



<b>Name of Sponsor/Company:</b> Celgene	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast	Volume: Page:	
<b>Name of Active Ingredient:</b> CC-10004		
<ul style="list-style-type: none"> <li>- Safety and tolerability</li> <li>- Efficacy</li> <li>- Physical function</li> <li>- Fatigue</li> <li>- Clinical disease activity</li> <li>• To evaluate the efficacy, safety, and tolerability of 2 doses of apremilast during up to 5 years' administration to subjects with active PsA.</li> </ul>		
<p><b>Methodology:</b></p> <p>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.</p> <p>Approximately 495 subjects were to be randomized 1:1:1 to receive apremilast 20 mg BID (APR 20 BID treatment group), apremilast 30 mg BID (APR 30 BID treatment group), or identically appearing placebo 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.</p> <p>At Week 16 (the primary endpoint), all subjects whose swollen or tender joint count (SJC or TJC, respectively) had not improved by <math>\geq 20\%</math> 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.</p> <p>At Week 24, all remaining subjects in the placebo group were to be re-randomized 1:1 in a blinded fashion to receive apremilast 20 mg BID (PBO/20 XO treatment group) or apremilast 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.</p> <p>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 to be assessed at Weeks 16, 24, 40, and 52. To maintain the blind at the site and subject level, individual subject treatment assignments were not to be revealed to the investigators until after the Week 52 database lock at Year 1, after all final analyses were completed and the final results were</p>		

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released. At that time, open-label study medication was to be provided.

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

Planned: 495 subjects

Analyzed: 504 subjects

**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  $\geq 18$  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  $\geq 6$  months' duration.
5. Met the Classification Criteria for Psoriatic Arthritis (CASPAR) at time of screening.
6. Had  $\geq 3$  swollen AND  $\geq 3$  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  $\leq 25$  mg/week; parenteral MTX  $\leq 25$  mg/week; LEF  $\leq 20$  mg/day; SSZ  $\leq 2$  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  $\leq 10$  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 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  $\geq 3000/\text{mm}^3$  ( $\geq 3.0 \times 10^9/\text{L}$ ) and  $< 14,000/\text{mm}^3$

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<p style="text-align: center;">(&lt; 14 X 10<sup>9</sup>/L)</p> <ul style="list-style-type: none"> <li>• Platelet count ≥ 100,000/mm<sup>3</sup> (≥ 100 X 10<sup>9</sup>/L)</li> <li>• Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)</li> <li>• Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamate-pyruvate transaminase [SGPT]) ≤ 2 X upper limit of normal (ULN)</li> <li>• Total bilirubin ≤ 2 mg/dL (≤ 34 μmol/L)</li> <li>• Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)</li> <li>• Hemoglobin A1c ≤ 9.0%</li> </ul> <p>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.</p> <p>14. Females of childbearing potential (FCBP) had a negative pregnancy test at Screening and Baseline. 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 [IUD], 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.</p> <p>The presence of any of the following excluded a subject from enrollment:</p> <ol style="list-style-type: none"> <li>1. History of clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease.</li> <li>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.</li> <li>3. Clinically significant abnormality on 12-lead electrocardiogram (ECG) at screening.</li> <li>4. Pregnant or breastfeeding female.</li> <li>5. History of allergy to any component of the investigational product (IP).</li> </ol>		

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6. Hepatitis B surface antigen positive at screening.
7. Hepatitis C antibody positive at screening.
8. AST (SGOT) and/or ALT (SGPT) > 1.5X ULN **and** total bilirubin > ULN or albumin < 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 or a history of incompletely treated tuberculosis.
11. Clinically significant abnormality based upon chest radiograph with at least posteroanterior (PA) 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 erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia.
19. Functional Class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis.
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.

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<ol style="list-style-type: none"> <li>22. Use of phototherapy within 4 weeks of randomization (ie, ultraviolet B light [UVB], psoralen ultraviolet light therapy [PUVA]).</li> <li>23. Use of adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab within 12 weeks of randomization.</li> <li>24. Use of alefacept or ustekinumab within 24 weeks of randomization.</li> <li>25. Previous treatment with any cell depleting therapies, including investigational agents (eg, rituximab, CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20).</li> <li>26. Treatment with intravenous gamma globulin, plasmapheresis, or ProSORBA<sup>®</sup> column within 6 months of baseline.</li> <li>27. Any previous treatment with alkylating agents such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.</li> <li>28. Prior treatment with apremilast.</li> <li>29. Therapeutic failure of &gt; 3 agents for PSA (small molecules or biologics), or &gt; 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.</li> <li>30. Use of any investigational drug within 4 weeks of randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever is longer).</li> </ol>		
<b>Test product, dose and mode of administration, batch number:</b> Apremilast administered orally as 10-, 20-, or 30-mg tablets. Batch numbers: Apremilast 10-mg tablets: 10B0013, 10B0036, 10B0200, 10B0353 Apremilast 20-mg tablets: 10B0014, 10B0037, 10B0201, 10B0202, 10B0203, 10B0355, 11B0109, 11B0159 Apremilast 30-mg tablets: 10B0015, 10B0016, 10B0341, 10B0356, 10B0204, 10B0210, 11B0098, 11B0104		
<b>Duration of treatment:</b> 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.		

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<p><b>Reference therapy, dose and mode of administration, batch number:</b></p> <p>Placebo administered orally as tablets.</p> <p>Batch numbers:</p> <p>Placebo 10-mg tablets: 10B0005, 10B0006, 10B0207, 10B0208, 10B0348, 11B0170, 11B0220</p> <p>Placebo 20-mg tablets: 10B0006, 10B0052, 10B0058, 10B0059, 10B0349, 10B0350, 11B0102, 11B0110, 11B0111</p> <p>Placebo 30-mg tablets: 10B0009, 10B0054, 10B0057, 10B0063, 10B0208, 10B0209, 10B0351, 11B0112, 11B0154</p>		
<p><b>Criteria for evaluation:</b></p> <p><b>Efficacy:</b> Efficacy was primarily assessed as the ACR 20 response at Week 16, which was defined as a <math>\geq 20\%</math> improvement from baseline in TJC and SJC plus <math>\geq 20\%</math> improvement from baseline in 3 of the following 5 assessments: subject's and physician's global assessment of disease activity, HAQ-DI score, subject assessment of pain, and the acute phase reactant (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]).</p> <p>The secondary efficacy endpoints were:</p> <p><u>Efficacy at Weeks 16 and 24</u></p> <ul style="list-style-type: none"> <li>• Change from baseline in physical function (HAQ-DI) after 16 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 20 response after 24 weeks of treatment</li> <li>• Change from baseline in physical function (HAQ-DI) after 24 weeks of treatment</li> <li>• Change from baseline in the 36-item Short Form Health Survey, version 2 (SF-36v2) physical function domain score after 16 weeks of treatment</li> <li>• Proportion of subjects who achieved a modified Psoriatic Arthritis Response Criteria (PsARC) response after 16 weeks of treatment</li> <li>• Change from baseline in subject's assessment of pain after 16 weeks of treatment</li> <li>• Change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Scale (MASSES) score in subjects with pre-existing enthesopathy after 16 weeks of treatment</li> <li>• Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis after 16 weeks of treatment</li> <li>• Change from baseline in Clinical Disease Activity Index (CDAI) score after 16 weeks of treatment</li> <li>• Change from baseline in 28-joint Disease Activity Score using CRP as acute phase reactant (DAS28[CRP]) after 16 weeks of treatment</li> <li>• Change from baseline in Functional Assessment of Chronic Illness Therapy – Fatigue subscale (FACIT-Fatigue) score after 16 weeks of treatment</li> <li>• Change from baseline in SF-36v2 physical function domain score after 24 weeks of treatment</li> </ul>		

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<ul style="list-style-type: none"> <li>• Proportion of subjects who achieved a modified PsARC response after 24 weeks of treatment</li> <li>• Change from baseline in subject’s assessment of pain after 24 weeks of treatment</li> <li>• Change from baseline in the MASES in subjects with pre-existing enthesopathy after 24 weeks of treatment</li> <li>• Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis after 24 weeks of treatment</li> <li>• Change from baseline in CDAI score after 24 weeks of treatment</li> <li>• Change from baseline in DAS28(CRP) after 24 weeks of treatment</li> <li>• Change from baseline in FACIT-Fatigue score after 24 weeks of treatment</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved by <math>\geq 20\%</math> after 16 weeks of treatment</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by <math>\geq 1</math> after 16 weeks of treatment</li> <li>• Proportion of subjects with a good or moderate European League Against Rheumatism (EULAR) response after 16 weeks of treatment</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES score improved by <math>\geq 20\%</math> after 24 weeks of treatment</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by <math>\geq 1</math> after 24 weeks of treatment</li> <li>• Proportion of subjects with a good or moderate EULAR response after 24 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 50 response after 16 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 70 response after 16 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 50 response after 24 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 70 response after 24 weeks of treatment</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 16 weeks of treatment</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 16 weeks of treatment</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 24 weeks of treatment</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 24 weeks of treatment</li> </ul> <p><u>Efficacy at Week 52</u></p> <ul style="list-style-type: none"> <li>• Proportion of subjects who achieved an ACR 20 response after 52 weeks of treatment</li> <li>• Change from baseline in physical function (HAQ-DI) after 52 weeks of treatment</li> </ul>		

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<ul style="list-style-type: none"> <li>• Change from baseline in the SF-36v2 physical function domain score after 52 weeks of treatment</li> <li>• Proportion of subjects who achieved a modified PsARC response after 52 weeks of treatment</li> <li>• Change from baseline in subject’s assessment of pain after 52 weeks of treatment</li> <li>• Change from baseline in MASES score in subjects with pre-existing enthesopathy after 52 weeks of treatment</li> <li>• Change from baseline in the dactylitis severity score subjects with pre-existing dactylitis after 52 weeks of treatment</li> <li>• Change from baseline in CDAI score after 52 weeks of treatment</li> <li>• Change from baseline in DAS28(CRP) after 52 weeks of treatment</li> <li>• Change from baseline in FACIT-Fatigue score after 52 weeks of treatment</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved by <math>\geq 20\%</math> after 52 weeks of treatment</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by <math>\geq 1</math> after 52 weeks of treatment</li> <li>• Proportion of subjects with a good or moderate EULAR response after 52 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 50 response after 52 weeks of treatment</li> <li>• Proportion of subjects who achieved an ACR 70 response after 52 weeks of treatment</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 52 weeks of treatment</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 52 weeks of treatment</li> </ul> <p>The exploratory endpoints were:</p> <ul style="list-style-type: none"> <li>• Proportion of subjects in each treatment group, whose psoriasis BSA at baseline was <math>\geq 3\%</math>, who achieved PASI-75 after 16, 24, or 52 weeks’ treatment</li> <li>• Change from baseline in BASDAI score in the subset of subjects in each treatment group with pre-existing axial arthropathy and baseline BASDAI score <math>\geq 4</math> after 16, 24, or 52 weeks’ treatment</li> <li>• ACR-N after 16, 24, or 52 weeks’ treatment</li> </ul> <p>Post hoc analyses were added for the following endpoints:</p> <ul style="list-style-type: none"> <li>• Change from baseline in the individual ACR component scores (TJC, SJC, patient’s [subject’s] global assessment of disease activity [PGA], evaluator’s [physician’s] global assessment of disease activity [EGA], and CRP) at Weeks 16, 24, 40 and 52</li> <li>• <math>\geq 0.13</math>-point and <math>\geq 0.30</math>-point reductions in HAQ-DI at Weeks 16, 24, 40 and 52</li> <li>• <math>\geq 2.5</math>-point improvement in SF-36 physical functioning domain score and SF-36v2 PCS at Weeks 16, 24, and 52.</li> </ul>		





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<p>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 AEs 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.</p> <p>Laboratory data were summarized by visit descriptively. 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.</p> <p>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 post-treatment, together with the number determined to be clinically significant, were provided.</p>		
<p><b>SUMMARY – CONCLUSIONS</b></p> <p><b>EFFICACY RESULTS:</b></p> <p>This report constitutes the analysis of data from up to 52 weeks of exposure to apremilast in this ongoing Phase 3, multicenter, randomized, double-blind, parallel-group study. A total of 504 subjects were included in the full analysis set for efficacy during the placebo-controlled period (168 placebo, 168 APR 20 BID, and 168 APR 30 BID). A total of 490 subjects who were initially randomized to apremilast, or who were re-randomized from placebo to apremilast at Week 16 or Week 24, were included in the analyses of efficacy during the apremilast-exposure period up to Week 52 (54 PBO/20 EE, 23 PBO/20 XO, 53 PBO/30 EE, 24 PBO/30 XO, 168 APR 20 BID, and 168 APR 30 BID). Of the subjects initially randomized to apremilast, 73.8% of subjects in the APR 20 BID treatment group and 77.4% of subjects in the APR 30 BID treatment group completed Weeks 0-52 of the study.</p> <p>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 22.9 (19.0), SJC of 12.7 (10.5), CRP of 0.938 (0.479) mg/dL, DAS28(CRP) of 4.85 (4.90), and psoriatic skin involvement of 7.53% (2%) BSA. The mean (median) disease duration was 7.53 (5.05) years. The majority of subjects (74.0%) had been inadequately controlled by prior treatment with small-molecule DMARDs only; an additional 23.6% had been inadequately controlled by prior treatment with biologic DMARDs. The majority of subjects (64.9%) were receiving at least one small-molecule DMARD at baseline; 10.5% of subjects were receiving prednisone (or its equivalent), and 71.6% of subjects were receiving NSAIDs.</p> <p>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. A dose effect was observed for the primary endpoint; the ACR 20 response rates at Week 16 were 19.0%, 30.4%, and 38.1% for the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The adjusted difference in ACR 20 response for the APR 20 BID and APR 30 BID treatment groups, compared with placebo, were 11.3% (p = 0.0166) and 19.0% (p = 0.0001), respectively. The observed positive treatment effect of apremilast</p>		

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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, NRI, LOCF). The statistically significant ACR 20 responses observed in the apremilast treatment groups at Week 16 were maintained at Week 24 (13.1%, 25.6% [p = 0.0038], and 35.1% [p < 0.0001] in the placebo, APR 20 BID and APR 30 BID treatment groups, respectively).

The reduction in the signs and symptoms of active PsA with apremilast treatment was further demonstrated at Weeks 16 and 24 by statistically significant ACR 50 and ACR 70 responses (nominal p-values < 0.05 versus placebo, except for ACR 70 at Week 16 in the APR 30 BID treatment group) and clinically meaningful improvements (> 20% reduction) across multiple ACR components.

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 LS mean changes in the HAQ-DI score at Week 16 compared to baseline were -0.086, -0.198, and -0.244 for the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The differences in change from baseline in HAQ-DI in the APR 20 BID and APR 30 BID treatment groups, compared with placebo, were -0.113 (p = 0.0252) and -0.159 (p = 0.0017), respectively. The improvement in physical function was evident in the maintenance of statistically significant reductions in HAQ-DI score at Week 24 (-0.076, -0.211 [p = 0.0091], and -0.258 [p = 0.0005] in the placebo, 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 MCID for HAQ-DI of -0.13 (Kwok, 2010) and approximated or exceeded the lower bound of the 95% CI for another estimated MCID for HAQ-DI of -0.30 (Mease, 2004a). The proportion of subjects achieving each of these MCIDs at Weeks 16 and 24 was numerically higher compared to placebo in the APR 20 BID treatment group, and nominally significantly higher compared to placebo 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 numerically higher in the APR 20 BID treatment group (38.7%) and statistically significant in the APR 30 BID treatment group (46.4%, p = 0.0017) compared with placebo (29.8%). The responses were generally maintained in the apremilast treatment groups at Week 24 (18.5%, 31.0% [nominal p = 0.0079], and 42.9% [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, statistically significant good/moderate EULAR responses were observed at Week 16 in the APR 20 BID (46.4%, nominal p = 0.0017) and APR 30 BID (48.8%, nominal p = 0.0003) treatment groups, compared with placebo (29.8%), which were maintained at Week 24 (30.4% and 42.3% versus 16.1%, respectively);

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nominal  $p = 0.0020$  and  $< 0.0001$ ).

The improvement of physical function produced by apremilast was further demonstrated by the statistically significant and clinically meaningful improvements in the SF-36v2 Physical Functioning domain score and PCS score in the APR 30 BID treatment group. At Week 16, the SF-36v2 Physical Functioning domain score improved from baseline by 1.81, 3.50 ( $p = 0.0504$ ), and 4.23 ( $p = 0.0056$ ) for the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. Similarly, the SF-36v2 PCS score improved from baseline by 2.39, 3.53, and 4.59 (nominal  $p = 0.0097$ ) in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The improvements in both the SF-36v2 Physical Functioning domain score and PCS score exceeded the estimated MCID of 2.5, and were maintained at Week 24.

Numerically greater improvements in enthesitis, as assessed by MASES score, were observed in the apremilast treatment groups, compared with placebo, at Weeks 16 and 24 among subjects with pre-existing enthesopathy. At Week 24, the mean reduction in MASES score in the APR 30 BID treatment group was nominally significantly higher compared with the placebo group. Similarly, numerically greater reductions in dactylitis severity score was observed in the APR 20 BID and APR 30 BID treatment groups, compared with placebo, at Weeks 16 and 24. Notably, the study population 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 and dose effect for apremilast on PASI-75 responses was observed in subjects with psoriasis involving  $\geq 3\%$  of their body surface at Weeks 16 and 24. The PASI-75 responses at Week 16 were 4.4%, 20.8% (nominal  $p = 0.0038$ ), and 22.0% (nominal  $p = 0.0022$ ) in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively. The responses were generally maintained in the apremilast treatment groups at Week 24 (4.4%, 16.9% [nominal  $p = 0.0177$ ], and 20.7% [nominal  $p = 0.0032$ ] 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.

Apremilast demonstrated a maintenance of therapeutic effect, across all measures of efficacy, with up to 52 weeks of treatment. 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 (63.0% [75/119] and 54.6% [71/130], 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 (-0.369 and -0.318, respectively), among subjects remaining in the study. In both apremilast treatment groups, the mean reductions in the HAQ-DI score at Week 52 exceeded the MCIDs of -0.13 and -0.3. 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.

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Among placebo 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.

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 both the APR 20 BID and APR 30 BID treatment groups; female subjects showed improvements compared to placebo in the APR 30 BID treatment group, and minimal improvements compared to placebo in the APR 20 BID treatment group. Importantly, a treatment effect in favor of apremilast versus placebo was observed irrespective of the number or type of prior small-molecule or prior biologic DMARD(s) used. Likewise, a favorable treatment effect was observed with apremilast versus placebo, regardless of whether apremilast was administered alone or with a concomitant small-molecule DMARD.

Although there was no formal comparison of efficacy between apremilast treatment regimens, the responses during the placebo-controlled period (ie, at Weeks 16 and 24) were generally more favorable and consistent in the APR 30 BID treatment group than in the APR 20 BID treatment group. This finding was observed for ACR 20, HAQ-DI, PASI-75 and other secondary endpoints. By Week 52, based on the data available, overall comparable response rates were observed in the APR 20 BID and APR 30 BID treatment groups across these endpoints, with the exception of PASI-75, where APR 30 BID continued to have higher response rates.

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. Maintenance of therapeutic effect was observed across all measures of efficacy among subjects receiving up to 52 weeks of treatment. During the placebo-controlled period, a generally greater magnitude and consistency of clinical response was observed with APR 30 BID over APR 20 BID.

**SAFETY RESULTS:**

During the 24-week, placebo-controlled period, the incidence of TEAEs was 48.2% in the placebo group and comparable in the APR 20 BID and APR 30 BID treatment groups (60.1% and 61.3%, respectively), and led to discontinuation in 4.8%, 6.0%, and 7.1% of subjects, respectively. The majority of TEAEs were mild to moderate in severity. The incidence of severe TEAEs was low and increased in a treatment- and dose-dependent manner (3.6%, 4.8%, 6.5% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively). The incidence of SAEs was low and comparable across treatment groups (4.2%, 4.8%, and 5.4% in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively). During the apremilast-exposure period (with up to 52 weeks' exposure to apremilast), the frequency of reports of TEAEs, both overall and by severity/seriousness/ relationship to drug, were similar to, or lower than, those observed in the apremilast treatment groups during the placebo-controlled period, thus indicating that the onset of new TEAEs tended to occur during the first 24 weeks of dosing.

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-

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dependent manner, and tended to be highest during the first 1-2 weeks of dosing. These events were predominantly mild to moderate in severity and most did not lead to discontinuation. Severe diarrhea occurred in two subjects: one subject in the placebo group, which led to discontinuation, and one in the APR 20 BID treatment group, which resolved without drug discontinuation. Severe nausea occurred in two subjects (one in each apremilast treatment group). None of these events led to discontinuation. One of these subjects (APR 30 BID treatment group) experienced serious nausea and vomiting during the placebo-controlled period, which resolved without discontinuation or interruption of apremilast. During the apremilast-exposure period, no new severe or serious events of diarrhea or nausea were reported with dosing of up to 52 weeks, or in subjects who were re-randomized from placebo to apremilast at Week 16 or 24. Among subjects treated with apremilast, the majority of diarrhea cases resolved within one month, nausea generally resolved within 2-3 weeks, and headaches generally resolved within 1-2 weeks.

Other frequently reported TEAEs during the placebo-controlled period included headaches (reported in approximately 5% of subjects in the placebo group and 10% of subjects in both apremilast treatment groups) and upper respiratory tract infections (reported in approximately 4% of subjects in the placebo, 6% in the APR 20 BID, and 4% in the APR 30 BID treatment groups). All other TEAEs were reported by fewer than 5% of subjects in any treatment group. All headaches and upper respiratory tract infections during the placebo-controlled period were mild to moderate in severity. During the apremilast-exposure period, two new cases of severe headache (one in each apremilast dose group) and one case of severe URI (in the APR 20 BID treatment group) were reported with dosing of up to 52 weeks, or in subjects who were re-randomized from placebo to apremilast at Week 16 or 24. Additionally, during the apremilast-exposure period, nasopharyngitis was reported by 6.9% and 6.5% of subjects in the APR 20 BID and APR 30 BID treatment groups.

Serious TEAEs were reported at a similar frequency across the placebo and apremilast treatment groups during the placebo-controlled period. Each SAE during this period was reported by one subject per treatment group. During the apremilast-exposure period, with dosing of up to 52 weeks, or in subjects who were re-randomized from placebo to apremilast at Week 16 or 24, the overall rate of SAEs was comparable between the APR 20 BID and APR 30 BID treatment groups (5.7% and 7.8%, respectively). Among subjects initially randomized to apremilast, there were few new SAEs (1 in the APR 20 BID treatment group and 3 in the APR 30 BID treatment group) reported between Weeks 24-52. All SAEs during this period, except for acute myocardial infarction (which was reported in two subjects in the APR 20 BID treatment group) were reported by one subject per treatment group.

There was one death during the study, which occurred during the placebo-controlled period. A [REDACTED] subject in the APR 20 BID treatment group experienced multi-organ failure secondary to pre-existing vitamin B<sub>12</sub> deficiency anemia (primary cause of death on the death certificate as reported) on Day 73. This TEAE was fatal, but was not considered by the investigator to be drug-related.

During the placebo-controlled period, the frequency of TEAEs was higher among female subjects than male subjects, and among subjects ≥ 65 years old than < 65 years old. During the apremilast-exposure period, the incidence of TEAEs was higher in females and in subjects ≥ 65 years of age only in the APR 30 BID treatment group. In both the placebo-controlled and apremilast-exposure periods, the frequency of TEAEs in the apremilast treatment groups was numerically lower among subjects who were taking concomitant DMARDs than subjects who were not taking concomitant DMARDs. The number of

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subjects in these subgroups is too small, however, to make meaningful conclusions.

The findings of the apremilast-exposure period analyses were corroborated by an analysis of the apremilast arms of the Safety Population through Week 52, in that the incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and SAEs did not notably increase with longer exposure to apremilast.

Laboratory abnormalities in hematology and chemistry tests were infrequent and comparable between the apremilast treatment groups and placebo, 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. There was no evidence for myelosuppression, based on routine hematology tests.

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.

Seven subjects reported serious infections, including four during the placebo-controlled period (2 on placebo, 2 on apremilast) and three additional events during the apremilast-exposure period. These events did not occur in a treatment- or dose-dependent manner. Subjects recovered from all events following standard courses of antibiotic treatment.

Seven subjects reported *Herpes* infections, including four during the placebo-controlled period (3 on placebo, 1 on apremilast) and three additional events during the apremilast-exposure period.

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 was no evidence of any effect of apremilast on the overall incidence of malignancies, or on the incidence of any individual malignancy.

There were 5 cardiac disorder SAEs reported during the placebo-controlled period, of which 2 were identified as possible MACE (acute myocardial infarction, 1 case each in the placebo and APR 20 BID treatment groups). Two additional possible MACE were reported during the apremilast-exposure period: one case of acute myocardial infarction in the PBO/20 XO treatment group and one case of myocardial infarction in the APR 30 BID treatment group. None of these events was reported as leading to discontinuation, although the subject in the APR 20 BID treatment group withdrew consent on the day of the event.

One subject, in the APR 20 BID treatment group, attempted suicide during the placebo-controlled period following an emotional disturbance leading to an overdose of sleeping pills that was successfully treated. The subject was discharged home in 2 days and was discontinued from the study at the sponsor's request. No new events of suicidal ideation or behavior were reported during the apremilast-exposure period up to Week 52. After Week 52, one subject, in the APR 30 BID treatment group, attempted suicide on Day 542 of the study after experiencing a worsening of depression, of which [REDACTED] had a 15-year history. [REDACTED] was hospitalized and discharged 3 days later, and continued in the study.

At the end of the placebo-controlled period, the placebo group had a mean weight gain of 0.12 kg,

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<p>compared with weight loss observed in the APR 20 BID and APR 30 BID treatment groups of -1.46 and -1.01 kg, respectively. The majority of subjects maintained their weight within <math>\pm 5\%</math> of baseline, and weight loss <math>&gt; 10\%</math> was infrequent (observed in 1 subject (0.6%) in the placebo group and 3 subjects (1.8%) in the apremilast treatment groups). At the end of the 52-week apremilast-exposure period, the mean weight loss was -1.19 kg in the APR 20 BID treatment group and -1.16 kg in the APR 30 BID treatment group. Weight loss <math>&gt; 10\%</math> was infrequent during the apremilast-exposure period (observed in 9 subjects [3.7%] in the APR 20 BID treatment group and 7 subjects [2.9%] in the APR 30 BID treatment group). No subjects experienced weight loss <math>&gt; 20\%</math>. The proportion of subjects reporting weight loss as a TEAE tended to increase among subjects with a higher baseline BMI.</p> <p>Apremilast demonstrated an acceptable safety profile following long-term (52 week) exposure in both the APR 20 BID and APR 30 BID treatment groups. The nature and severity of TEAEs did not change with long-term exposure, and no increased risk for laboratory abnormalities was observed. Longer exposure to apremilast did not result in an increased incidence of TEAEs for any category presented.</p> <p><b>CONCLUSION:</b></p> <p>This study demonstrated that apremilast, a selective PDE4 inhibitor, was an effective treatment, with an acceptable safety profile, for subjects with active PsA, and confirms the results of a previous phase 2 study 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 or 30 mg BID. This benefit is seen in 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. During the placebo-controlled period, the magnitude of treatment effect for patients in the APR 30 BID group was generally greater compared to the APR 20 BID group. The therapeutic effect was maintained across all measures of efficacy among subjects receiving 52 weeks of treatment.</p> <p>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 52 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 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 active PsA.</p> <p><b>Date of the report:</b> 26 September 2013</p>		