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## 2. SYNOPSIS

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| **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 who have not been previously treated with disease-modifying antirheumatic drugs

**Principal Investigator:**

**Investigators:** A list of investigators is provided in Appendix 16.1.4.

**Study center(s):** The study was conducted at 99 centers in Australia, Bulgaria, Canada, the Czech Republic, Estonia, France, Hungary, Italy, Lithuania, New Zealand, Poland, Romania, the Russian Federation, the United Kingdom, and the United States of America.

**Publications (reference):** Not applicable

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| **Studied period (years):**<br>Date first subject enrolled: 09 December 2010<br>Date last subject completed Week 24 visit: 14 January 2013 | **Phase of development:** 3 |

**Objectives:**

Primary:

The primary objective of this study was to evaluate the clinical efficacy of two doses of apremilast (20 mg or 30 mg orally twice daily [BID]), compared with placebo, 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 apremilast or placebo 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 apremilast for up to 52 weeks:

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  - Safety and tolerability
  - Efficacy
  - Physical function
  - Fatigue
  - Clinical disease activity
- To evaluate the efficacy, safety, and tolerability of two doses of apremilast during up to 5 years' administration in subjects with active PsA.

**Methodology:**

This Phase 3 parallel-group study with two active treatment groups consisted of two treatment phases: a 24-week, randomized, double-blind, placebo-controlled phase, and a 236-week active treatment/long-term safety phase consisting of two 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.

The study was planned to randomize 495 subjects in a 1:1:1 ratio to receive placebo, apremilast 20 mg BID (APR 20 BID), or apremilast 30 mg BID (APR 30 BID) during the 24-week, placebo-controlled phase. The dose of apremilast was titrated from 10 mg BID, to 20 mg BID, to 30 mg BID over the first 7 days of treatment; blinding was maintained by use of identical blister cards for all subjects.

At Week 16 (the primary endpoint), all subjects whose tender and swollen joint counts (TJC and SJC, respectively) had not improved by ≥ 20% were required to enter early escape (EE) to blinded active treatment. Subjects in the placebo (PBO) group who met EE criteria were to be re randomized 1:1 in a blinded fashion to receive either apremilast 20 mg BID (PBO/20 EE treatment group) or apremilast 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.

At Week 24, all of the subjects in the placebo treatment group who had not entered EE at Week 16 were re-randomized in a 1:1 ratio, in a blinded fashion, to receive 20 mg BID or 30 mg BID of apremilast until Week 52 of the study; the dose of apremilast was titrated during the first 7 days of active treatment. Subjects who were receiving apremilast at Week 24 (ie, those who were originally randomized to an apremilast treatment group or those who entered EE at Week 16) continued to receive their randomized treatments in a blinded fashion. All of the subjects received blister cards that were identical in appearance at Week 24.

Clinical efficacy for amelioration of signs and symptoms of PsA (ie, American College of Rheumatology 20% [ACR 20] response) and physical function (ie, Health Assessment Questionnaire Disability Index [HAQ-DI]) were assessed at Weeks 16, 24, and 52. To maintain the blind at the site and subject level, individual subject treatment assignments will not be revealed to the investigators until the 52-week database has been locked, all final analyses have been completed, and the final results through Week 52

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have been released. At that time, open-label IP (apremilast) will be provided and the subjects will be transitioned to their open-label dose of apremilast based on the dose that they received at the end of Week 52.

**Number of subjects (planned and analyzed):**

Planned: 495 subjects

Analyzed: 527 subjects

**Diagnosis and main criteria for inclusion:**

Subjects who satisfied all of the following criteria were eligible for the study:

1. Male or female, aged ≥ 18 years at the time of consent.
2. Able to understand and voluntarily sign an informed consent document before any study-related assessments/procedures were conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Documented diagnosis of PsA (by any criteria) of ≥ 3 months in duration.
5. Met the Classification Criteria for Psoriatic Arthritis (CASPAR) at the time of screening.
6. Had ≥ 3 swollen joints and ≥ 3 tender joints.
7. Had not previously been treated with DMARDs (small molecules or biologics).
8. Were receiving treatment on an outpatient basis.
9. If taking oral corticosteroids, had been on a stable dose of prednisone ≤ 10 mg/day or equivalent for at least 1 month before screening.
10. If taking nonsteroidal anti-inflammatory drugs (NSAIDs) or narcotic analgesics, had been on a stable dose for at least 2 weeks before screening and dose would remain stable until completion of 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 who had 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 were not to use these treatments within 24 hours before the clinic visit.
12. Met the following laboratory criteria:
    - White blood cell (WBC) 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).

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- Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L).
- Serum aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; serum glutamate-pyruvate transaminase [SGPT]) ≤ 2 x upper limit of normal (ULN).
- Serum total bilirubin ≤ 2 mg/dL (≤ 34 µmol/L).
- Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L).
- Hemoglobin A1c (HbA1c) ≤ 9.0%.

13. Male subjects (including those who had had a vasectomy) who engaged in activity in which conception was possible must have agreed to used barrier contraception (male latex condom or nonlatex condom not made out of natural [animal] membrane [for example, polyurethane]) while taking the IP and for at least 28 days after the last dose of IP.
14. Females of childbearing potential (FCBPs) must have had a negative pregnancy test at screening and baseline. Females of childbearing potential who engaged in activity in which conception was possible must have agreed to use contraception while on IP and for at least 28 days after taking the last dose of IP with either: 1) one highly effective form (hormonal contraception [oral, injection, implant, transdermal patch, vaginal ring], intrauterine device, tubal ligation, vasectomized partner), or 2) 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, or 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, or immunologic disease or other major uncontrolled disease.
2. Any condition, including the presence of laboratory abnormalities, that would have placed the subject at unacceptable risk if he or she were to participate in the study or that would have confounded the ability to interpret the study data.
3. Clinically significant abnormality on 12-lead electrocardiogram (ECG) at screening.
4. Pregnancy or breastfeeding.
5. History of allergy to any component of the IP (apremilast or placebo).
6. Positive for hepatitis B surface antigen at screening.
7. Positive for hepatitis C antibody at screening.
8. Serum AST (SGOT) and/or ALT (SGPT) > 1.5 x ULN and serum total bilirubin greater than the

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ULN or albumin less than the lower limit of normal (LLN).

9. History of positive human immunodeficiency virus (HIV) 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 must be taken within 12 weeks before screening or during the screening visit). An additional lateral view was strongly recommended but was not required.
12. Active substance abuse or a history of substance abuse within 6 months before screening.
13. Bacterial infections that required 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 before 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 before 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 erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia.
19. Functional Class IV as defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis.
20. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, RA, ankylosing spondylitis, Lyme disease).
21. Prior use of DMARDs (small molecules or biologics).
22. Use of systemic therapy(ies) within 4 weeks of randomization, including but not limited to, corticosteroids (except as noted in the inclusion criteria), oral retinoids, and fumaric acid esters.
23. Use of phototherapy within 4 weeks of randomization (ie, ultraviolet B light [UVB], psoralen ultraviolet light therapy [PUVA]).

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24. Previous treatment with any cell-depleting therapies, including investigational agents (eg, rituximab, alemtuzumab [CAMPATH], anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20).
25. Treatment with intravenous gamma globulin, plasmapheresis, or Prosorba® column within 6 months before baseline.
26. Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
27. Prior treatment with apremilast.
28. 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, batch number:**

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

Batch numbers:

Apremilast 10-mg tablets: 10B0036, 10B0200, 10B0353, and11B0158

Apremilast 20-mg tablets: 10B0037, 10B0201, 10B0202, 10B0355, 11B0109, 11B0159, and 11B0162

Apremilast 30-mg tablets: 10B0041, 10B0063, 10B0081, 10B0204, 10B0206, 10B0210, 10B0211, 10B0239, 11B0098, 11B0099, 11B0104, 11B0105, 11B0107, 11B0163, and 11B0195

**Duration of treatment:**

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

This interim report represents a data cutoff date after all subjects had reached Week 24.

**Reference therapy, dose and mode of administration, batch number:**

Placebo administered orally as tablets.

Batch numbers:

Placebo 10-mg tablets: 10B0005, 10B0207, 10B0348, 11B0170, and 11B0220

Placebo 20-mg tablets: 10B0006, 10B0044, 10B0052, 10B0058, 10B0059, 10B0060, 10B0241, 10B0270, 10B0350, 11B0102, 11B0103, 11B0110, 11B0111, 11B0151, 11B0164, and 11B0165

Placebo 30-mg tablets: 10B0008, 10B0045, 10B0054, 10B0061, 10B0062, 10B0063, 10B0081, 10B0209, 10B0240, 10B0351, 10B0363, 11B0112, 11B0154, 11B0155, and 11B0157

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**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 three of the following five 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 assessment of pain, and the acute phase reactant (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]).

The secondary efficacy endpoints were:

- Change from baseline in physical function (as assessed by the HAQ-DI) after 16 weeks of treatment
- Proportion of subjects who achieved an ACR 20 response after 24 weeks of treatment
- Change from baseline in physical function (HAQ-DI) after 24 weeks of treatment
- Change from baseline in SF-36v2 physical functioning domain score 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 the 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 the Clinical Disease Activity Index (CDAI) score after 16 weeks of treatment
- Change from baseline in the Disease Activity Score (28-joint) using C-reactive protein as acute phase reactant [DAS28(CRP)] score after 16 weeks of treatment
- Change from baseline in the Functional Assessment of Chronic Illness Therapy – Fatigue subscale (FACIT-Fatigue) score after 16 weeks of treatment
- Change from baseline in the 36-Item Short Form, version 2 (SF-36v2) physical functioning domain score after 24 weeks of treatment
- Proportion of subjects who achieved a modified PsARC response after 24 weeks of treatment
- Change from baseline in the subject's assessment of pain after 24 weeks of treatment

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- 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 the CDAI score after 24 weeks of treatment
- Change from baseline in DAS28(CRP) after 24 weeks of treatment
- Change from baseline in the 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 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 European League Against Rheumatism (EULAR) response after 24 weeks of treatment
- Proportion of subjects who achieved an ACR 50, compared with baseline, after 16 weeks of treatment
- Proportion of subjects who achieved an ACR 70, compared with baseline, after 16 weeks of treatment
- Proportion of subjects who achieved an ACR 50 response, compared with baseline, after 24 weeks of treatment
- Proportion of subjects who achieved an ACR 70 response, compared with baseline, after 24 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved to zero after 16 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to zero after 16 weeks of treatment

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- Proportion of subjects with pre-existing enthesopathy whose MASES improved to zero after 24 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to zero after 24 weeks of treatment

The exploratory endpoints were:

- Proportion of subjects in each treatment group whose psoriasis body surface area (BSA) at baseline was ≥ 3% and who achieve 75% or greater improvement in the Psoriasis Area and Severity Index score (PASI-75) after 16, 24, or 52 weeks of treatment
- Change from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score in the subset of subjects in each treatment group who had pre-existing axial arthropathy and a baseline BASDAI score ≥ 4 after 16, 24, or 52 weeks of treatment
- American College of Rheumatology N index (ACR-N) after 16, 24 or 52 weeks of treatment

**Safety:** Safety was measured with adverse events (AEs); chest radiographs; vital signs, including height and weight; physical examination; clinical laboratory variables; pregnancy test; and 12-lead ECG.

**Statistical methods:**

**Demographics:**

Summary statistics were to be provided by treatment group for the continuous variables (age, weight, height, body mass index [BMI]). Number and percentage were to be provided by treatment group for the categorical variables (age category, sex, race, ethnicity, region, weight category, 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 (the change from baseline in the HAQ-DI score at Week 16).

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

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

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Planned statistical tests were conducted between each apremilast dose and placebo for the primary endpoint and those secondary endpoints that were evaluated at Week 16 or 24. To control the experiment-wise Type I error rate at the 0.05 significance level, formal statistical tests were carried out sequentially for these endpoints, starting with the primary endpoint and then the secondary endpoints that were evaluated at Week 16 or 24 and the pairwise comparisons (APR 30 BID versus placebo and APR 20 BID versus placebo) for each endpoint were performed using the Hochberg procedure.

Specifically, for the primary endpoint (ACR 20 response at Week 16), if the two-sided p-values from both of the pairwise comparisons were $\leq 0.050$, then both test results were to be considered statistically significant and both apremilast doses were to be declared efficacious. If the two-sided p-value from one of the two pairwise comparisons was $> 0.050$, but the 2-sided p-value from the other comparison was $\leq 0.025$, then the latter test result was to be considered statistically significant and the corresponding apremilast dose tested was to be declared efficacious. In other situations, neither of the apremilast doses was to be declared efficacious.

Formal pairwise comparisons with respect to the first secondary endpoint (change from baseline in the HAQ-DI score at Week 16) were conducted 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 two pairwise comparisons for the HAQ-DI score were to be performed using the Hochberg procedure at the $\alpha = 0.050$ level, as described above for ACR 20 response. If only the test result of ACR 20 response for one apremilast dose was statistically significant, then only the comparison between that apremilast dose and placebo was to be conducted for the HAQ-DI score, at the $\alpha = 0.025$ level. If neither test result of ACR 20 response was statistically significant, then formal statistical tests were not to be performed for the HAQ-DI score or for the remaining secondary endpoints that were evaluated at Week 16 or 24.

Formal statistical tests for the remaining secondary endpoints that were evaluated at Week 16 or 24 were conducted in the same manner as described above.

For planned statistical tests that were not formally performed as a result of the aforementioned multiplicity adjustment strategy, nominal two-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 two-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 one dose of study drug). Safety analyses for the apremilast-exposure period were performed using the Apremilast Subjects as Treated Population (all subjects who received at least one dose of apremilast).

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. Adverse events that occurred during the placebo-controlled period and the apremilast-exposure period were tabulated separately. Treatment-emergent adverse events (TEAEs) were

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summarized by System Organ Class, severity, and relationship to the investigational product. Adverse events that led to death or to discontinuation from treatment and serious adverse events (SAEs) were also tabulated. In the by-subject analysis, a subject who had the same event more than once was counted only once at the greatest severity.

Laboratory data were summarized descriptively by visit. In addition, shift tables showing the number of subjects with values below, within, and above the normal ranges pretreatment versus posttreatment, together with the number determined to be clinically significant, 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 below, within and above the normal reference ranges pretreatment versus posttreatment, together with the number determined to be clinically significant, were provided.

**SUMMARY – CONCLUSIONS**

**EFFICACY RESULTS:**

This report constitutes the analysis of data from up to 24 weeks of exposure to apremilast in this ongoing Phase 3, multicenter, randomized, double-blind, parallel group study. A total of 527 subjects with active PsA who had previously not been treated with DMARDs were randomized per protocol and were included in the FAS for efficacy during the 24-week placebo-controlled period (176, 175, and 176 subjects in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively). Of the subjects initially randomized to apremilast, 91.4% of subjects in the APR 20 BID treatment group and 88.1% of subjects in the APR 30 BID treatment group completed the placebo-controlled phase (Weeks 0-24) of the study.

Baseline demographics, disease characteristics, prior history of PsA medications, and baseline use of PsA medications were consistent with an active PsA population who had previously not been treated with DMARDs. The study was well balanced for baseline disease characteristics, with an overall mean (median) TJC of 20.1 (16.0), SJC of 11.2 (9.0), CRP of 0.937 (0.399) mg/dL, DAS28(CRP) of 4.6 (4.62), and psoriatic skin involvement of 8.03% (3.0%) BSA. The mean (median) PsA disease duration was 3.41 (1.10) years. The majority of subjects (73.1%) were receiving NSAIDs at baseline; 7.2% of subjects were receiving oral prednisone (or its equivalent).

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 placebo. Comparable treatment effects were observed for the primary endpoint; the ACR 20 response rates at Week 16 were 15.9%, 28.0%, and 30.7% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The differences in ACR 20 response rates for APR 20 BID and APR 30 BID treatment groups, compared with placebo, were 12.1% ($p = 0.0062$) and 14.8% ($p = 0.0010$), respectively. The observed positive treatment effect of apremilast on the signs and symptoms of active PsA was supported by multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (eg, NRI, LOCF). The statistically significant ACR 20 responses that were observed in the apremilast treatment groups at Week 16 were maintained at Week 24 (13.1%, 29.1% [$p = 0.0002$], and 24.4% [$p = 0.0063$] in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively).

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The reduction in the signs and symptoms of active PsA with apremilast treatment was further demonstrated by nominally significant ACR 50 and ACR 70 responses (nominal p values < 0.05 versus placebo) observed in the APR 20 BID and APR 30 BID treatment groups at Week 16. The proportions of subjects who achieved ACR 50 responses at Week 24 were modestly numerically greater in the apremilast treatment groups compared with placebo. The proportions of subjects in the apremilast treatment groups achieving ACR 70 responses at Week 24 were comparable to that in the placebo treatment group. Clinically meaningful improvements (> 20% reduction) were observed across multiple ACR components, including TJC, SJC, and EGA in both apremilast treatment groups, and the subject's assessment of pain score in the APR 30 BID treatment group.

Apremilast produced statistically significant and clinically meaningful improvements in physical function, as measured by the HAQ-DI score at Week 16, the key secondary endpoint. A dose effect was observed; the mean changes in HAQ-DI at Week 16, relative to baseline, were 0.012, -0.156, and -0.205 for the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The LS mean differences in the change from baseline in HAQ-DI in the APR 20 BID and APR 30 BID treatment groups, compared with placebo, were 0.168 ($p = 0.008$) and -0.217 ($p < 0.0001$), respectively. The improvement in physical function was evident in the maintenance of statistically significant reductions in HAQ-DI score at Week 24 (0.012, -0.156 [$p = 0.0014$], and -0.207 [$p < 0.0001$] in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively).

Notably, the mean changes in the HAQ-DI score in the apremilast treatment groups at Weeks 16 and 24 exceeded the estimated MCID for HAQ-DI of -0.13 (Kwok, 2010). The proportions of subjects achieving this MCID, or the MCID of -0.3 (Mease, 2004a) at Weeks 16 and 24 was nominally significant higher, compared to placebo, in the APR 20 BID and APR 30 BID treatment groups.

The majority of secondary 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 20 BID treatment group (38.9%, $p = 0.0037$) and the APR 30 BID treatment group (45.5%, $p < 0.0001$), compared with placebo (24.4%). The responses were maintained at Week 24 (17.0%, 36.6% [nominal $p < 0.0001$], and 35.2% [nominal $p = 0.0001$] for the placebo, 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 placebo. 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 placebo, 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 (41.1%, nominal $p = 0.0013$) and APR 30 BID (44.3%, nominal $p = 0.0001$) treatment groups, compared with placebo (25.0%), which were maintained at Week 24 (17.0%, 34.9% [nominal $p = 0.0001$], and 28.4% [nominal $p = 0.0110$] for the placebo, APR 20 BID and APR 30 BID treatment groups, respectively.

The improvement in subjects' physical function produced by apremilast was further demonstrated by the

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statistically significant and clinically meaningful improvements in the SF-36v2 physical functioning domain score and PCS score at Week 16 and 24. At Week 16, the SF-36v2 physical functioning domain score improved from baseline by 0.01, 2.39 [p = 0.0043], and 3.19 [p =-0.0002] for the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. Similarly, the SF-36v2 PCS score improved from baseline by 0.93, 3.15 [nominal p = 0.0034], and 4.20 [nominal p < 0.0001] in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The improvements in the SF-36v2 Physical Functioning domain score exceeded the estimated MCID of 2.5 in the APR 30 BID treatment group, and were maintained at Week 24. The improvements in the SF-36v2 PCS score exceeded the estimated MCID of 2.5 in both apremilast treatment groups, and were maintained at Week 24.

A treatment effect for apremilast on enthesitis was observed in the APR 30 BID treatment group in subjects with pre-existing enthesitis. The decrease from baseline (improvement) in the MASES score, relative to placebo, was statistically significant at Week 16 and nominally significant at Week 24 for the APR 30 BID treatment group. There was also a significant improvement in the proportion of subjects who achieved a > 20% improvement in MASES and in the proportion of subjects who achieved a MASES of zero. No significant differences in the change from baseline in the MASES were observed between the placebo and APR 20 BID treatment groups at either Week 16 or 24. Notably, the study population was not enriched for pre-existing enthesopathy, nor was the study powered to demonstrate a true effect on enthesitis.

A treatment effect for apremilast on dactylitis was also shown. The decrease from baseline (improvement) in the dactylitis severity score, relative to placebo, was nominally significant in the APR 20 BID treatment group at Weeks 16 and 24 and nominally significant in the APR 30 BID treatment group at Week 16. Notably, the study population was not enriched for pre-existing dactylitis, nor was the study powered to demonstrate a true effect on 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 at Weeks 16 and 24 in subjects with psoriasis involving ≥ 3% of their body surface. The PASI-75 responses at Week 16 were 10.8%, 17.3%, and 22.1% (nominal p = 0.0044) in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The responses were maintained in the apremilast treatment groups at Week 24 (11.8%, 23.1% [nominal p = 0.0392], and 25.7% [nominal p = 0.0129] for the placebo, 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 (Jacobson, 2004). 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.

Subgroup analyses of ACR 20 responses were conducted using factors including age, sex, weight, BMI, race, geographic region, as well as PsA subtype and disease duration. Overall, a treatment effect in favor of apremilast versus placebo was observed in each of these subgroups at both Week 16 and Week 24. There was an apparent difference in treatment effect favoring male subjects, compared with female subjects, in the APR 30 BID treatment group at Weeks 16 and 24. An apparent neutral effect of treatment

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in North America was observed, which may have been due to differences in baseline demographics and disease characteristics.

This study was not designed to make formal comparisons between the apremilast treatment groups. The 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, was comparable in the APR 20 BID and APR 30 BID treatment groups. However, outcomes in the APR 30 BID treatment group were generally greater that those in the APR 20 BID treatment group for endpoints relating to physical function (eg, HAQ-DI and SF-36v2 physical functioning domain scores). Of additional note, the PASI-75 responses also suggested a dose response in favor of the APR 30 BID treatment group. Improvement in fatigue (as determined by mean change in FACIT-Fatigue) achieved nominal p-values $\leq 0.05$ only in the APR 30 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 who had not been previously treated with DMARDs. The overall magnitude and consistency of therapeutic effect was greater with the 30-mg BID dose.

**SAFETY RESULTS:**

During the 24-week, placebo-controlled period, the incidence of TEAEs was 41.5%, 49.7%, and 56.6% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. TEAEs that led to discontinuation occurred in 2.3%, 2.3%, and 3.4% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs and SAEs was low and not dose-dependent (severe TEAEs: 3.4%, 2.3%, and 1.1%; SAEs: 2.8%, 1.7%, and 0.6% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively). No deaths were reported.

During the placebo-controlled period, nausea, diarrhea, and headache were the most frequently reported TEAEs, the frequency of which increased in a dose-dependent manner. These events were all mild to moderate in severity, occurred at the highest frequency within the first week of dosing, and tended to resolve within 15 days. Headache, diarrhea, and nausea were also the most frequently reported reasons for discontinuation of treatment. (Most cases of these events did not result in discontinuation, however.)

During the placebo-controlled period, the frequency of TEAEs was comparable between female and male subjects in the APR 20 BID treatment group, and higher among female subjects than male subjects in the APR 30 BID treatment group. The frequency of TEAEs was higher in subjects $\geq 65$ years old than subjects $< 65$ years old in the APR 20 BID treatment group, and comparable between age subgroups in the APR 30 BID treatment group.

No trends or patterns were observed in the frequency of markedly abnormal laboratory parameters (hematology or clinical chemistry), vital signs, or ECGs. Treatment with apremilast was associated with small decreases in body weight.

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.

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Three subjects reported serious infections, on in each treatment group (placebo, APR 20 BID, and APR 30 BID). 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 no cases of MACE, malignancies, suicidal ideation and behavior, or vasculitis reported.

At the end of the placebo-controlled period, the placebo group had a mean weight gain of 0.21 kg, compared with weight loss observed in the APR 20 BID and APR 30 BID treatment groups of -0.55 and -1.11 kg, respectively. The majority of subjects maintained their weight within ± 5% of baseline, and weight loss > 10% was infrequent (observed in 4 subjects in the APR 20 BID treatment group and 2 subjects in the APR 30 BID treatment group). No subject experienced weight loss of > 20%.

Apremilast demonstrated an acceptable safety profile following 24 weeks of exposure in both the APR 20 BID and APR 30 BID treatment groups.

**CONCLUSION:**

Overall, the results of this study demonstrated that apremilast, a selective PDE4 inhibitor, was an effective, safe, and well-tolerated treatment for subjects with active PsA who have not previously been treated with DMARDs. Apremilast provided statistically significant reductions in the signs and symptoms of active PsA when used in dosing regimens of either 20 mg or 30 mg BID. Both dose regimens of apremilast also resulted in statistically significant and clinically meaningful improvements in physical function. 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.

Apremilast was generally well tolerated, with both doses (20 mg BID and 30 mg BID) demonstrating comparable and acceptable safety profiles with up to 24 weeks' exposure in this ongoing 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 apremilast 30 mg BID over that for apremilast 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:**

26 September 2013

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