

CELGENE PROPRIETARY INFORMATION

## 2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier  Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Apremilast		
Name of Active Ingredient: 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		
<b>Principal Investigator:</b> [REDACTED]		
<b>Investigators:</b> A list of investigators is provided in [REDACTED]		
<b>Study Centers:</b> 83 centers in Australia; Austria; Canada; France; Germany; Hungary; New Zealand; Poland; Russia; South Africa; Spain; the United Kingdom; and the United States.		
<b>Publications (reference):</b> Not applicable		
<b>Studied Period (years):</b>		<b>Phase of Development: 3</b>
Date first subject enrolled:	02 June 2010	
Date last subject completed final visit (Week 260):	27 October 2016	
<b>Objectives:</b> Primary: The primary objective of this study was to evaluate the clinical efficacy of 2 doses of apremilast (20 mg or 30 mg orally twice daily [BID]), compared with placebo (PBO), on the signs and symptoms of psoriatic arthritis (PsA) after 16 weeks' administration. Secondary: The secondary objectives of the study were: <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 PBO for up to 24 weeks: <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> </ul> </li> </ul>		

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- To evaluate the following in subjects with active PsA who are treated with 2 doses of apremilast for up to 52 weeks:
  - Safety and tolerability
  - Efficacy
  - Physical function
  - Fatigue
  - Clinical disease activity
- To evaluate the efficacy, safety, and tolerability of 2 doses of apremilast during up to 5 years' administration to subjects with active PsA.

The pharmacokinetic (PK) and pharmacodynamic (PD) objectives of this study were:

- To estimate the systemic exposure of apremilast and to measure plasma biomarkers in a subset of subjects in each dose group during the first 24 weeks of treatment.
- To develop a mechanistic PK/PD model to assess changes in clinical efficacy, safety, and biomarkers.

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

- Psoriatic skin lesions
- Axial disease

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

- General health state
- Worker productivity
- Sleep

**Methodology:**

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

Approximately 495 subjects were to be randomized 1:1:1 to receive apremilast (APR) 20 mg BID (APR 20 BID treatment group), APR 30 mg BID (APR 30 BID treatment group), or identically appearing PBO

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<p>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 tender and swollen joint counts (TJC or SJC, respectively) had not improved by <math>\geq 20\%</math> were required to enter early escape (EE) to blinded active treatment. Subjects in the PBO group who met EE criteria were to be re-randomized 1:1 in a blinded fashion to receive either 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 PBO group were to be re-randomized 1:1 in a blinded fashion to receive APR 20 mg BID (PBO/20 crossover [XO] treatment group) or APR 30 mg BID (PBO/30 XO treatment group) and dose-titrated during the first week of active treatment. Subjects who were receiving apremilast at Week 24 (ie, those originally assigned to apremilast or those who entered EE at Week 16) were to remain in their assigned dose groups, in a blinded fashion. All subjects received blister cards of identical appearance at Week 24.</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>Optional population-based PK and biomarker assessments were performed at selected sites in a total of 150 subjects; the biomarker subset included 51 subjects in the PBO group, 51 subjects in the APR 20 BID group, and 48 subjects in the APR 30 BID group.</p> <p>To maintain the blind at the site and subject levels, individual subject treatment assignments were not revealed to the investigators until after the Week 52 database lock at Year 1, and after all analyses were completed and results were released. At that time, open-label apremilast 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: 504 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> </ol>		

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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  $< 14,000/\text{mm}^3$  ( $< 14 \times 10^9/\text{L}$ )
  - Platelet count  $\geq 100,000/\text{mm}^3$  ( $\geq 100 \times 10^9/\text{L}$ )
  - Serum creatinine  $\leq 1.5$  mg/dL ( $\leq 132.6 \mu\text{mol}/\text{L}$ )
  - Aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; serum glutamate-pyruvate transaminase [SGPT])  $\leq 2 \times$  upper limit of normal (ULN)
  - Total bilirubin  $\leq 2$  mg/dL ( $\leq 34 \mu\text{mol}/\text{L}$ )
  - Hemoglobin  $\geq 9$  g/dL ( $\geq 5.6 \text{ mmol}/\text{L}$ )
  - Hemoglobin A1c  $\leq 9.0\%$
13. Male subjects (including those who have had a vasectomy) who engaged in activity in which conception was possible were to use 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.

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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 were to use contraception while on study medication and for at least 28 days after taking the last dose of study medication with either: 1) one highly effective form (non-oral hormonal, intrauterine device, tubal ligation, vasectomized partner); or 2) an oral hormonal contraceptive PLUS one additional form of barrier contraception (male or female latex condom or nonlatex [eg, polyurethane] condom NOT made out of natural [animal] membrane, diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide); or 3) two forms of barrier contraception (male or female latex condom or nonlatex [eg, polyurethane] condom NOT made out of natural [animal] membrane) PLUS one of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide.

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

1. History of clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other 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 if it could have confounded the ability to interpret data from the study.
3. Clinically significant abnormality on 12-lead electrocardiogram (ECG) at screening.
4. Pregnant or breastfeeding female.
5. History of allergy to any component of the IP.
6. Hepatitis B surface antigen positive at screening.
7. Hepatitis C antibody positive at screening.
8. AST (SGOT) and/or ALT (SGPT) > 1.5 x ULN **and** total bilirubin > ULN or albumin < lower limit of normal.
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 must have been 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.

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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.
15. 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).
16. Rheumatic autoimmune disease other than PsA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia.
17. Functional Class IV as defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis.
18. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease).
19. 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.
20. Use of phototherapy within 4 weeks of randomization (ie, ultraviolet B light, psoralen ultraviolet light therapy).
21. Use of adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, or tocilizumab within 12 weeks of randomization.
22. Use of alefacept or ustekinumab within 24 weeks of randomization.
23. Previous treatment with any cell depleting therapies, including investigational agents (eg, rituximab, alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20).
24. Treatment with intravenous  $\gamma$  globulin, plasmapheresis, or ProSORBA™ column within 6 months of baseline.
25. Any previous treatment with alkylating agents such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
26. Prior treatment with apremilast.
27. Therapeutic failure of > 3 agents for PsA (small molecules or biologics), or > 1 biologic tumor necrosis factor blocker. Subjects who terminated previous treatment with small molecules or biologics due to cost or safety, such as discomfort with the subcutaneous injections, could have participated in this study after adequate washout.

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28. Use of any investigational drug within 4 weeks of randomization, or 5 PK/PD half-lives, if known (whichever was longer).		
<b>Test Product, Dose, and Mode of Administration:</b> Apremilast was administered orally as 10-, 20-, or 30-mg tablets.		
<b>Duration of Treatment:</b> Subjects were to be treated with PBO, 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 identical in appearance to the 10-, 20-, and 30-mg apremilast 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, evaluator's (physician's) global assessment of disease activity, HAQ-DI score, subject's assessment of pain, and C-reactive protein (CRP). 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 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 (MASES) 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> </ul>		

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<ul style="list-style-type: none"> <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> <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 a 50% response in ACR score (ACR 50) after 16 weeks of treatment</li> <li>• Proportion of subjects who achieved a 70% response in ACR score (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</li> </ul>		

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<p>after 24 weeks of treatment</p> <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 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><u>Efficacy Beyond Week 52</u></p> <p>Summaries are provided for the measures listed below at each visit to Week 260:</p> <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 function domain</li> <li>• Proportion of subjects who achieved a modified PsARC</li> <li>• Change from baseline in subject's assessment of pain</li> <li>• Change from baseline in MASES score in subjects with pre-existing enthesopathy</li> <li>• Change from baseline in the dactylitis severity score subjects with pre-existing dactylitis</li> <li>• Change from baseline in CDAI score</li> </ul>		

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

The exploratory endpoints were:

- Proportion of subjects in each treatment group, whose psoriasis body surface area (BSA) at baseline was  $\geq 3\%$ , who achieved a 75% or greater improvement in Psoriasis Area and Severity Index (PASI-75) score after 16, 24, or 52 weeks of treatment
- 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  $\geq 4$  after 16, 24, or 52 weeks of treatment
- American College of Rheumatology N index after 16, 24, or 52 weeks of treatment

Post hoc analyses were added for the following endpoints:

- Change from baseline in the individual ACR component scores (TJC, SJC, Patient's [Subject's] Global Assessment of Disease Activity, Evaluator's [Physician's] Global Assessment of Disease Activity, and CRP) at Weeks 16, 24, 40, and 52
- Proportion of subjects in each treatment group whose psoriasis BSA at baseline was  $\geq 3\%$ , who achieved PASI-50
- $\geq 0.13$ -point and  $\geq 0.30$ -point reductions in HAQ-DI at Weeks 16, 24, 40, and 52
- $\geq 2.5$ -point improvement in SF-36 physical functioning domain score and SF-36v2 PCS at Weeks 16, 24, and 52.
- Categorical change from baseline in CDAI at Weeks 16, 24, and 52
- Categorical change from baseline in DAS28(CRP) at Weeks 16, 24, 40, and 52
- $\geq 10$ -point reduction in subject's assessment of pain visual analog scale at Weeks 16, 24, 40, and 52
- $\geq 3.56$ -point improvement in FACIT- Fatigue score at Weeks 16, 24, and 52

Health-related quality of life endpoints included:

- Change from baseline in the 25-item Work Limitations Questionnaire at Weeks 16, 24, and 52
- Change from baseline in the European Quality of Life 5-Dimensional Questionnaire at Weeks 16, 24, and 52
- Change from baseline in the Medical Outcomes Study Sleep Scale at Weeks 16, 24, and 52

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<p>For data collected beyond 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 MOS Sleep score in each treatment group</li> <li>• Change in EQ-5D score in each treatment group</li> </ul> <p><b>Safety:</b> Safety was assessed according to adverse events (AEs); chest radiographs; vital sign measurements, including height and weight; physical examinations; clinical laboratory variables; pregnancy test findings; and 12-lead ECG findings.</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, and body mass index [BMI]). Number and percentage were provided by treatment group for the categorical variables (age category, sex, race, ethnicity, region, weight category, and 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 (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 260. The AAR Population consisted of all subjects who were randomized or re-randomized to receive apremilast at any time during the study (ie, subjects initially randomized to an apremilast treatment group at Week 0, subjects initially randomized to PBO who entered EE and were re-randomized to apremilast at Week 16, and subjects initially randomized to PBO who completed 24 weeks of treatment on PBO and, as per the protocol, were re-randomized to apremilast at Week 24). For the analyses using the AAR Population, subjects were included in the treatment group to which they were randomized or re-randomized, irrespective of the IP they actually received.</p> <p>The analyses of the primary and secondary endpoints evaluated at Weeks 16 and 24 were performed and presented by treatment group (PBO, APR 20 BID, and APR 30 BID). Treatment differences were evaluated only between each apremilast treatment group and the PBO group and calculated as apremilast minus PBO.</p> <p>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.</p> <p>[REDACTED]</p>		

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

Specifically, for the primary endpoint (ACR 20 response at Week 16), if the 2-sided p-values from both pair-wise comparisons were  $\leq 0.050$ , then both test results were considered statistically significant and both apremilast doses were declared efficacious. If the 2-sided p-value from 1 of the 2 pair-wise comparisons was  $> 0.050$  but the 2-sided p-value from the other comparison was  $\leq 0.025$ , then the latter test result was considered statistically significant and the corresponding apremilast dose tested was declared efficacious. In other situations, neither of the apremilast doses was declared efficacious.

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

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

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

**Safety:**

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

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

Vital sign measurements, including weight, were summarized descriptively by visit (mean, median, standard deviation, minimum, and maximum). In addition, shift tables showing the number of subjects with values low, normal, and high based on the normal reference ranges pretreatment versus post-treatment were provided.

**SUMMARY – CONCLUSIONS**

**EFFICACY RESULTS:**

A total of 504 subjects were included in the FAS for efficacy during the placebo-controlled period (168 PBO, 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 PBO 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. Of the 349 subjects who continued study participation past Week 52, 213 subjects completed the full 5 years of the treatment (29 PBO/APR 20 BID, 32 PBO/APR 30 BID, 72 APR 20 BID, and 80 APR 30 BID). The majority (349/428; 81.5%) of subjects who completed the active treatment phase (Week 24 to 52) entered the active treatment/long-term safety phase. Of the 504 subjects who entered the study, 286 subjects (56.7%) completed 2 years of study participation, 259 subjects (51.4%) completed 3 years of study participation, 229 subjects (45.4%) completed 4 years of study participation, and 213 subjects (42.3%) completed the full 5 years of study participation.

Baseline demographics, disease characteristics, prior history of PsA medication, and baseline use of PsA medications were consistent with an active PsA population. The study was well-balanced for baseline disease characteristics, with an overall mean (median) TJC of 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 1 small-molecule DMARD at baseline; 10.5% of subjects were receiving prednisone (or its equivalent), and 71.6% of subjects were receiving NSAIDs.

Apremilast demonstrated statistically significant reductions in the signs and symptoms of PsA, as measured by ACR 20 response at Week 16, the primary endpoint, for both the APR 20 BID and APR 30 BID treatment groups, compared with PBO. 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 PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The adjusted differences in ACR 20 response for APR 20 BID and APR 30 BID treatment groups, compared with PBO, were 11.3% (p = 0.0166) and 19.0% (p = 0.0001), respectively. The observed positive treatment effect of apremilast on the signs and symptoms of active PsA is supported by multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (eg, nonresponder imputation,

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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] for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

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 (LS) mean changes in the HAQ-DI score at Week 16 compared to baseline were -0.086, -0.198, and -0.244 for the PBO, APR 20 BID, and APR 30 BID treatment groups, 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 PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

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

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

Apremilast produced modified PsARC responses at Week 16 that were statistically significant in the APR 30 BID group (46.4%, p = 0.0017) but not significant in the APR 20 BID group (38.7%, p = 0.0862) compared with PBO (29.8%). The responses were generally maintained in the APR 20 BID treatment group at Week 24 (18.5%, 31.0% [nominal p = 0.0079], and 42.9% [nominal p < 0.0001] for the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively).

Apremilast treatment reduced the activity of PsA in this study population, as measured by DAS28(CRP) and CDAI, both of which are composite, objective, and subjective, assessments of disease activity. The proportion of subjects with high disease activity (DAS28[CRP] > 5.1 or CDAI > 22) decreased in the APR 20 BID and APR 30 BID treatment groups, compared with PBO. Correspondingly, the proportion of subjects with a DAS28(CRP) < 2.6, indicating remission, or a CDAI ≤ 10, indicating low disease activity or remission, was higher in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, at both Weeks 16 and 24. Consistent with these observations, 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 PBO (29.8%), which were maintained at Week 24 (30.4% and 42.3% vs 16.1%, respectively; nominal p = 0.0020 and < 0.0001, respectively).

In addition to the reduction in HAQ-DI score mentioned above, 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 PBO, 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 PBO, 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

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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 PBO, at Weeks 16 and 24 among subjects with pre-existing enthesopathy. Similarly, numerically greater reductions in dactylitis severity score were observed in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, 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 effect 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 PBO, 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 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 Psoriasis Area and Severity Index (PASI) scores (median  $< 6$ ). If there is a low PASI score or low BSA at baseline, the PASI scale is less sensitive to change and may underestimate the magnitude of improvement. Therefore, the ability of apremilast to improve the PASI score in this population is an important indicator of the treatment effect on the psoriatic component of PsA.

Analyzed using data as observed, the ACR 20 response rates among subjects initially randomized to the APR 20 BID and APR 30 BID treatment groups were comparable at Week 52 (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.

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 or greater than 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 score was maintained in both the APR 20 BID and APR 30 BID treatment groups. A positive PASI-75 response rate was maintained in both the APR 20 BID and APR 30 BID treatment groups at Week 260.

Subgroup analyses of ACR 20 responses were conducted using factors including age, sex, weight, BMI, race, and geographic region, as well as PsA subtype and disease duration. Overall, a treatment effect in

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favor of apremilast 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. Importantly, a treatment effect in favor of apremilast 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 apremilast versus PBO, 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 260, 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 260 weeks of treatment. During the placebo-controlled period, a generally greater magnitude and consistency of clinical response was observed with APR 30 mg BID over APR 20 mg BID.

**SAFETY RESULTS:**

During the 24-week, placebo-controlled period, the incidence of TEAEs was 48.2% in the PBO 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 PBO, 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 PBO, APR 20 BID, and APR 30 BID treatment groups, respectively). During the apremilast-exposure period (with up to 260 weeks' exposure to apremilast), the incidence of TEAEs was 82.9% in the APR 20 BID and 86.9% in the APR 30 BID treatment group, and led to discontinuation in 11.0% and 12.2% of subjects, respectively. The majority of TEAEs were mild to moderate in severity. The incidence of severe TEAEs was similar between treatment groups (14.3% and 12.2% in the APR 20 BID and APR 30 BID groups, respectively). The incidence of SAEs was comparable across treatment groups (16.7% and 20.0% in the APR 20 BID and APR 30 BID treatment groups, respectively).

During the placebo-controlled period, gastrointestinal events, particularly diarrhea and nausea, accounted for the most frequently reported TEAEs. The frequency of diarrhea and nausea increased in a dose-dependent manner, and tended to be highest during the first 1 to 2 weeks of dosing. These events were predominantly mild to moderate in severity and most did not lead to discontinuation. Severe diarrhea occurred in 2 subjects: 1 subject in the PBO group, which led to discontinuation, and 1 in the 20 BID treatment group, which resolved without drug discontinuation. Severe nausea occurred in 2 subjects (one in each apremilast treatment group). None of these events led to discontinuation. One of these subjects

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(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, 1 case of severe diarrhea (APR 20 BID group) where drug was discontinued, 2 cases of severe nausea (one in the APR 20 BID group and one in the APR 30 BID group) with no drug discontinuation, and 1 case of serious nausea (one in the APR 30 BID group) with no drug discontinuation were reported with dosing of up to 260 weeks. Among subjects treated with apremilast, the majority of diarrhea cases resolved within 1 month, nausea generally resolved within 2-3 weeks, and headaches generally resolved within 1 to 2 weeks.

Other frequently reported TEAEs during the placebo-controlled period included headaches (reported in approximately 5% of subjects in the PBO group and 10% of subjects in both apremilast treatment groups) and upper respiratory tract infections (reported in approximately 4% of subjects in the PBO, 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, 4 cases of severe headache (3 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 20 BID treatment group) were reported with dosing of up to 260 weeks. Additionally, during the apremilast-exposure period, nasopharyngitis was reported by 12.2% and 12.7% of subjects in the APR 20 BID and APR 30 BID treatment groups.

Serious TEAEs were reported at a similar frequency across the PBO and apremilast treatment groups during the placebo-controlled period. Each SAE during this period was reported by 1 subject per treatment group. During the apremilast-exposure period, with dosing of up to 260 weeks, the overall rate of SAEs was comparable between the APR 20 BID and APR 30 BID treatment groups (16.7% and 20.0%, respectively) and most SAEs were reported by at most 1 subject per treatment group. The SAEs that were reported by > 1 subject in either treatment group included osteoarthritis, psoriasis, pneumonia, rotator cuff syndrome, coronary artery disease, depression, arthralgia, breast cancer, and acute myocardial infarction.

There were 4 deaths reported during the study, 1 of which occurred > 28 days after the last dose of apremilast. 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. There were 3 additional reports of death as of the end of the study, including 2 subjects randomized to APR 30 BID, and 1 subject randomized to PBO/APR 20 BID. A [redacted] subject in the APR 30 BID treatment group died on Day 695 of study participation due to chest and head trauma associated with a [redacted] accident. A [redacted] subject in the APR 30 BID treatment group died on Day 1700 of study participation due to necrotizing fasciitis of the anterior abdominal wall, acute renal failure, and shock. A [redacted] subject in the PBO/APR 20 BID treatment group died on Day 1048 of study participation (47 days after the last dose of apremilast) due to cardiogenic shock, myocardial infarction, sepsis, and hypoxic respiratory failure.

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

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period, the incidence of TEAEs was similar in males and females in the APR 20 BID and APR 30 BID treatment groups, and no difference in TEAE frequency was noted when subjects were sorted by age group and study treatments.

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 subjects in these subgroups is too small, however, to make meaningful conclusions. During the apremilast-exposure period, no difference in the frequency of TEAEs was noted in either apremilast treatment group when evaluated by concomitant DMARD or MTX use.

Laboratory abnormalities in hematology and chemistry tests over 260 weeks of study participation were infrequent and comparable between the apremilast treatment groups and PBO, and showed no evidence of organ toxicity requiring laboratory monitoring. Individual, markedly abnormal values were infrequent and limited to isolated (single values) excursions outside the normal range. There were no cases of liver enzyme elevations meeting Hy's Law. 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.

Twenty-four subjects reported serious infections, including 4 during the placebo-controlled period (2 on PBO, 2 on apremilast) and 20 during the apremilast-exposure period. These events did not occur in a treatment- or dose-dependent manner. Subjects recovered from all events.

Seventeen subjects reported herpes infections, including 4 during the placebo-controlled period (3 on PBO, 1 on APR 20 mg BID) and 14 during the apremilast-exposure period. Eight of these cases were herpes zoster, none of which involved more than 1 dermatome.

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 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 MACEs (acute myocardial infarction, 1 case each in the PBO and APR 20 BID treatment groups). Three possible MACEs were reported during the apremilast-exposure period (1 case of acute myocardial infarction in the PBO/APR 20 BID treatment group, 1 case of myocardial infarction in the APR 20 BID treatment group, and 1 case of myocardial infarction in the APR 30 BID treatment group) and 1 possible MACE was reported > 28 days after the last dose of apremilast (1 case of myocardial infarction in the PBO/APR 20 BID treatment group). All of these events were reported as SAEs and 1 event was fatal (the myocardial infarction in the PBO/APR 20 BID treatment group).

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 benzodiazepines that was successfully treated. The subject was discharged home in 2 days and was discontinued from the study at the sponsor's

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<p>request. During the apremilast-exposure period, 1 subject in the APR 30 BID treatment group attempted suicide on Day 542 of the study after experiencing a worsening of depression. [REDACTED] was hospitalized and discharged 3 days later, and continued in the study.</p> <p>At the end of the placebo-controlled period, the PBO group had a mean weight gain of 0.12 kg, 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 PBO group and 3 subjects [1.8%] in the apremilast treatment groups). At the end of the apremilast-exposure period, the mean weight loss was -1.07 kg in the APR 20 BID treatment group and -1.04 in the APR 30 BID treatment group. Weight loss <math>&gt; 10\%</math> to <math>\leq 20\%</math> was infrequent during the apremilast-exposure period (observed in 19 subjects [7.9%] in the APR 20 BID treatment group and 23 subjects [9.4%] in the APR 30 BID treatment group). No subjects experienced weight loss <math>&gt; 20\%</math> in either the APR 20 BID or APR 30 BID treatment groups at the end of 5 years of treatment. 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 (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.</p> <p><b>CONCLUSIONS:</b></p> <p>This study demonstrated that apremilast, a selective phosphodiesterase 4 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 was 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 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' 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 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>		
Date of the report: 29 May 2018		