

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> Celgene Corporation	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		
<b>Title of Study:</b> 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 and a qualifying psoriasis lesion		
<b>Principal Investigator:</b> [REDACTED]		
<b>Investigators:</b> A list of investigators is provided in [REDACTED]		
<b>Study Centers:</b> 78 centers in Australia; Canada; Finland; France; Germany; Italy; Korea; Poland; Romania; Russia; Slovak Republic, South Korea; Spain; Switzerland; the United Kingdom; and the United States.		
<b>Publications (reference):</b> Not applicable		
<b>Studied Period (years):</b> Date first subject enrolled: 02 Jun 2010 Date last subject completed final (Week 260) visit: 09 Feb 2017		<b>Phase of development: 3</b>
<b>Objectives:</b> 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, on the signs and symptoms of psoriatic arthritis (PsA) after 16 weeks' administration. Secondary: The secondary objectives of the study were: <ul style="list-style-type: none"> <li>• To evaluate the following in subjects with active PsA who are treated with 2 doses of apremilast or placebo for up to 24 weeks:                         <ul style="list-style-type: none"> <li>– Safety and tolerability</li> <li>– Efficacy</li> <li>– Physical function</li> <li>– Psoriatic skin lesions</li> <li>– Fatigue</li> </ul> </li> </ul>		

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<ul style="list-style-type: none"> <li>– Clinical disease activity</li> <li>• To evaluate the following in subjects with active PsA who are treated with 2 doses of apremilast for up to 52 weeks:                             <ul style="list-style-type: none"> <li>– Safety and tolerability</li> <li>– Efficacy</li> <li>– Physical function</li> <li>– Psoriatic skin lesions</li> <li>– Fatigue</li> <li>– Clinical disease activity</li> </ul> </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>The exploratory objectives of the study were:</p> <ul style="list-style-type: none"> <li>• To evaluate the effect of 2 doses of apremilast on the following disease manifestation for up to 52 weeks of treatment:                             <ul style="list-style-type: none"> <li>– Axial disease</li> </ul> </li> </ul> <p>The health-related quality of life objectives of the study were to evaluate the impact of up to 5 years of treatment with 2 doses of apremilast on:</p> <ul style="list-style-type: none"> <li>• General health state</li> <li>• Worker productivity</li> <li>• Sleep</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>		

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<p>At Week 16 (the primary endpoint), all subjects whose swollen and tender joint count (SJC and 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 [crossover] 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.</p> <p>To maintain the blind at the site and subject level, individual subject treatment assignments were not revealed to the investigators until after the Week 52 database lock at Year 1, and after all final analyses of the Year 1 data were completed and results were released. At that time, open-label APR was provided at the dose the subject was receiving at the end of the 52-week phase of the study.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> Planned: 495 subjects Analyzed: 505 subjects randomized receiving at least 1 dose of investigational product (IP)</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Subjects must have satisfied the following criteria in order to be enrolled in the study:</p> <ol style="list-style-type: none"> <li>1. Males or females, aged <math>\geq 18</math> years at time of consent.</li> <li>2. Understood and voluntarily signed an informed consent document prior to any study related assessments/procedures being conducted.</li> <li>3. Able to adhere to the study visit schedule and other protocol requirements.</li> <li>4. Had a documented diagnosis of PsA (by any criteria) of <math>\geq 6</math> months' duration.</li> <li>5. Met the Classification Criteria for Psoriatic Arthritis at time of screening.</li> <li>6. Had <math>\geq 3</math> swollen AND <math>\geq 3</math> 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).</li> <li>7. Had at least one <math>\geq 2</math> cm plaque psoriasis lesion.</li> </ol>		

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8. Received treatment on an outpatient basis.
9. 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.
10. 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.
11. 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.
12. 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.
13. Met the following laboratory criteria:
  - White blood cell count  $\geq$  3000/mm<sup>3</sup> ( $\geq$  3.0 X 10<sup>9</sup>/L) and  $<$  14,000/mm<sup>3</sup> ( $<$  14 X 10<sup>9</sup>/L)
  - Platelet count  $\geq$  100,000/mm<sup>3</sup> ( $\geq$  100 X 10<sup>9</sup>/L)
  - Serum creatinine  $\leq$  1.5 mg/dL ( $\leq$  132.6  $\mu$ mol/L)
  - Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamate-pyruvate transaminase [SGPT])  $\leq$  2 X upper limit of normal (ULN)
  - Total bilirubin  $\leq$  2 mg/dL ( $\leq$  34  $\mu$ mol/L)
  - Hemoglobin  $\geq$  9 g/dL ( $\geq$  5.6 mmol/L)
  - Hemoglobin A1c  $\leq$  9.0%
14. 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 IP and for at least 28 days after the last dose of IP.
15. 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 IP and for at least 28 days after taking the last dose of IP 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

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[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 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) > 1.5X 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.

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<ol style="list-style-type: none"> <li>16. Erythrodermic, guttate, or generalized pustular psoriasis at randomization.</li> <li>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).</li> <li>18. Rheumatic autoimmune disease other than PsA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia.</li> <li>19. Functional Class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis.</li> <li>20. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease).</li> <li>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.</li> <li>22. Use of phototherapy within 4 weeks of randomization (ie, ultraviolet B light, psoralen ultraviolet light therapy).</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:</b> Apremilast administered orally as 10-, 20-, or 30-mg tablets.		

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<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.		
<b>Reference Therapy, Dose, and Mode of Administration:</b> Placebo administered orally as tablets.		
<b>Criteria for Evaluation:</b> <b>Efficacy:</b> Efficacy was primarily assessed as the ACR 20 response at Week 16, which was defined as a $\geq 20\%$ improvement from baseline in TJC and SJC plus $\geq 20\%$ 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 assessment of pain, and the acute phase reactant (C-reactive protein [CRP] or erythrocyte sedimentation rate). The secondary efficacy endpoints were: <u>Efficacy at Weeks 16 and 24</u> <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 Functioning 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>• Proportion of subjects in each treatment group, whose psoriasis BSA at baseline was <math>\geq 3\%</math>, who achieved PASI-75 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 Score (MASES) 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> </ul>		

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<ul style="list-style-type: none"> <li>• Change from baseline in SF-36v2 Physical Functioning domain score after 24 weeks of treatment</li> <li>• Proportion of subjects who achieved a modified PsARC response after 24 weeks of treatment</li> <li>• Proportion of subjects in each treatment group, whose psoriasis BSA at baseline was <math>\geq 3\%</math>, who achieved PASI-75 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 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 American College of Rheumatology 50% (ACR 50) response after 16 weeks of treatment</li> <li>• Proportion of subjects who achieved an American College of Rheumatology 50% (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> </ul>		

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<ul style="list-style-type: none"> <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> <li>• Change from baseline in the SF-36v2 Physical Functioning 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>• Proportion of subjects in each treatment group, whose psoriasis BSA at baseline was <math>\geq 3\%</math>, who achieved PASI-75 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 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><u>Overall Efficacy</u></p> <p>For data collected after Week 52, summaries are provided for the efficacy measures listed below at each visit assessed to Week 260.</p>		

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<ul style="list-style-type: none"> <li>• Proportion of subjects who achieved an ACR 20 response</li> <li>• Change from baseline in physical function (HAQ-DI)</li> <li>• Change from baseline in the SF-36v2 Physical Functioning domain</li> <li>• Proportion of subjects who achieved a modified PsARC</li> <li>• Proportion of subjects who achieved 75% or greater improvement in Psoriasis Area and Severity Index score (PASI-75) among subjects whose psoriasis body surface area (BSA) at baseline was <math>\geq 3\%</math></li> <li>• Change from baseline in subject's assessment of pain</li> <li>• Change from baseline in MASES in subjects with pre-existing enthesopathy</li> <li>• Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis</li> <li>• Change from baseline in CDAI score</li> <li>• Change from baseline in DAS28(CRP)</li> <li>• Change from baseline in FACIT-Fatigue score</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved by <math>\geq 20\%</math> from baseline</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by <math>\geq 1</math> from baseline</li> <li>• Proportion of subjects with a good or moderate EULAR response</li> <li>• Proportion of subjects who achieved an ACR 50 response</li> <li>• Proportion of subjects who achieved an ACR 70 response</li> <li>• Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 from baseline</li> <li>• Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 from baseline</li> </ul> <p>The exploratory endpoints were as follows:</p> <ul style="list-style-type: none"> <li>• 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 <math>\geq 4</math></li> <li>• American College of Rheumatology N index</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, PGA, EGA, and CRP)</li> <li>• <math>\geq 0.13</math>-point and <math>\geq 0.30</math>-point reductions in HAQ-DI</li> <li>• Change from baseline SF-36v2 component summary scores and individual domain scores</li> </ul>		

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<ul style="list-style-type: none"> <li>• <math>\geq 2.5</math>-point improvement in SF-36 Physical Functioning domain score and SF-36v2 Physical Component Summary (PCS)</li> <li>• Categorical change from baseline in CDAI</li> <li>• Categorical change from baseline in DAS28(CRP)</li> <li>• <math>\geq 10</math>-mm reduction in subject's assessment of pain visual analog scale</li> <li>• <math>\geq 3.56</math>-point improvement in FACIT-Fatigue score</li> </ul> <p>Health-related quality of life endpoints included:</p> <ul style="list-style-type: none"> <li>• Change from baseline in the 25-item Work Limitations Questionnaire (WLQ-25) at Weeks 16, 24, and 52</li> <li>• Change from baseline in the European Quality of Life 5-Dimensional Questionnaire (EQ-5D) at Weeks 16, 24, and 52</li> </ul> <p>For data collected after Week 52, summaries are provided for the measures listed below at each visit to Week 260.</p> <ul style="list-style-type: none"> <li>• Change in WLQ-25 score in each treatment group</li> <li>• Change in EQ-5D score in each treatment group</li> </ul> <p><b>Safety:</b> 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.</p>		
<p><b>Statistical Methods:</b></p> <p><b>Demographics:</b></p> <p>Summary statistics were provided by treatment group for the continuous variables (age, weight, height, body mass index [BMI]). Number and percentage were provided by treatment group for the categorical variables (age category, sex, race, ethnicity, weight category, BMI category).</p> <p><b>Efficacy:</b></p> <p>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).</p> <p>The Apremilast Subjects as Randomized/Re-randomized (AAR) Population was used for the analyses of efficacy during the apremilast-exposure period up to Week 52. 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 apremilast treatment group at Week 0, subjects initially randomized to placebo who entered EE and were re-randomized to apremilast at Week 16, and subjects initially randomized to placebo who completed 24 weeks of treatment on placebo 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.</p>		

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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 calculated as apremilast minus placebo.

For efficacy analyses, [REDACTED] missing data [REDACTED] 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 placebo for the primary endpoint and those secondary endpoints 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 evaluated at Week 16 or 24 [REDACTED]. Then, the pair-wise 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 2-sided p-values from both of the pair-wise 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 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  $\leq 0.025$ , 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 pair-wise 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 2 pair-wise 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 and 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 as described above.

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,

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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 IP). 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 apremilast).

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.

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 post-treatment, 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 post-treatment, 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 260 weeks of exposure to APR in this Phase 3, multicenter, randomized, double-blind, parallel-group study. A total of 505 subjects were included in the full analysis set for efficacy during the 24 week placebo-controlled period (169 PBO, 169 APR 20 BID, and 167 APR 30 BID). A total of 483 subjects, who were either initially randomized to APR or re-randomized from PBO to APR at Week 16 or Week 24, were included in the analyses of efficacy during the APR exposure period up to Week 52 (47 PBO/20 EE, 20 PBO/20 XO, 50 PBO/30 EE, 25 PBO/30 XO, 169 APR 20 BID, and 167 APR 30 BID). Of the subjects initially randomized to APR, 71.0% of subjects in the APR 20 BID treatment group and 75.4% of subjects in the APR 30 BID treatment group completed Weeks 0-52 of the study. Of the 505 subjects who entered the study, 286 (56.6%) subjects completed 2 years of study participation, 249 (49.3%) subjects completed 3 years of study participation, 228 (45.1%) subjects completed 4 years of study participation, and 211 (41.8%) subjects completed the full 5 years of study participation (30 PBO/APR 20 BID, 41 PBO/APR 30 BID, 68 APR 20 BID, and 72 APR 30 BID).

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 11.4 (9.0), CRP of 1.037 (0.422) mg/dL, DAS28(CRP) of 4.57 (4.53), and psoriatic skin involvement of 7.46%

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(3.00%) BSA. The mean (median) PsA disease duration was 7.33 (5.10) years. The majority of subjects (71.9%) had been inadequately controlled by prior treatment with small-molecule DMARDs only; an additional 27.9% had been inadequately controlled by prior treatment with biologic DMARDs. The majority of subjects (60.6%) were receiving at least 1 small-molecule DMARD at baseline; 14.5% of subjects were receiving prednisone (or its equivalent), and 70.7% 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. A dose effect was observed for the primary endpoint. The ACR 20 response rates at Week 16 were 18.3%, 28.4%, and 40.7% for the PBO, 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 PBO were 9.8% ( $p = 0.0295$ ) and 22.3% ( $p < 0.0001$ ), respectively. The observed positive treatment effect of APR 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 APR treatment groups at Week 16 were maintained at Week 24 (15.4%, 26.6% [ $p = 0.0110$ ], and 31.1% [ $p = 0.0007$ ] in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

A nominally significantly greater proportion of subjects in the APR 30 BID treatment group, but not in the APR 20 BID treatment group, achieved an ACR 50 response at Week 24, compared with PBO (nominal  $p$ -value = 0.0180). The proportion of subjects who achieved an ACR 70 response at Week 16 and 24 in both treatment groups did not separate from PBO. Clinically meaningful improvements (> 20% reduction) across multiple ACR component scores were observed in both APR treatment groups. A dose effect was apparent for most of the ACR component responses in favor of APR 30 BID.

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 least-squares mean changes in HAQ-DI at Week 16 were 0.065, -0.131, and -0.192 for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The difference, compared with PBO, in change from baseline in HAQ-DI was statistically significant in the APR 30 BID treatment group (-0.127 [ $p = 0.0073$ ]) but not the APR 20 BID treatment group (-0.066 [ $p = 0.1619$ ]). The improvement in physical function was evident in the maintenance, in the APR 30 BID treatment group, of the statistically significant reductions in HAQ-DI score at Week 24 (0.258 [ $p = 0.0005$ ]).

Notably, the mean changes in HAQ-DI score in the APR treatment groups at Weeks 16 and 24 exceeded the estimated minimally 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 and APR 30 BID treatment groups.

The majority of secondary endpoints incorporated in this study supported the efficacy of APR 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 nominally significant in the APR 20 BID group (37.9%,  $p = 0.0372$ ) and statistically significant in the APR 30 BID group (52.7%,  $p < 0.0001$ ) compared with PBO (27.2%). The responses were generally maintained at Week 24

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(23.1%, 32.0%, and 44.3% [ $p < 0.0001$ ] 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 a dose-dependent manner 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 greater 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 response rates were observed at Week 16 in the APR 20 BID (40.2%, nominal  $p = 0.0309$ ) and APR 30 BID (51.5%, nominal  $p < 0.0001$ ) treatment groups compared with PBO (29.0%), which were maintained at Week 24 (20.1%, 32.0% [ $p = 0.0123$ ], and 42.5% [ $p < 0.0001$ ] for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

The improvement in subjects' physical function produced by APR was further demonstrated by the statistically significant and clinically meaningful improvements in the SF-36v2 Physical Functioning domain score at Week 16 in the APR 30 BID treatment group. The mean changes from baseline in SF-36v2 Physical Functioning domain scores were 1.14, 2.29, and 3.47 ( $p = 0.0053$ ) for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. Similarly, the SF-36v2 PCS score improved from baseline by 1.26, 3.23 (nominal  $p = 0.0100$ ), and 3.37 (nominal  $p = 0.0060$ ) in the PBO, 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 APR treatment groups, and were maintained at Week 24.

Numerically greater improvements in enthesitis, as assessed by MASES, were observed in the APR 30 BID treatment group, compared with PBO, at Weeks 16 and 24 among subjects with pre-existing enthesopathy. Numerically greater reductions in dactylitis severity score was observed in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, at Weeks 16 and 24. At Week 24, the mean reduction in the dactylitis severity score was nominally significantly higher in the APR 30 BID treatment group compared with the PBO group. 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 APR treatment. A positive treatment and dose effect for APR 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, a secondary endpoint of the study, were 7.9%, 20.9% (nominal  $p = 0.0134$ ), and 22.2% (nominal  $p = 0.0062$ ), in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The responses were generally maintained in the APR treatment groups at Week 24 (11.2%, 22.2% [nominal  $p = 0.0515$ ], and 25.6% [nominal  $p = 0.0099$ ], 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

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scale is less sensitive to change and may underestimate the magnitude of improvement. Therefore, the ability of APR to improve the PASI score in this population is an important indicator of the treatment effect on the psoriatic component of PsA.

Sustained improvement in signs and symptoms of PsA, as measured by ACR 20 response, continued up to Week 52. 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 (56.0% [65/116] and 63.0% [80/127], 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 (-0.332 and -0.350, respectively), among subjects remaining in the study (n = 122 and 127, respectively). In both APR treatment groups, the mean reduction in HAQ-DI met or exceeded the MCID 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.

Among PBO subjects who switched to APR, responses were generally supportive of the effect of APR 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 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 Physical Functioning domain score and PCS score improvements were maintained in both treatment groups to Week 260. Improvement in MASES was maintained in both the APR 20 BID and APR 30 BID treatment groups. A positive PASI-75 response rate, even in these subjects with psoriasis involving  $\geq 3\%$  of their body surface at baseline, was maintained in both the APR 20 BID and APR 30 BID treatment groups at Week 260.

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 APR versus PBO 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 at Week 16. This difference was not observed at Week 24. Importantly, a treatment effect in favor of APR versus PBO 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 APR versus PBO, regardless of whether APR was administered alone or with a concomitant small-molecule DMARD.

Although there was no formal comparison of efficacy between APR 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

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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, APR, 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 treatment.

**SAFETY RESULTS:**

During the 24-week, placebo-controlled period, the incidence of TEAEs was 49.4% in the PBO group and comparable in the APR 20 BID and APR 30 BID treatment groups (58.8% and 62.3%, respectively), and led to discontinuation in 6.0%, 7.6%, and 7.2% of subjects, respectively. The majority of TEAEs were mild to moderate in severity. The incidence of severe TEAEs was low and increased in a dose-dependent, but not clearly treatment-dependent manner (4.8%, 2.9%, and 6.0% in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively). The incidence of SAEs was higher with PBO than either dose of APR (5.4%, 1.8%, and 3.6% in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively). During the apremilast-exposure period (with up to 260 weeks of exposure to APR), the frequency of TEAEs, both overall and by severity/seriousness/relationship to drug, were similar to, or lower than, those observed in the APR 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. One subject died during the apremilast-exposure period, which was not considered drug related.

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 treatment-dependent manner, and tended to be highest during the first 1 to 2 weeks of dosing. These events were predominantly mild to moderate in severity and none was serious. One subject in the APR 20 BID treatment group experienced severe nausea and severe diarrhea, which led to discontinuation. Another subject in the APR 20 BID treatment group experienced severe nausea, which did not lead to study discontinuation. During the apremilast-exposure period, no new severe or serious events of nausea were reported after the end of the placebo-controlled period with dosing of up to 260 weeks, or in subjects who were re-randomized from PBO to APR at Week 16 or 24. One new case of severe diarrhea was reported after the end of the placebo-controlled period in the APR 30 BID treatment group. Among subjects treated with APR, the majority of diarrhea cases resolved within 1 month, nausea generally resolved within 2 to 3 weeks, and headaches generally resolved within 1 to 2 weeks.

Other frequently reported TEAEs during the placebo-controlled period included headaches (reported for approximately 5% of subjects in the PBO group and 15% of subjects in both APR treatment groups) and URIs (reported for approximately 2% of subjects in the PBO and 7% of subjects in the APR treatment groups). All other TEAEs were reported for fewer than 5% of subjects in any treatment group. Most headaches and all URIs during the placebo-controlled period were generally mild to moderate in severity. One subject in the PBO group and 1 subject in the APR 30 BID treatment group

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experienced severe headaches during the placebo-controlled period; neither of these events led to discontinuation. During the apremilast-exposure period, 3 new cases of severe headache (2 in the APR 20 BID treatment group and 1 in the APR 30 BID treatment group) and 1 case of severe upper respiratory tract infection (in the APR 30 BID treatment group) were reported after the end of the placebo-controlled period with dosing of up to 260 weeks, or in subjects who were re-randomized from PBO to APR at Week 16 or 24. Additionally, during the apremilast-exposure period, nasopharyngitis was reported for 14.1% and 14.9% of subjects in the APR 20 BID and APR 30 BID treatment groups, respectively.

Serious TEAEs were reported at a similar frequency across the PBO and APR treatment groups during the placebo-controlled period; each SAE during this period was reported by 1 subject per APR treatment group. During the apremilast-exposure period, with dosing of up to 260 weeks, or in subjects who were re-randomized from PBO to APR at Week 16 or 24, most SAEs were reported in 1 subject per APR treatment group, except for psoriatic arthropathy (n = 2 and 7 in the APR 20 BID and APR 30 BID treatment groups, respectively), osteoarthritis (n = 3 and 2, respectively), unstable angina (n = 2 and 2, respectively), and pneumonia (n = 2 and 1, respectively). Based on a comparison of the EAIRs per 100 subject-years between the placebo-controlled period and the apremilast-exposure period in the APR 20 BID and APR 30 BID treatment groups, there was no evidence of an increased incidence of SAEs with longer apremilast exposure.

No notable effects of age were observed on the overall proportion of subjects reporting TEAEs in either APR treatment group. The overall incidence of TEAEs was higher among female subjects than male subjects in the APR 30 BID treatment group. There were no apparent, consistent trends across treatment groups regarding the incidence of TEAEs by baseline DMARD, including MTX use. Apremilast did not appear to increase any toxicity of DMARDs, including MTX.

The findings of the apremilast-exposure period analyses were corroborated by an analysis of TEAEs through Week 260 among subjects initially randomized to an apremilast treatment group, in that the incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and SAEs generally did not increase with longer exposure to APR.

Laboratory abnormalities in hematology and chemistry tests were infrequent and comparable between the APR 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. There was no evidence of 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.

Fourteen subjects reported serious infections, all 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.

Nine subjects reported herpes zoster infections, including 1 subject in the APR 20 BID treatment group during the placebo-controlled period and 8 additional subjects during the apremilast-exposure period.

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There was no testing for latent TB (eg, tuberculin skin test or Quantiferon) in this trial, which included countries with higher prevalence 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 APR on the overall incidence of malignancies, or on the incidence of any individual malignancy. One MACE (acute myocardial infarction) was reported during the apremilast-exposure period.

One subject in the APR 20 BID treatment group with a history of bipolar disorder and depression attempted suicide during the placebo-controlled period, and 1 subject in the APR 20 BID treatment group with a history of alcohol abuse reported suicidal ideation, concurrent with an episode of alcohol poisoning, on Day 404 of the apremilast-exposure period. Neither event was suspected to be related to APR by the investigator.

At the end of the placebo-controlled period, the PBO group had a mean weight loss of 0.21 kg, compared with weight loss observed in the APR 20 BID and APR 30 BID treatment groups of -1.26 and -1.20 kg, respectively. The majority of subjects maintained their weight within  $\pm 5\%$  of baseline, and weight loss  $> 10\%$  was infrequent (observed in 1 subject in the PBO treatment group, 3 subjects in the APR 20 BID treatment group and 3 subjects in the APR 30 BID treatment group). At the end of the apremilast-exposure period, the mean percentage change in weight was -0.94% in the APR 20 BID treatment group and -0.72% in the APR 30 BID treatment group. The majority of subjects maintained their weight within  $\pm 5\%$  of baseline. Weight loss of  $> 5\%$  to  $\leq 10\%$  was observed in 14.3% and 15.2% of subjects in the APR 20 BID and APR 30 BID treatment groups, respectively. In addition, 4.6% of subjects in the APR 20 BID treatment group and 6.3% of subjects in the APR 30 BID treatment group experienced weight loss of  $> 10\%$  to  $\leq 20\%$ . No subject in the APR 20 BID treatment group and 3 subjects in the APR 30 BID treatment group experienced weight loss  $> 20\%$ . The distribution of subjects across categories of weight loss did not appear to be dose dependent. The proportion of subjects reporting weight loss tended to increase among subjects with a higher baseline BMI.

Apremilast demonstrated an acceptable safety profile following long-term (260-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 APR 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 confirms 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 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 that were maintained over 260 weeks of treatment. Although comparable treatment effects were observed for the primary endpoint of the modified ACR 20 response during the placebo-controlled period, the other measures of efficacy were more consistently positive for the APR 30 BID

<b>Name of Sponsor/Company:</b> Celgene Corporation	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		
<p>treatment group compared to those for the APR 20 BID group. The therapeutic effect was maintained across all measures of efficacy among subjects receiving 260 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 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 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 for improvement in physical function in patients with PSA.</p> <p>Date of the report:                  26 Apr 2018</p>		

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