic failure, loss of insurance, intolerance, adverse effects, or other reasons for discontinuation).
7. Were receiving treatment on an outpatient basis.
8. If taking methotrexate (MTX), leflunomide (LEF), or sulfasalazine (SSZ), had been treated for at least 16 weeks and on a stable dose (oral MTX ≤ 25 mg/week; parenteral MTX ≤ 25 mg/week; LEF ≤ 20 mg/day; SSZ ≤ 2 g/day) for at least 4 weeks prior to screening and through Week 24 of the study. One reduction in DMARD dose was permitted after Week 24.
9. If taking oral corticosteroids, were on a stable dose of prednisone ≤ 10 mg/day or equivalent for at least 1 month prior to screening.
10. If taking nonsteroidal anti-inflammatory drugs (NSAIDs) or narcotic analgesics, were on stable

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

dose for at least 2 weeks prior to screening and through the Week 24 study visit.

11. Low potency topical corticosteroids were allowed as background therapy for treatment of psoriasis on the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study. Subjects with scalp psoriasis were permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. A nonmedicated skin emollient (eg, Eucerin™ cream) was permitted for body lesions only. Subjects must not have used these treatments within 24 hours prior to the clinic visit.
12. Met the following laboratory criteria:
    - White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L)
    - Platelet count ≥ 100,000/mm^3 (≥ 100 x 10^9/L)
    - Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
    - Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamate-pyruvate transaminase [SGPT]) ≤ 2 x upper limit of normal (ULN)
    - Total bilirubin ≤ 2 mg/dL (≤ 34 μmol/L)
    - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)
    - Hemoglobin A1c ≤ 9.0%
13. Male subjects (including those who have had a vasectomy) who engaged in activity in which conception was possible used barrier contraception (male latex condom or nonlatex [eg, polyurethane] condom NOT made out of natural [animal] membrane) while on study medication and for at least 28 days after the last dose of study medication.
14. Females of childbearing potential (FCBP) had a negative pregnancy test at screening and baseline. A FCBP who engaged in activity in which conception was possible used contraception while on study medication and for at least 28 days after taking the last dose of study medication with either: 1) one highly effective form (non-oral hormonal, intrauterine device, tubal ligation, vasectomized partner); or 2) an oral hormonal contraceptive PLUS one additional form of barrier contraception (male or female latex condom or nonlatex [eg, polyurethane] condom NOT made out of natural [animal] membrane, diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide); or 3) two forms of barrier contraception (male or female latex condom or nonlatex [eg, polyurethane] condom NOT made out of natural [animal] membrane) PLUS one of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide.

The presence of any of the following excluded a subject from enrollment:

1. History of clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Apremilast		
Name of Active Ingredient: CC-10004		

major uncontrolled disease.

2. Any condition, including the presence of laboratory abnormalities that placed the subject at unacceptable risk if he/she were to participate in the study or would confound the ability to interpret data from the study.
3. Clinically significant abnormality on 12-lead electrocardiogram (ECG) at screening.
4. Pregnant or breastfeeding female.
5. History of allergy to any component of the IP.
6. Hepatitis B surface antigen positive at screening.
7. Hepatitis C antibody positive at screening.
8. AST (SGOT) and/or ALT (SGPT) > 1.5 x ULN and total bilirubin > ULN or albumin < lower limit of normal (LLN).
9. History of positive human immunodeficiency virus, or congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
10. Active tuberculosis (TB) or a history of incompletely treated TB.
11. Clinically significant abnormality based upon chest radiograph with at least posteroanterior view (radiograph had to be taken within 12 weeks prior to screening or during the screening visit). An additional lateral view was strongly recommended but not required.
12. Active substance abuse or a history of substance abuse within 6 months prior to screening.
13. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of screening. Any treatment for such infections must have been completed at least 4 weeks prior to screening.
14. Malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas and treated [ie, cured] cervical intraepithelial neoplasia or carcinoma in situ of the cervix).
15. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.
16. Erythrodermic, guttate, or generalized pustular psoriasis at randomization.
17. Topical therapy for psoriasis, except as noted in the Inclusion Criteria, within 2 weeks of randomization (including but not limited to topical corticosteroids, topical retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin).
18. Rheumatic autoimmune disease other than PsA, including systemic lupus erythematosis, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia.
19. Functional Class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis.

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

20. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease).
21. Use of the following systemic therapy(ies) within 4 weeks of randomization, including but not limited to: cyclosporine or other calcineurin inhibitors, corticosteroids and small molecule DMARDs (except as noted in inclusion criteria), oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, tacrolimus, azathioprine, fumaric acid esters.
22. Use of phototherapy within 4 weeks of randomization (ie, ultraviolet B light, psoralen ultraviolet light therapy).
23. Use of adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab within 12 weeks of randomization.
24. Use of alefacept or ustekinumab within 24 weeks of randomization.
25. Previous treatment with any cell depleting therapies, including investigational agents (eg, rituximab, Campath®, anti-cluster of differentiation (CD)4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20).
26. Treatment with intravenous gamma globulin, plasmapheresis, or Prosorba™ column within 6 months of baseline.
27. Any previous treatment with alkylating agents such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
28. Prior treatment with apremilast.
29. Therapeutic failure of > 3 agents for PsA (small molecules or biologics), or > 1 biologic tumor necrosis factor blocker. Subjects who terminated previous treatment with small molecules or biologics due to cost or safety, such as discomfort with the subcutaneous injections, may participate in this study after adequate washout.
30. Use of any investigational drug within 4 weeks of randomization, or 5 pharmacokinetic/ pharmacodynamic half-lives, if known (whichever was longer).

Test product, dose and mode of administration:

Apremilast administered orally as 10-, 20-, or 30-mg tablets.

Duration of treatment:

Subjects were to be treated with PBO, APR 20 mg BID, or APR 30 mg BID for up to 24 weeks, followed by an active treatment period in which all subjects were to be treated with APR 20 mg BID or APR 30 mg BID for up to 5 years (260 weeks) in total.

Reference therapy, dose and mode of administration:

Placebo was administered orally as tablets identical in appearance to the 10-, 20-, and 30-mg apremilast tablets.

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Apremilast		
Name of Active Ingredient: CC-10004		

Criteria for evaluation:

Efficacy: Efficacy was primarily assessed as the ACR 20 response at Week 16, which was defined as a ≥ 20% improvement from baseline in TJC and SJC plus ≥ 20% improvement from baseline in 3 of the following 5 assessments: Patient's (Subject's) Global Assessment of Disease Activity (PGA), Evaluator's (Physician's) Global Assessment of Disease Activity (EGA), HAQ-DI score, subject's assessment of pain, and C-reactive protein (CRP) values.

The secondary efficacy endpoints were:

Efficacy at Weeks 16 and 24

- Change from baseline in physical function (HAQ-DI) after 16 weeks of treatment
- Proportion of subjects who achieved an ACR 20 after 24 weeks of treatment
- Change from baseline in physical function (HAQ-DI) after 24 weeks of treatment
- Change from baseline in the 36-item Short Form Health Survey, version 2 (SF-36v2) Physical Functioning Score (PFS) after 16 weeks of treatment
- Proportion of subjects who achieved a modified Psoriatic Arthritis Response Criteria (PsARC) response after 16 weeks of treatment
- Change from baseline in subject's assessment of pain after 16 weeks of treatment
- Change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) in subjects with pre-existing enthesopathy after 16 weeks of treatment
- Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis after 16 weeks of treatment
- Change from baseline in Clinical Disease Activity Index (CDAI) score after 16 weeks of treatment
- Change from baseline in 28-joint Disease Activity Score (DAS28) using CRP as acute phase reactant (DAS28[CRP]) after 16 weeks of treatment
- Change from baseline in Functional Assessment of Chronic Illness Therapy – Fatigue subscale (FACIT-Fatigue) score after 16 weeks of treatment
- Change from baseline in SF-36v2 PFS after 24 weeks of treatment
- Proportion of subjects who achieved a modified PsARC response after 24 weeks of treatment
- Change from baseline in subject's assessment of pain after 24 weeks of treatment
- Change from baseline in the MASES in subjects with pre-existing enthesopathy after 24 weeks of treatment
- Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis after 24 weeks of treatment
- Change from baseline in CDAI score after 24 weeks of treatment
- Change from baseline in DAS28(CRP) after 24 weeks of treatment

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

- Change from baseline in FACIT-Fatigue score after 24 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved by ≥ 20% after 16 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 16 weeks of treatment
- Proportion of subjects with a good or moderate European League Against Rheumatism (EULAR) response after 16 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved by ≥ 20% after 24 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 24 weeks of treatment
- Proportion of subjects with a good or moderate EULAR response after 24 weeks of treatment
- Proportion of subjects who achieved an ACR 50 after 16 weeks of treatment
- Proportion of subjects who achieved an ACR 70 after 16 weeks of treatment
- Proportion of subjects who achieved an ACR 50 response after 24 weeks of treatment
- Proportion of subjects who achieved an ACR 70 response after 24 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 16 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 16 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 24 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 24 weeks of treatment

Efficacy at Week 52

- Proportion of subjects who achieved an ACR 20 response after 52 weeks of treatment
- Change from baseline in physical function (HAQ-DI) after 52 weeks of treatment
- Change from baseline in the SF-36v2 PFS after 52 weeks of treatment
- Proportion of subjects who achieved a modified PsARC response after 52 weeks of treatment
- Change from baseline in subject's assessment of pain after 52 weeks of treatment
- Change from baseline in MASES in subjects with pre-existing enthesopathy after 52 weeks of treatment
- Change from baseline in the dactylitis severity score subjects with pre-existing dactylitis after 52 weeks of treatment
- Change from baseline in CDAI score after 52 weeks of treatment

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

- Change from baseline in DAS28(CRP) after 52 weeks of treatment
- Change from baseline in FACIT-Fatigue score after 52 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved by ≥ 20% after 52 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 52 weeks of treatment
- Proportion of subjects with a good or moderate EULAR response after 52 weeks of treatment
- Proportion of subjects who achieved an ACR 50 response after 52 weeks of treatment
- Proportion of subjects who achieved an ACR 70 response after 52 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 52 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 52 weeks of treatment

Overall Efficacy

For data collected beyond Week 52, summaries are provided for the measures listed below at each visit to Week 260:

- Proportion of subjects who achieved an ACR 20 response
- Change from baseline in physical function (HAQ-DI)
- Change from baseline in the SF-36v2 PFS
- Proportion of subjects who achieved a modified PsARC
- Change from baseline in subject's assessment of pain
- Change from baseline in MASES in subjects with pre-existing enthesopathy
- Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis
- Change from baseline in CDAI score
- Change from baseline in DAS28(CRP)
- Change from baseline in FACIT-Fatigue score
- Proportion of subjects with pre-existing enthesopathy whose MASES improved by ≥ 20%
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1
- Proportion of subjects with a good or moderate EULAR response
- Proportion of subjects who achieved an ACR 50 response
- Proportion of subjects who achieved an ACR 70 response
- Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

The exploratory endpoints were:

- Proportion of subjects in each treatment group, whose psoriasis body surface area (BSA) at baseline was ≥ 3%, who achieved a 75% or greater improvement in Psoriasis Area and Severity Index score (PASI-75)
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score in the subset of subjects in each treatment group with pre-existing axial arthropathy and baseline BASDAI score ≥ 4
- ACR N index (ACR-N)

Post hoc analyses were added for the following endpoints:

- Change from baseline in the individual ACR component scores (TJC, SJC, PGA, EGA, and CRP) at Weeks 16, 24, 40, and 52
- ≥ 0.13-point and ≥ 0.30-point reductions in HAQ-DI at Weeks 16, 24, 40, and 52
- ≥ 2.5-point improvement in SF-36 PFS and SF-36v2 Physical Component Summary (PCS) at Weeks 16, 24, and 52
- Categorical change from baseline in CDAI at Weeks 16, 24, and 52
- Categorical change from baseline in DAS28(CRP) at Weeks 16, 24, 40 and 52
- ≥ 10-point reduction in subject's assessment of pain VAS at Weeks 16, 24, 40, and 52
- ≥ 3.56-point improvement in FACIT- Fatigue at Weeks 16, 24, and 52
- Proportion of subjects in each treatment group, whose psoriasis BSA at baseline was ≥ 3%, who achieved 50% or greater improvement in PASI score (PASI-50)

Health-related quality of life endpoints included:

- Change from baseline in the 25-item Work Limitations Questionnaire (WLQ-25) at Weeks 16, 24, and 52
- Change from baseline in the European Quality of Life 5-Dimensional Questionnaire (EQ-5D) at Weeks 16, 24, and 52
- Change from baseline in the Medical Outcomes Study (MOS) Sleep Score at Weeks 16, 24, and 52

For data collected beyond Week 52, summaries were provided for the measures listed below at each visit to Week 260:

- Change in WLQ-25 score in each treatment group
- Change in EQ-5D score in each treatment group

Safety: Safety was assessed according to the adverse events (AEs); chest radiographs; vital sign measurements, including height and weight; physical examinations; clinical laboratory variables; pregnancy test findings; and 12-lead ECG findings.

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

Statistical methods:

Demographics:

Summary statistics were provided by treatment group for the continuous variables (age, weight, height, and body mass index [BMI]). Number and percentage were provided by treatment group for the categorical variables (age category, sex, race, ethnicity, geographic region, weight category, and BMI category).

Efficacy:

The Full Analysis Set (FAS) was the primary population for the efficacy analyses for the placebo-controlled period. In addition, supportive analyses using the Per-protocol (PP) Population were conducted for the primary endpoint (ACR 20 response at Week 16) and the key secondary endpoint (change from baseline in the HAQ-DI score at Week 16).

The Apremilast Subjects as Randomized/Re-randomized (AAR) Population was used for the analyses of efficacy during the apremilast-exposure period up to Week 260. The AAR Population consisted of all subjects who were randomized or re-randomized to receive apremilast at any time during the study (ie, subjects initially randomized to an APR treatment group at Week 0, subjects initially randomized to PBO who entered EE and were re-randomized to apremilast at Week 16, and subjects initially randomized to PBO who completed 24 weeks of treatment on PBO and, as per the protocol, were re-randomized to apremilast at Week 24). For the analyses using the AAR Population, subjects were included in the treatment group to which they were randomized or re-randomized, irrespective of the IP they actually received.

The analyses of the primary and secondary endpoints evaluated at Weeks 16 and 24 were performed and presented by treatment group (PBO, APR 20 BID, and APR 30 BID). Treatment differences were evaluated only between each APR treatment group and the PBO group and calculated as apremilast minus PBO.

For efficacy analyses, missing data were also subject to the last observation carried forward (LOCF) imputation for the analyses and summaries based on LOCF.

Planned statistical tests were conducted between each apremilast dose and PBO for the primary endpoint and those secondary endpoints evaluated at Week 16 or 24. To control the experiment-wise Type I error rate, formal statistical tests were carried out sequentially for these endpoints, starting with the primary endpoint and then the secondary endpoints evaluated at Week 16 or 24. Then the pair-wise comparisons (APR 30 BID versus PBO and APR 20 BID versus PBO) for each endpoint were performed using the Hochberg procedure.

Specifically, for the primary endpoint (ACR 20 response at Week 16), if the 2-sided p-values from both

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

pair-wise comparisons were ≤ 0.050, then both test results were considered statistically significant and both APR doses were declared efficacious. If the 2-sided p-value from 1 of the 2 pair-wise comparisons was > 0.050 but the 2-sided p-value from the other comparison was ≤ 0.025, then the latter test result was considered statistically significant and the corresponding APR dose tested was declared efficacious. In other situations, neither of the apremilast doses was declared efficacious.

Performing formal pair-wise comparisons with respect to the first secondary endpoint (change from baseline in the HAQ-DI score at Week 16) was conditional on the test results for ACR 20 response at Week 16. If the test results of ACR 20 response for both apremilast doses were statistically significant, then the 2 pair-wise comparisons for the HAQ-DI score were performed using the Hochberg procedure at the $\alpha = 0.050$ level, as described above for ACR 20 response. If the test result of ACR 20 response was statistically significant for only 1 apremilast dose, then comparison between only that apremilast treatment group and the PBO group was conducted for the HAQ-DI score, at the $\alpha = 0.025$ level. If neither ACR 20 response test result was statistically significant, then formal statistical tests were not performed for the HAQ-DI score or the remaining secondary endpoints evaluated at Week 16 or 24.

Formal statistical tests for the remaining secondary endpoints evaluated at Week 16 or 24 were carried out in the same manner.

For planned statistical tests that were not formally performed as a result of the aforementioned multiplicity adjustment strategy, nominal 2-sided p-values (without adjustment for multiplicity) were computed as a measure of the strength of the association between the endpoint and the treatment effect, rather than formal tests of hypotheses. In addition, nominal 2-sided p-values were also computed for other efficacy analyses.

Safety:

The safety analyses for the placebo-controlled period were performed using the Safety Population (all subjects who were randomized and received at least 1 dose of APR or PBO). Safety analyses for the apremilast-exposure period were performed using the Apremilast Subjects as Treated Population (all subjects who received at least 1 dose of APR).

Adverse events were coded according to the Medical Dictionary for Drug Regulatory Activities, Version 14.0. Adverse events occurring during the placebo-controlled period and the apremilast-exposure period were tabulated separately. Treatment-emergent adverse events (TEAEs) were summarized by system organ class, severity, and relationship to IP. Adverse events leading to death or to discontinuation from treatment and serious adverse events (SAEs) were also tabulated. In the by-subject analysis, a subject having the same event more than once was counted only once and by greatest severity.

Laboratory data were summarized by visit descriptively. In addition, shift tables showing the number of subjects with values low, normal, and high based on the normal ranges pretreatment versus post-treatment were provided.

Vital sign measurements, including weight, were summarized descriptively by visit (mean, median, standard deviation, minimum, and maximum). 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 were provided.

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

A total of 484 subjects were included in the FAS for efficacy during the placebo-controlled period (159 PBO, 163 APR 20 BID, and 162 APR 30 BID). A total of 468 subjects who were initially randomized to APR or who were re-randomized from PBO to APR at Week 16 or Week 24 were included in the analyses of efficacy during the apremilast-exposure period up to Week 52 (44 PBO/20 EE, 27 PBO/20 XO, 44 PBO/30 EE, 28 PBO/30 XO, 163 APR 20 BID, and 162 APR 30 BID). Of subjects initially randomized to APR, 91.2% of subjects in the APR 20 BID group and 85.1% of subjects in the APR 30 BID group completed Weeks 0-52 of the study. Of the 346 subjects who continued study participation past Week 52, 211 subjects completed the full 5 years of the treatment (33 PBO/APR 20 BID, 37 PBO/APR 30 BID, 72 APR 20 BID, and 69 APR 30 BID). The majority (346/361; 95.8%) of subjects who completed the Week 52 visit continued in the study. Of the 484 subjects who were randomized and received 1 dose of IP in the study, 301 subjects (62.2%) completed 2 years of study participation, 261 subjects (53.9%) completed 3 years of study participation, 233 subjects (48.1%) completed 4 years of study participation, and 211 subjects (43.6%) completed the full 5 years of study participation.

Baseline demographics, disease characteristics, prior history of PsA medication, and baseline use of PsA medications were consistent with an active PsA population. The study was well-balanced for baseline disease characteristics, with an overall mean (median) TJC of 20.0 (15.0), SJC of 10.0 (8.0), CRP of 0.998 (0.457) mg/dL, DAS28(CRP) of 4.60 (4.53), and psoriatic skin involvement of 6.93% (2.00%) BSA. The mean (median) disease duration was 7.47 (4.75) years. The majority of subjects (83.5%) had been inadequately controlled by prior treatment with small molecule DMARDs only; an additional 15.3% had been inadequately controlled by prior treatment with biologic DMARDs. The majority of subjects (70.2%) were receiving at least one small-molecule DMARD at baseline; 16.7% of subjects were receiving prednisone or its equivalent, and 69.6% of subjects were receiving NSAIDs.

Apremilast demonstrated statistically significant reductions in the signs and symptoms of PsA, as measured by ACR 20 response at Week 16, the primary endpoint, for both the APR 20 BID and APR 30 BID treatment groups, compared with PBO. Comparable treatment effects were observed for the primary endpoint; the ACR 20 response rates at Week 16 were 18.9%, 37.4%, and 32.1% for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The adjusted differences in ACR 20 response rates for APR 20 BID and APR 30 BID treatment groups, compared with PBO, were 18.7% ($p = 0.0002$) and 13.4% ($p = 0.0060$), respectively. The observed positive treatment effect of apremilast on the signs and symptoms of active PsA is supported by multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (eg, nonresponder imputation, LOCF). The statistically significant ACR 20 responses observed in the apremilast treatment groups at Week 16 were maintained at Week 24 (15.7%, 31.3% [$p = 0.0009$], and 24.7% [$p = 0.0394$] for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

Apremilast produced statistically significant and clinically meaningful improvement in physical function, as measured by the HAQ-DI score at Week 16, the key secondary endpoint. A dose effect was observed; the least-squares (LS) mean changes in the HAQ-DI score at Week 16, compared to baseline, were -0.053, -0.157, and -0.193 for the PBO, APR 20 BID, and APR 30 BID treatment groups,

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

respectively. The differences in change from baseline in HAQ-DI with APR 20 BID and APR 30 BID treatment groups, compared with PBO, were -0.104 (p = 0.0320) and -0.140 (p = 0.0042), respectively. The improvement in physical function was evident in the maintenance of statistically significant reductions in HAQ-DI score at Week 24 in the APR 30 BID treatment group. The LS mean change from baseline in the HAQ-DI score at Week 24 was -0.085, -0.165, and -0.206 (p = 0.0191) for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively.

Notably, the mean changes in HAQ-DI score in the apremilast treatment groups at Weeks 16 and 24 exceeded the estimated minimal clinically important difference (MCID) for HAQ-DI of -0.13. The proportion of subjects achieving this MCID, or the MCID of -0.3, at Weeks 16 and 24 was numerically higher compared to PBO in the APR 20 BID treatment group, and nominally significantly higher compared to PBO in the APR 30 BID treatment group.

The majority of other efficacy endpoints incorporated in this study supported the efficacy of apremilast in the reduction of signs and symptoms and improvement of physical function in subjects with active PsA.

Apremilast produced modified PsARC responses at Week 16 that were statistically significant in the APR 30 BID group (48.1%, p = 0.0065), and nominally significant in the APR 20 BID group (47.9%, p = 0.0071), compared with PBO (33.3%). The responses were maintained in the APR 20 BID treatment group at Week 24 (24.5%, 39.9% [nominal p = 0.0026], and 32.1% for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

Apremilast treatment reduced the severity of PsA in this study population, as measured by DAS28(CRP) and CDAI, both of which are composite, objective and subjective, assessments of disease activity. The proportion of subjects with high disease activity (DAS28[CRP] > 5.1 or CDAI > 22) decreased in the APR 20 BID and APR 30 BID treatment groups, compared with PBO. Correspondingly, the proportion of subjects with a DAS28(CRP) < 2.6, indicating remission, or a CDAI ≤ 10, indicating low disease activity or remission, was higher in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, at both Weeks 16 and 24. Consistent with these observations, nominally significant good/moderate EULAR responses were observed at Week 16 in the APR 20 BID (53.4%, nominal p = 0.0001) and APR 30 BID (48.8%, nominal p = 0.0014) treatment groups, compared with PBO (31.4%), which were maintained at Week 24 (21.4%, 41.7% [nominal p = 0.0001] and 33.3% [nominal p = 0.0142] for the PBO, APR 20 BID and APR 30 BID treatment groups, respectively.

The improvement of physical function produced by apremilast was further demonstrated by the statistically significant and clinically meaningful improvements in the SF-36v2 PFS in the APR 30 BID treatment group. The change from baseline in SF 36v2 PFS at Week 16 was 0.81, 2.17, and 2.91 (p = 0.0237) for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. Similarly, the SF-36v2 PCS improved from baseline at Week 16 by 1.96, 3.22, and 3.70 (nominal p = 0.0335) in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The improvements in both the SF-36v2 PFS and PCS exceeded the estimated MCID of 2.5 in the APR 30 BID treatment group, and were generally maintained at Week 24.

Numerically greater improvements in enthesitis, as assessed by MASES, were observed in the apremilast treatment groups compared with PBO at Weeks 16 and 24 among subjects with pre-existing enthesopathy. Similarly, a numerically greater reduction in dactylitis severity score was observed in the APR 30 BID treatment group compared with PBO at Weeks 16 and 24. Notably, the study population

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

was not enriched for pre-existing enthesopathy or dactylitis, nor was the study powered to demonstrate a true effect on enthesitis and dactylitis.

A key feature of PsA is psoriatic skin involvement, which improved significantly with apremilast treatment. A positive treatment effect and dose effect for apremilast on PASI-75 responses was observed in subjects with psoriasis involving ≥ 3% of their body surface at Weeks 16 and 24. The PASI-75 responses at Week 16 were 2.7%, 18.8% (nominal p = 0.0014), and 22.1% (nominal p = 0.0002) in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The responses were maintained in the apremilast treatment groups at Week 24 (4.1%, 25.0% [nominal p = 0.0002], and 27.3% [nominal p = 0.0001] for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively). It should be noted that these results were obtained in a population with low baseline PASI scores (median < 6). If there is a low PASI score or low BSA at baseline, the PASI scale is less sensitive to change and may underestimate the magnitude of improvement. Therefore, the ability of apremilast to improve the PASI score in this population is an important indicator of the treatment effect on the psoriatic component of PsA.

Analyzed using data as observed, the ACR 20 response rates among subjects initially randomized to the APR 20 BID and APR 30 BID treatment groups were comparable at Week 52 (52.9% [64/121] and 52.6% [61/116], respectively) among subjects remaining in the study. Improved physical function, as measured by HAQ-DI, continued up to Week 52. The improvements in HAQ-DI score observed in subjects initially randomized to the APR 20 BID and APR 30 BID treatment groups were comparable at Week 52 (-0.192 and -0.330, respectively) among subjects remaining in the study (n = 125 and 117, respectively). In both apremilast treatment groups, the mean reduction in the HAQ-DI score at Week 52 exceeded the MCID of -0.13, and for the APR 30 BID treatment group, the mean reduction in HAQ-DI exceeded the MCID of -0.30. Across all other endpoints, including those assessing signs and symptoms, physical function, disease activity, psoriasis, and enthesitis and dactylitis, sustained improvements were generally observed up to Week 52 among subjects remaining in the study.

Among PBO subjects who switched to apremilast, responses were generally supportive of the effect of apremilast over time, with the onset of effect observed after 8 weeks (PBO/EE groups) or 16 weeks (PBO/XO groups), and the maintenance of effect observed up to Week 52 among subjects remaining in the study.

Among subjects remaining in the study after Week 52, efficacy parameter findings were maintained or improved over time. The ACR 20/50/70 response rates over time were similar to the results seen at Week 52. The TJC and SJC improvements were maintained in both the APR 20 BID and APR 30 BID groups over 5 years of treatment. The HAQ-DI scores were maintained or improved over time in both the APR 20 BID and APR 30 BID treatment groups. The modified PsARC response rates were maintained in both the APR 20 BID and APR 30 BID treatment groups through Week 260. Improvements in the DAS28 and CDAI scores were maintained in both the APR 20 BID and APR 30 BID treatment groups at Week 260. The SF-36v2 PFS and PCS improvements were maintained or improved in both the APR 20 BID and APR 30 BID treatment groups at Week 260. Improvements in MASES were maintained in the APR 20 BID and APR 30 BID treatment groups. A positive PASI-75 response rate was maintained in both the APR 20 BID and APR 30 BID treatment groups to Week 260.

This study was not designed to make formal comparisons between the apremilast treatment groups. The

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

observed positive treatment effect of apremilast on the signs and symptoms of active PsA as measured by the ACR 20 response during the placebo-controlled period were comparable for the APR 20 BID and APR 30 BID treatment groups. However, outcomes for APR 30 BID were generally greater than those for APR 20 BID for endpoints relating to physical function (eg, HAQ-DI and SF-36v2 physical domain). Of additional note, exploratory PASI-75 responses also suggested a dose response in favor of apremilast 30 mg BID. Improvement in fatigue (as determined by mean change in FACIT-Fatigue) achieved nominal significance only for the apremilast 30 mg BID dose. At Week 52, in subjects who remained in the study, ACR 20 responses were comparable between the APR 20 BID and APR 30 BID treatment groups, and the improvement in the HAQ-DI score was greater in the APR 30 BID treatment group than in the APR 20 BID treatment group.

Thus, apremilast, at dosages of 20 and 30 mg BID, significantly reduced disease signs and symptoms, and improved physical function and psoriatic skin disease, in subjects with active PsA. During the placebo-controlled period, a generally greater magnitude and consistency of clinical response was observed with APR 30 BID over APR 20 BID. Maintenance of therapeutic effect was observed across all measures of efficacy among subjects receiving up to 260 weeks of apremilast treatment.

SAFETY RESULTS:

During the 24-week, placebo-controlled period, the incidence of TEAEs was 45.3% in the PBO group but was higher in the APR 20 BID and APR 30 BID treatment groups (65.0% and 59.3%, respectively). TEAEs that led to discontinuation occurred in 1.9%, 3.1%, and 7.4% of subjects in the PBO, APR 20 BID and APR 30 BID groups, respectively. The majority of TEAEs were mild to moderate in severity; the incidence of severe TEAEs was low and increased in a treatment-dependent, but not clearly dose-dependent manner (3.1%, 1.8%, and 6.8% in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively). The incidence of SAEs was low and comparable across treatment groups (1.9%, 3.7%, and 2.5%, respectively). During the apremilast-exposure period (with up to 260 weeks of exposure to apremilast), the incidence of TEAEs was 86.3% in the APR 20 BID treatment group and 88.5% in the APR 30 BID treatment group and led to discontinuation in 10.3% and 12.8% of subjects, respectively. The majority of TEAEs were mild to moderate in severity. The incidence of severe TEAEs was similar between treatment groups (15.0% and 15.8% in the APR 20 BID and APR 30 BID groups, respectively). The incidence of SAEs was comparable between treatment groups (17.5% for both the APR 20 BID and APR 30 BID treatment groups).

During the placebo-controlled period, gastrointestinal events, particularly diarrhea and nausea, accounted for the most frequently reported TEAEs. The frequency of diarrhea and nausea increased in a dose-dependent manner, and tended to be highest during the first week of dosing, with approximately two-thirds of such events resolving within 1 month. These events were predominantly mild to moderate in severity and most of these events did not lead to discontinuation.

Other frequently reported TEAEs during the placebo-controlled period included headache (reported in 4.4%, 5.5% and 11.7% of subjects in the PBO, APR 20 BID and APR 30 BID groups, respectively) and upper respiratory tract infection (reported in 3.8%, 8.6% and 6.8% of subjects in the three groups, respectively). All other TEAEs were reported by fewer than 5% of subjects in any treatment group. All upper respiratory tract infections during the placebo-controlled period were mild to moderate in severity. In the apremilast-exposure period, headache was reported in 9.8% and 12.8% of subjects in the APR 20

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

BID and APR 30 BID groups, respectively, and upper respiratory tract infection was reported in 17.9% and 15.8% of subjects in the two groups, respectively. Additionally, during the apremilast-exposure period, nasopharyngitis was reported by 12.0% and 12.8% of subjects in the APR 20 BID and APR 30 BID treatment groups, respectively.

Serious TEAEs were reported at a slightly higher frequency in the APR treatment groups compared with the PBO group during the placebo-controlled period; each individual SAE during this period was reported by 1 subject per treatment group. During the apremilast-exposure period, with prolonged dosing of up to 260 weeks, or in subjects who were re-randomized from PBO to APR at Week 16 or 24, the overall rate of SAEs was comparable between the APR 20 BID and APR 30 BID treatment groups (17.5% for both). Most SAEs during this period were reported for ≤ 2 subjects, except for depression, osteoarthritis, and psoriatic arthropathy (n = 4 each), as well as diverticulitis and intervertebral disc protrusion (n = 3 each). Among subjects initially randomized to apremilast, there were several new SAEs (25 in the APR 20 BID treatment group and 22 in the APR 30 BID treatment group) reported between Weeks 24 and 260.

There were 2 deaths reported during the apremilast-exposure period. A subject in the APR 30 BID treatment group died on Day 1339 of study participation (Day 1227 of apremilast dosing) due to a cerebrovascular accident. A subject in the APR 30 BID treatment group died on Day 1291 of study participation due to cerebral infarction. Neither death was considered by the investigators to be related to study drug.

The frequency of TEAEs was higher among female subjects than male subjects treated with apremilast in both the placebo-controlled period and the apremilast-exposure period. During the placebo-controlled period, there was a slightly higher overall proportion of TEAEs among subjects who were < 65 years old at baseline compared with subjects who were ≥ 65 years old at baseline. This imbalance was primarily driven by diarrhea; however, the number of subjects was too small to draw meaningful conclusions. During the apremilast-exposure period, no effect of age on overall proportions of TEAEs was noted. The number of subjects in these subgroups (sex and age) is too small, however, to make meaningful conclusions. In both the placebo-controlled and apremilast-exposure periods, the frequency of TEAEs in the APR treatment groups was numerically lower among subjects who were taking concomitant DMARDs than subjects who were not taking concomitant DMARDs.

The findings of the apremilast-exposure period analyses were corroborated by an analysis of the apremilast arms of the Safety Population through Week 260, in that the overall incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and SAEs did not increase with prolonged exposure to apremilast.

Laboratory abnormalities in hematology and chemistry tests were infrequent and comparable between the apremilast treatment groups and PBO, and showed no evidence of organ toxicity requiring laboratory monitoring. Individual, markedly abnormal values were infrequent and limited to isolated (single values) excursions outside the normal range. There were no cases of liver enzyme elevations meeting Hy's Law. Apremilast did not cause myelosuppression based on routine complete blood count.

Adverse events of special interest (based on mechanism of action, possible class effects, known comorbidities of PsA, and other factors) were infections (including TB), MACE, malignancies, suicidal ideation and behavior, gastrointestinal events, and vasculitis. While infections were reported in a higher proportion of apremilast-treated subjects than PBO subjects during the placebo-controlled period, there

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Apremilast	Volume:	
Name of Active Ingredient: CC-10004	Page:	

was no apparent dose effect observed in either study period. Serious infections were reported in 15 subjects during the apremilast-exposure period; most of these were reported by 1 subject each, with the exception of diverticulitis, which was experienced by 2 subjects in the APR 20 BID treatment group and occurred twice in 1 subject in the APR 30 BID treatment group. Diverticulitis resulted in a dosing interruption for 1 of these subjects in the APR 20 BID treatment group and in no change in dosing for the other 2 subjects, and resolved in all cases.

There were 2 cases of *Herpes* infection reported during the placebo-controlled period, one in the PBO group and one in the APR 20 BID group. There were 12 cases of *Herpes* infection reported for 3 subjects in the APR 20 BID treatment group, 1 subject in the APR 20/30 BID treatment group, and 8 subjects in the APR 30 BID treatment group during the apremilast-exposure period. Six of these 12 cases were nonserious herpes zoster infections (n = 2, 1, and 3, respectively).

There was no testing for latent tuberculosis (eg, tuberculin skin test or Quantiferon) in this trial, which included countries with higher prevalent rates of TB than North America or western Europe. There were no cases of de novo or reactivation of TB among subjects with TB-related medical history during the study.

There were 2 cardiac disorders identified as possible MACEs during the study. Both myocardial infarctions were experienced by subjects who were randomized to the APR 20 BID treatment group, but neither of these events was considered drug related, and both subjects continued in the study. There was no evidence of any effect of apremilast on the overall incidence of malignancies, or on the incidence of any individual malignancy. There was 1 case of suicidal ideation in a subject who was hospitalized for worsening depression following the death of a family member. Three additional subjects were hospitalized for worsening depression, 1 of whom discontinued apremilast as a result.

At the end of the apremilast-exposure period, the mean percentage weight loss was 2.22% in the APR 20 BID treatment group and 1.08% in the APR 30 BID treatment group. The majority of subjects maintained their weight within ± 5% of baseline; however, weight loss > 5 kg to ≤ 10 kg was observed in 11.7% of subjects who received apremilast (11.3% in the APR 20 BID treatment group and 10.4% in the APR 30 BID treatment group). Three subjects experienced weight loss of > 20% (1 subject randomized to the APR 20 BID treatment group and 2 subjects randomized to the APR 30 BID treatment group. The proportion of subjects who reported weight loss tended to increase among subjects with higher baseline BMI.

Apremilast demonstrated an acceptable safety profile following long-term (up to 260-week) exposure in both the APR 20 BID and APR 30 BID treatment groups. Based on the exposure-adjusted incidence rate, there was no increase in the incidence of TEAEs. The nature and severity of TEAEs did not change with long-term exposure, and no increased risk for laboratory abnormalities was observed. Prolonged exposure to apremilast did not result in an increased incidence of TEAEs for any category presented.

CONCLUSION:

This study demonstrated that apremilast, a selective PDE4 inhibitor, was an effective treatment with an acceptable safety profile for subjects with active PsA and confirmed the results of previous Phase 2 and Phase 3 studies of apremilast in subjects with PsA. Apremilast, used alone or in combination with other small-molecule DMARDs, provided statistically significant reductions in the signs and symptoms of active PsA when used in dosing regimens of either 20 mg BID or 30 mg BID. This benefit is seen in

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Apremilast		
Name of Active Ingredient: CC-10004		

subjects previously treated with small molecule or biologic DMARDs. Both dose regimens of apremilast also resulted in statistically significant and clinically meaningful improvements in physical function that were maintained for up to 260 weeks of treatment. Although comparable treatment effects were observed for the primary endpoint of modified ACR 20 response during the placebo-controlled period, the other measures of efficacy were more consistently positive for the APR 30 BID treatment group compared to the APR 20 BID group. The therapeutic effect was maintained across all measures of efficacy among subjects receiving up to 260 weeks of treatment.

Apremilast was generally well tolerated, with both dose levels (20 mg BID and 30 mg BID) demonstrating comparable and acceptable safety profiles with up to 260 weeks of exposure in this study. Based on a generally greater magnitude of clinical response and a comparable safety and tolerability profile, a more favorable benefit:risk profile was observed for APR 30 mg BID over that for APR 20 mg BID. Apremilast provides a novel, oral therapeutic option for the reduction of signs and symptoms and improvement in physical function in patients with PsA.

Date of the report:
08 May 2018