2. SYNOPSIS

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

Title of Study: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis who have not been treated with disease-modifying antirheumatic drugs

Principal Investigator:

Investigators: A list of investigators is provided in

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

Publications (reference): Not applicable

Studied period (years):		**Phase of development:** 3
Date first subject enrolled:	09 Dec 2010	
Date last subject completed last visit:	16 Aug 2017	

Objectives:

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, on the signs and symptoms of psoriatic arthritis (PsA) after 16 weeks' administration.

Secondary:

The secondary objectives of the study were:

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

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

Methodology:

This Phase 3 parallel-group study with 2 active treatment groups consisted of 3 treatment phases: 1) a 24-week, randomized, double-blind, placebo-controlled phase, 2) a randomized, double-blind active treatment phase of at least 28 weeks' duration, and 3) an open-label, long-term safety phase of up to 4 years' duration. The overall study duration is 5 years (260 weeks).

Approximately 495 subjects were to be randomized in a 1:1:1 ratio 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/day increments over the first week of treatment; blinding was maintained by the use of identical blister cards for all subjects.

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

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

Clinical efficacy for amelioration of signs and symptoms of PsA (ie, 20% improvement per the American College of Rheumatology response criteria [ACR 20]) and physical function (ie, Health Assessment Questionnaire – Disability Index [HAQ-DI]) were to be assessed at Weeks 16, 24, 40, and 52. To maintain the blind at the site and subject level, individual subject treatment assignments were not to be

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revealed to the investigators until after the Week 52 database lock at Year 1, after all final analyses were completed and the final results were released. At that time, open-label investigational product (IP) (apremilast) was provided and the subjects were transitioned to their open-label dose of apremilast based on the dose that they received at the end of Week 52.

Number of subjects (planned and analyzed):

Planned: 495 subjects

Analyzed: 527 subjects

Diagnosis and main criteria for inclusion:

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

1. Male or female, aged ≥ 18 years at the time of consent.
2. Able to understand and voluntarily sign an informed consent document before any study-related assessments/procedures were conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Had a documented diagnosis of PsA (by any criteria) of ≥ 3 months in duration.
5. Met the Classification Criteria for Psoriatic Arthritis (CASPAR) at the time of screening.
6. Had ≥ 3 swollen joints and ≥ 3 tender joints.
7. Had not previously been treated with disease-modifying antirheumatic drugs (DMARDs) (small molecules or biologics).
8. Were receiving treatment on an outpatient basis.
9. If taking oral corticosteroids, had been on a stable dose of prednisone ≤ 10 mg/day or equivalent for at least 1 month before screening.
10. If taking nonsteroidal anti-inflammatory drugs (NSAIDs) or narcotic analgesics, had been on a stable dose for at least 2 weeks before screening and dose would remain stable until completion of the Week 24 study visit.
11. Low potency topical corticosteroids were allowed as background therapy for treatment of psoriasis on the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study. Subjects who had scalp psoriasis were permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. A nonmedicated skin emollient (eg, Eucerin® cream) was permitted for body lesions only. Subjects were not to use these treatments within 24 hours before the clinic visit.
12. Met the following laboratory criteria:
    - White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L) and < 14,000/mm^3 (< 14 x 10^9/L).

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- Platelet count ≥ 100,000/mm3 (≥ 100 x 10^9/L).
- Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L).
- Serum aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; serum glutamate-pyruvate transaminase [SGPT]) ≤ 2 x upper limit of normal (ULN).
- Serum total bilirubin ≤ 2 mg/dL (≤ 34 µmol/L).
- Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L).
- Hemoglobin A1c (HbA1c) ≤ 9.0%.

13. Male subjects (including those who had had a vasectomy) who engaged in activity in which conception was possible must have agreed to use barrier contraception (male latex condom or nonlatex condom not made out of natural [animal] membrane [for example, polyurethane]) while taking the IP and for at least 28 days after the last dose of IP.
14. Females of childbearing potential must have had a negative pregnancy test at screening and baseline. Females of childbearing potential who engaged in activity in which conception was possible must have agreed to use contraception while on IP and for at least 28 days after taking the last dose of IP with either: 1) one highly effective form (hormonal contraception [oral, injection, implant, transdermal patch, vaginal ring], intrauterine device, tubal ligation, vasectomized partner), or 2) two forms of barrier contraception (male or female latex condom or nonlatex [eg, polyurethane] condom not made out of natural [animal] membrane) plus one of the following: diaphragm with spermicide, cervical cap with spermicide, or contraceptive sponge with spermicide.

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

1. History of clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, or immunologic disease or other major uncontrolled disease.
2. Any condition, including the presence of laboratory abnormalities, that would have placed the subject at unacceptable risk if he or she were to participate in the study or that would have confounded the ability to interpret the study data.
3. Clinically significant abnormality on 12-lead electrocardiogram (ECG) at screening.
4. Pregnancy or breastfeeding.
5. History of allergy to any component of the IP (apremilast or placebo).
6. Positive for hepatitis B surface antigen at screening.

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7. Positive for hepatitis C antibody at screening.
8. Serum AST (SGOT) and/or ALT (SGPT) > 1.5 x ULN and serum total bilirubin greater than the ULN or albumin less than the 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 before screening or during the screening visit). An additional lateral view was strongly recommended but was not required.
12. Active substance abuse or a history of substance abuse within 6 months before screening.
13. Bacterial infections that required treatment with oral or injectable antibiotics or significant viral or fungal infections within 4 weeks of screening. Any treatment for such infections must have been completed at least 4 weeks before screening.
14. Malignancy or history of malignancy except for treated (ie, cured) basal cell or squamous cell in situ skin carcinomas and treated (ie, cured) cervical intraepithelial neoplasia or carcinoma in situ of the cervix.
15. Major surgery (including joint surgery) within 8 weeks before screening or planned major surgery within 6 months following randomization.
16. Erythrodermic, guttate, or generalized pustular psoriasis at randomization.
17. Topical therapy for psoriasis, except as noted in the inclusion criteria, within 2 weeks of randomization (including, but not limited to, topical corticosteroids, topical retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin).
18. Rheumatic autoimmune disease other than PsA, including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, or fibromyalgia.
19. Functional Class IV as defined by the ACR Classification of Functional Status in Rheumatoid Arthritis.
20. Prior history of or current inflammatory joint disease other than PsA (eg, gout, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease).
21. Prior use of DMARDs (small molecules or biologics).
22. Use of systemic therapy(ies) within 4 weeks of randomization, including but not limited to, corticosteroids (except as noted in the inclusion criteria), oral retinoids, and fumaric acid esters.

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23. Use of phototherapy within 4 weeks of randomization (ie, ultraviolet B light, psoralen plus ultraviolet A light).
24. Previous treatment with any cell-depleting therapies, including investigational agents (eg, rituximab, alemtuzumab [CAMPATH], anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20).
25. Treatment with intravenous gamma globulin, plasmapheresis, or Prosorba® column within 6 months before baseline.
26. Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.
27. Prior treatment with apremilast.
28. Use of any investigational drug within 4 weeks of randomization, or 5 pharmacokinetic/ pharmacodynamic half-lives, if known (whichever was longer).

Test product, dose and mode of administration, batch number:

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

Duration of treatment:

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

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

Placebo administered orally as tablets.

Criteria for evaluation:

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

The secondary efficacy endpoints were:

Efficacy at Weeks 16 and 24

- Change from baseline in physical function (as assessed by the HAQ-DI) after 16 weeks of treatment (key secondary endpoint)
- Proportion of subjects who achieved anACR 20 response after 24 weeks of treatment

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

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≥ 1 after 16 weeks of treatment

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

Efficacy at Week 52

- Proportion of subjects who achieved an ACR 20 response after 52 weeks of treatment
- Change from baseline in physical function (as assessed by the HAQ-DI) after 52 weeks of treatment
- Change from baseline in the SF-36v2 PFS after 52 weeks of treatment
- Proportion of subjects who achieved a modified PsARC response after 52 weeks of treatment

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- Change from baseline in subject's assessment of pain after 52 weeks of treatment
- Change from baseline in the MASES in subjects with pre-existing enthesopathy after 52 weeks of treatment
- Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis after 52 weeks of treatment
- Change from baseline in CDAI score after 52 weeks of treatment
- Change from baseline in DAS28(CRP) after 52 weeks of treatment
- Change from baseline in FACIT-Fatigue score after 52 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved by ≥ 20% after 52 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 after 52 weeks of treatment
- Proportion of subjects who achieved an ACR 50 response, compared with baseline, after 52 weeks of treatment
- Proportion of subjects who achieved an ACR 70 response, compared with baseline, after 52 weeks of treatment
- Proportion of subjects with pre-existing enthesopathy whose MASES improved to 0 after 52 weeks of treatment
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 after 52 weeks of treatment

Overall Efficacy

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

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

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- Change from baseline in the dactylitis severity score in subjects with pre-existing dactylitis
- Change from baseline in CDAI score
- Change from baseline in DAS28(CRP)
- Change from baseline in FACIT-Fatigue score
- Proportion of subjects with pre-existing enthesopathy whose MASES improved by ≥ 20% from baseline
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved by ≥ 1 from baseline
- 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 from baseline
- Proportion of subjects with pre-existing dactylitis whose dactylitis severity score improved to 0 from baseline

The exploratory endpoints were:

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

In addition to the endpoints described in the protocol, the following analyses at key time points were prespecified in the Statistical Analysis Plan. For data collected beyond Week 52, summaries are provided for the measures listed below at each visit to Week 260.

- Change from baseline in the individual ACR component scores (TJC, SJC, PGA, EGA, and CRP)
- Proportion of subjects with ≥ 0.13-point and ≥ 0.30-point reductions in HAQ-DI
- Change from baseline SF-36v2 component summary scores and individual domain scores

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- Proportion of subjects with ≥ 2.5-point improvement in SF-36v2 PFS and SF-36v2 Physical Component Summary (PCS)
- Proportion of subjects with ≥ 10-mm reduction in subject's assessment of pain Visual Analog Scale
- Categorical change from baseline in CDAI
- Categorical change from baseline in DAS28(CRP)
- Proportion of subjects with ≥ 3.56-point improvement in FACIT-Fatigue score

The following post hoc analysis was also added:

- Proportion of subjects in each treatment group, whose psoriasis BSA at baseline was ≥ 3%, who achieved 50% or greater improvement in the Psoriasis Area and Severity Index score (PASI-50) after 16, 24, or 52 weeks of treatment

Health-related quality of life endpoints listed below at each visit to Week 260:

- Change in the 25-item Work Limitations Questionnaire (WLQ-25) in each treatment group
- Change in the EuroQol 5 Dimensions Questionnaire (EQ-5D) score in each treatment group

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

Statistical methods:

Demographics:

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

Efficacy:

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

The 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

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they actually received.

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

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

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

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

Formal pairwise comparisons with respect to the first secondary endpoint (change from baseline in the HAQ-DI score at Week 16) were conducted conditional on the test results for the ACR 20 response at Week 16. If the test results of ACR 20 response for both apremilast doses were statistically significant, then the 2 pairwise comparisons for the HAQ-DI score were to be performed using the Hochberg procedure at the $\alpha = 0.050$ level, as described above for the ACR 20 response. If only the test result of the ACR 20 response for 1 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 the ACR 20 response was statistically significant, then formal statistical tests were not to be performed for the HAQ-DI score or for the remaining secondary endpoints that were evaluated at Week 16 or 24.

Formal statistical tests for the remaining secondary endpoints that were evaluated at Week 16 or 24 were

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conducted in the same manner as described above.

For planned statistical tests that were not formally performed as a result of the aforementioned multiplicity adjustment strategy, nominal 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 one dose of study drug). Safety analyses for the apremilast-exposure period were performed using the Apremilast Subjects as Treated Population (all subjects who received at least 1 dose of apremilast).

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

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

Vital sign measurements, including weight, were summarized descriptively by visit (mean, median, standard deviation, minimum and maximum). In addition, shift tables showing the number of subjects with values below, within and above the normal reference ranges pretreatment versus posttreatment, together with the number determined to be clinically significant, were provided.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

This report constitutes the analysis of data for up to 260 weeks of exposure to apremilast in this Phase 3, multicenter, randomized, double-blind, parallel-group study. A total of 527 subjects with active PsA who were DMARD-naïve were randomized per protocol and were included in the FAS for efficacy during the 24-week placebo-controlled period (176, 175, and 176 subjects in the placebo, APR 20 BID, and APR 30 BID treatment groups, respectively). A total of 506 subjects, who were initially randomized to apremilast or who were re-randomized from placebo to apremilast at Week 16 or Week 24, were included in the analyses of efficacy during the apremilast-exposure period up to Week 52 (51 PBO/20 EE, 26 PBO/20 XO, 52 PBO/30 EE, 26 PBO/30 XO, 175 APR 20 BID, and 176 APR 30 BID). Among subjects initially randomized to apremilast, 75.4% (132 of 175) of subjects in the APR 20 BID group and 80.1% (141 of 176) of subjects in the APR 30 BID group completed Weeks 0–52 of the study. Additionally, 73.3% (129 of 176) of subjects randomized to the placebo group completed Week 52. Of the 527 subjects who were randomized and received 1 dose of IP in the study, 229 subjects (43.5%) completed the full 5 years of the treatment (37 PBO/APR 20 BID, 41 PBO/APR 30 BID, 71 APR 20 BID, and 80 APR 30 BID).

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Baseline demographics, disease characteristics, prior history of PsA medications, and baseline use of PsA medications were consistent with an active PsA population who were DMARD-naïve. The treatment groups were well balanced for baseline disease characteristics, with an overall mean (median) TJC of 20.1 (16.0), SJC of 11.2 (9.0), CRP of 0.937 (0.399) mg/dL, DAS28(CRP) of 4.6 (4.62), and psoriatic skin involvement of 8.03% (3.00%) BSA. The mean (median) PsA disease duration was 3.41 (1.10) years. The majority of subjects (73.1%) were receiving NSAIDs at baseline and 7.2% of subjects were receiving oral prednisone (or its equivalent).

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

The reduction in the signs and symptoms of active PsA with apremilast treatment was further demonstrated by a nominally significantly greater proportion of subjects in both APR treatment groups who achieved an ACR 50 response at Weeks 16 and 24 compared with PBO (nominal $p < 0.05$). No notable differences were observed between the APR 20 BID or the APR 30 BID treatment group and the PBO treatment group in the ACR 70 response at either Week 16 or Week 24.

Treatment with apremilast resulted in statistically significant and clinically meaningful improvements in physical function, as measured by the HAQ-DI score at Week 16, the key secondary endpoint. The mean change in HAQ-DI from baseline at Week 16 were 0.012, -0.156, and -0.205 in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The LS mean differences in the change from baseline in HAQ-DI in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, were -0.168 ($p = 0.008$) and -0.217 ($p < 0.0001$), respectively. The statistically significant improvement in HAQ-DI scores in the APR 20 BID and APR 30 BID treatment groups compared with PBO were maintained at Week 24 (-0.156 [$p = 0.0014$] and -0.207 [$p < 0.0001$] versus 0.012, respectively). A dose effect was observed at Weeks 16 and 24.

The mean improvement in the HAQ-DI score exceeded the estimated minimally clinically important difference (MCID) for improvement from baseline in HAQ-DI score of 0.13 (Kwok, 2010) in both the APR 20 BID and APR 30 BID treatment groups at Weeks 16 and 24, and approximated the lower bound of the 95% CI (0.24 to 0.35) for the estimated MCID for improvement in HAQ-DI score from baseline of 0.30 (Mease, 2004) in the APR 30 BID treatment group at Weeks 16 and 24.

Nominally significantly greater proportions of subjects in both the APR 20 BID and APR 30 BID treatment groups, compared with PBO, achieved the MCID of an improvement from baseline in HAQ-DI score of 0.13 or 0.30.

The majority of secondary endpoints incorporated in this study supported the efficacy of apremilast in the

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reduction of signs and symptoms and improvement of physical function in subjects with active PsA.

Treatment with apremilast resulted in modified PsARC responses at Week 16 that were statistically significantly greater in the APR 20 BID treatment group (38.9%, p = 0.0037) and the APR 30 BID treatment group (45.5%, p < 0.0001), compared with PBO (24.4%). A dose effect was observed at Week 16. The significant responses in the APR 20 BID and APR 30 BID treatment groups, compared with PBO were maintained at Week 24 (36.6% [nominal p < 0.0001] and 35.2% [nominal p = 0.0001] versus 17.0%, respectively). Apremilast treatment reduced the severity of PsA in this study population, as measured by DAS28(CRP), which is a composite, objective, and subjective assessment of disease activity. The proportion of subjects with high disease activity (DAS28[CRP] > 5.1) decreased in the APR 20 BID and APR 30 BID treatment groups, compared with PBO. Correspondingly, the proportion of subjects with low disease activity (DAS28[CRP] ≥ 2.6 to < 3.2) or remission (DAS28[CRP] < 2.6) increased from Baseline to Week 16 by approximately 6.2% in the PBO group, 16.0% in the APR 20 BID treatment group, and 18.2% in the APR 30 BID treatment group. The increase in the proportion of subjects with low disease activity or remission was approximately 10% higher in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, at Weeks 16 and 24. This indicated an overall improvement in subjects' disease activity, as assessed using subjective (PGA) and objective (TJC, SJC, and CRP) measures of disease activity.

Consistent with these observations, nominally significant good/moderate EULAR responses were observed at Week 16 in the APR 20 BID (41.1%, nominal p = 0.0013) and APR 30 BID (44.3%, nominal p = 0.0001) treatment groups, compared with PBO (25.0%), which were maintained at Week 24 (17.0%, 34.9% [nominal p = 0.0001], and 28.4% [nominal p = 0.0110] for the PBO, APR 20 BID and APR 30 BID treatment groups, respectively.

The improvement in subjects' physical function produced by apremilast was further demonstrated by the statistically significant and clinically meaningful improvements in the SF-36v2 PFS and PCS score at Weeks 16 and 24. At Week 16, the SF-36v2 PFS improved from baseline in the APR 20 BID and APR 30 BID treatment groups compared with PBO (2.39 [p = 0.0043], and 3.19 [p = 0.0002] versus 0.01, respectively. Similarly, the SF-36v2 PCS score improved from baseline in the APR 20 BID and APR 30 BID treatment groups compared with PBO (3.15 [nominal p = 0.0034], and 4.20 [nominal p < 0.0001] versus 0.93, respectively). A dose effect was observed at Weeks 16 and 24.

The improvements in the SF-36v2 PFS exceeded the estimated MCID of 2.5 in the APR 30 BID treatment group at Weeks 16 and 24. The improvements in the SF-36v2 PCS score exceeded the estimated MCID of 2.5 in both apremilast treatment groups at Weeks 16 and 24.

A nominally significantly greater proportion of subjects in the APR 20 BID and APR 30 BID treatment groups achieved ≥ 2.5-point improvement from baseline in the SF-36v2 Physical Functioning domain, compared with PBO, at Weeks 16 and 24, and in the PCS score in the APR 20 BID group at Week 16 and in the APR 30 BID treatment group at Weeks 16 and 24.

Subjects in the APR 30 BID treatment group had a nominally significantly greater mean improvement (increase from baseline) in the FACIT-Fatigue score at Week 16 compared with placebo (nominal p = 0.0045), which was maintained at Week 24. No significant differences in the FACIT-Fatigue scores were observed between the APR 20 BID treatment group and PBO.

A treatment effect for apremilast on enthesitis was observed in the APR 30 BID treatment group in

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subjects with pre-existing enthesitis. The decrease from baseline (improvement) in the MASES, compared with PBO, was statistically significant at Week 16 and nominally significant at Week 24 in the APR 30 BID treatment group. There was also a nominally significant improvement in the proportion of subjects who achieved a > 20% improvement in MASES and in the proportion of subjects who achieved a MASES of zero in the APR 30 BID treatment group, compared with PBO, at Weeks 16 and 24. No significant differences in the change from baseline in the MASES were observed between the PBO and APR 20 BID treatment groups at either Week 16 or 24.

A treatment effect for apremilast on dactylitis was also shown. The decrease from baseline (improvement) in the dactylitis severity score, compared with PBO, was nominally significant in the APR 20 BID treatment group at Weeks 16 and 24 and nominally significant in the APR 30 BID treatment group at Week 16.

A key feature of PsA is psoriatic skin involvement, which improved significantly with apremilast treatment. A positive treatment effect and dose effect for apremilast on PASI-75 responses was observed at Weeks 16 and 24 in subjects with psoriasis involving ≥ 3% of their body surface. The PASI-75 responses at Week 16 were 10.8%, 17.3%, and 26.6% (nominal p = 0.0044) in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The PASI-75 responses, in the APR 20 BID and APR 30 BID treatment groups, compared with PBO, were maintained at Week 24 (23.1% [nominal p = 0.0392] and 25.7% [nominal p = 0.0129] versus 11.8%, 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 (Jacobson, 2004). Therefore, the ability of apremilast to improve the PASI score in this population is an important indicator of the treatment effect on the psoriatic component of PsA.

Apremilast demonstrated a maintenance of therapeutic effect, across all measures of efficacy, with up to 52 weeks of treatment. Analyzed using data as observed, sustained improvement in the ACR 20 response rates was observed at Week 52 in both the APR 20 BID and APR 30 BID treatment groups. Among subjects initially randomized to the APR 20 BID and APR 30 BID treatment groups, the ACR 20 response at Week 52 was 53.4% and 58.7%, respectively. A dose effect was observed at Weeks 40 and 52. This finding was corroborated by a sensitivity analysis using NRI. Using this approach, the ACR 20 response in the APR 20 BID and APR 30 BID treatment groups, at Week 52, was 40% and 45.5% respectively. Improved physical function, as measured by HAQ-DI, continued through Week 52. Among subjects remaining in the study, a dose effect was observed in the improvements in HAQ-DI score in subjects initially randomized to the APR 20 BID and APR 30 BID treatment groups at Week 52 (-0.319 and -0.392, respectively). Using data as observed, in both apremilast treatment groups, the mean reduction in the HAQ-DI score at Week 52 exceeded the MCID of -0.30. Across all other endpoints, including those assessing signs and symptoms, physical function, disease activity, psoriasis, and enthesitis and dactylitis, sustained improvements were generally observed up to Week 52 among subjects remaining in the study.

Among subjects remaining in the study after Week 52, efficacy parameter findings were maintained or improved over time. The ACR 20/50/70 response rates and the mean HAQ-DI scores were maintained or improved over time in both the APR 20 BID and APR 30 BID treatment groups. The modified PsARC

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response rates were maintained in both the APR 20 BID and APR 30 BID treatment groups through Week 260. Improvements in the CDAI scores were maintained in both the APR 20 BID and APR 30 BID treatment groups through Week 260. The 28-joint Disease Activity Scores were further improved in both the APR 20 BID and APR 30 BID treatment groups through Week 260. The SF-36v2 PFS improvements were maintained or improved in both treatment groups through Week 260. The SF-36v2 PCS score improvements were maintained in both treatment groups through Week 260. Improvements in the MASES were maintained in both the APR 20 BID and APR 30 BID treatment groups through Week 260. The PASI-75 response rate was maintained or improved in both the APR 20 BID and APR 30 BID treatment groups through Week 260.

Subgroup analyses of the ACR 20 responses were conducted using factors that included sex, age, weight, BMI, race, geographic region, as well as PsA subtype, disease duration, and baseline CRP. Overall, a treatment effect in favor of APR versus PBO was observed in each of these subgroups at both Week 16 and Week 24, with the exception of an apparent neutral effect of treatment in North America was observed, which may have been due to differences in baseline demographics and disease characteristics.

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

This study was not designed to make formal comparisons between the APR treatment groups. The observed positive treatment effect of apremilast on the signs and symptoms of active PsA, as measured by the ACR 20 response during the placebo-controlled period, was comparable in the APR 20 BID and APR 30 BID treatment groups. However, outcomes in the APR 30 BID treatment group were generally greater than those in the APR 20 BID treatment group for endpoints relating to physical function, health-related quality of life measures, including FACIT-Fatigue, extra-articular manifestations of PsA, including enthesitis and psoriatic skin manifestations at Weeks 16 and 24, indicating better early disease control. Improvements in HAQ-DI score and SF-36v2 PFS were greater in the APR 30 BID treatment group compared with the APR 20 BID treatment group. Improvement in other health-related quality of life measures, including fatigue (as determined by mean change in FACIT-Fatigue) achieved nominal p-values ≤ 0.05 only in the APR 30 BID treatment group. All endpoints evaluating enthesitis were significantly greater in the APR 30 BID treatment group compared with PBO. The PASI-75 responses in subjects with psoriasis involving $\geq 3\%$ of their body surface also demonstrated a dose response in favor of the APR 30 BID treatment group. At Week 52, based on data as observed and supported by NRI analysis, a dose effect was observed in the ACR 20/50/70. The improvement in the HAQ-DI score was also greater in the APR 30 BID treatment group than in the APR 20 BID treatment group at Week 52.

Apremilast, at dosages of 20 and 30 mg BID, significantly reduced disease signs and symptoms, and improved physical function and psoriatic skin disease, in subjects with active PsA who were DMARD-naïve. Maintenance of the therapeutic effect was observed, across all efficacy measures, in subjects receiving up to 260 weeks of treatment. The overall magnitude of effect and consistency of response was greater with the 30 mg BID dose of apremilast during the placebo-controlled period and provided better early disease control compared with the 20 mg BID dose.

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SAFETY RESULTS:

During the 24-week placebo-controlled period, the overall incidence of TEAEs was higher in the APR 20 BID and APR 30 BID treatment groups (49.7% and 56.6%, respectively) than in the PBO group (41.5%). The incidence of TEAEs that led to discontinuation was 2.3%, 2.3%, and 3.4% in the PBO, APR 20 BID, and APR 30 BID treatment groups, respectively. The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs and SAEs was low and not treatment or dose dependent; in the PBO, APR 20 BID, and APR 30 BID treatment groups, the incidence of severe TEAEs was 3.4%, 2.3%, and 1.1%, respectively, and the incidence of SAEs was 2.8%, 1.7%, and 0.6%, respectively. During the apremilast exposure period (with up to 260 weeks' exposure to APR), the EAIRs per 100 subject-years, overall, and by severity were similar to or lower than those observed in the apremilast treatment groups during the placebo-controlled period. These results indicate that the onset of new TEAEs tended to occur during the first 24 weeks of dosing; however, the majority of SAEs occurred during the apremilast-exposure period.

During the placebo-controlled period, gastrointestinal events, particularly nausea and diarrhea, were the most frequently reported TEAEs. The frequency of these events increased in a dose dependent manner and tended to be highest within the first 1 to 2 weeks of dosing. The majority of nausea cases generally resolved within 2 weeks and diarrhea cases within 1 to 2 months. These events were predominantly mild to moderate in severity, and most did not lead to discontinuation. There were no SAEs of nausea or diarrhea. During the apremilast-exposure period, only 1 SAE of diarrhea was reported with dosing of up to 260 weeks, or in subjects who were re-randomized from PBO to APR at Week 16 or 24.

Other frequently reported TEAEs during the placebo-controlled period included headache (reported in 2.3%, 3.4%, and 8.6% of subjects in the placebo, APR 20 BID and APR 30 BID treatment groups, respectively). The majority of cases of headache were mild to moderate in severity and generally resolved within 2 weeks. All other TEAEs were reported by fewer than 5% of subjects in any treatment group. During the apremilast-exposure period, headache was reported in 6.0% and 10.3% of subjects in the APR 20 BID and APR 30 BID treatment groups, respectively. Corresponding percentages for upper respiratory tract infection were 10.3% and 12.3%, respectively. The incidence of upper respiratory tract infection did not increase over time, and no subject discontinued from the study because of upper respiratory tract infection. Additionally, during the apremilast-exposure period, nasopharyngitis was reported for 7.9% and 9.1% of subjects in the APR 20 BID and APR 30 BID treatment groups. During the apremilast-exposure period, as in the placebo-controlled period, the majority of TEAEs were mild to moderate in severity.

Serious TEAEs were reported at a slightly higher frequency in the PBO treatment group compared with the APR treatment groups during the placebo-controlled period. No individual SAE was reported in more than 1 subject. 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, the overall rate of SAEs was comparable between the APR 20 BID and APR 30 BID treatment groups (13.9% and 14.3%, respectively). All SAEs during this period, except for inguinal hernia (which was reported for 5 subjects), were reported for ≤ 3 subjects. Based on a comparison of the EAIRs per 100 subject-years between the placebo-controlled period and the apremilast-exposure period, there was no evidence of an increased incidence of SAEs with longer apremilast exposure.

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During the placebo-controlled period, the incidence of TEAEs was comparable between female and male subjects in the APR 20 BID treatment group and higher among female subjects than male subjects in the APR 30 BID treatment group. During the apremilast-exposure period, the incidence of TEAEs was higher in female subjects than that in male subjects in the total apremilast treatment group. During both treatment periods, higher percentages of subjects ≥ 65 years of age in the APR 20 BID group experienced TEAEs compared with those < 65 years of age. Too few subjects were randomized to each treatment group to permit a meaningful analysis by age. Based on a comparison of the EAIRs per 100 subject-years between the placebo-controlled period and the apremilast-exposure period, there was no evidence of an increased incidence of age- or sex-related TEAEs with longer apremilast exposure.

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

Abnormalities in hematology and chemistry parameters 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 LFT elevations meeting Hy's Law criteria. Apremilast did not cause myelosuppression based on routine complete blood count.

Adverse events of special interest (based on mechanism of action, possible class effects, known comorbidities of PsA, and other factors) were infections (including TB), MACE, malignancies, suicidal ideation and behavior, gastrointestinal events, and vasculitis. Only the most common AEs of special interest (ie, nausea, diarrhea, and upper respiratory tract infection) were clearly study drug related. However, there was no difference in the incidence of these events between the placebo controlled period (Weeks 0 to 24) and the apremilast-exposure period (Weeks 0 to 260); the EAIRs did not increase for any of these events.

No dose effect was observed for serious infections during the placebo-controlled or apremilast exposure periods. During the placebo-controlled period, 3 subjects reported serious infections: 1 in each treatment group (placebo, APR 20 BID, and APR 30 BID). Eleven new cases of serious infection were reported after 24 weeks in the APR 30 BID treatment group. There was no requirement for latent TB screening prior to enrollment; it was left to the investigator's discretion whether or not to test for latent TB. There were no cases of de novo TB or reactivation of TB among subjects with TB-related medical histories during the study.

During the placebo-controlled period, there were no cases of MACE or vasculitis reported. One case of basal cell carcinoma occurred in a placebo-treated subject before administration of apremilast. During the apremilast-exposure period, acute myocardial infarction and cutaneous vasculitis were reported in 1 subject each; both events resolved and the subjects continued in the study with no change to apremilast dosing. No cases of suicidal ideation or behavior were reported.

At the end of the apremilast-exposure period, the mean (median) percentage weight loss was 0.69% (0.35%) in the APR 20 BID treatment group and 0.41% (0.65%) in the APR 30 BID treatment group. The majority of subjects maintained their weight within ± 5% of baseline. However, weight loss > 5% to ≤ 10% was observed in 10.5% and 14.6% of subjects in the APR 20 BID and APR 30 BID treatment groups, respectively. In addition, 6.0% of subjects in the APR 20 BID treatment group and 7.3% of

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subjects in the APR 30 BID treatment group experienced weight loss of > 10%. The proportion of subjects reporting weight loss tended to increase among subjects with a higher baseline BMI.

Markedly abnormal laboratory test results were infrequent and transient. There were no cases of LFT elevations meeting Hy's Law criteria. There was no imbalance between placebo and apremilast in renal or metabolic laboratory parameters. There is no evidence of myelosuppression with apremilast treatment.

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 apremilast did not result in an increased incidence of TEAEs for any category presented.

CONCLUSION:

Overall, the results of this study demonstrated that apremilast, a selective phosphodiesterase type 4 inhibitor, was an effective, safe, and well-tolerated treatment for subjects with active PsA who were DMARD-naïve. Apremilast provided statistically significant reductions in the signs and symptoms of active PsA, statistically significant and clinically meaningful improvements in physical function, reduced disease activity and/or resulted in low disease activity of PsA, and improved extra-articular manifestations of PsA and other health-related quality of life measures, when used in dosing regimens of either 20 mg or 30 mg BID in subjects with active PsA who were DMARD-naïve. Maintenance of the therapeutic effect was observed across all efficacy measures in subjects receiving up to 52 weeks of treatment.

Apremilast was generally well tolerated, with both doses (20 mg BID and 30 mg BID) demonstrating comparable and acceptable safety profiles with up to 260 weeks of exposure in this study. Overall, based on a comparison of the EAIRs per 100 subject-years between the placebo-controlled period and the apremilast-exposure period, there was no evidence of an increased risk with longer apremilast exposure.

Based on a generally greater magnitude and consistency of clinical response with the apremilast 30 mg BID dose during the placebo-controlled period, which provided better early disease control and demonstrated a comparable safety and tolerability profile to the 20 mg BID dose, a more favorable benefit:risk profile was observed for apremilast 30 mg BID over that for apremilast 20 mg BID. Apremilast is a novel, oral therapeutic option for the reduction of signs and symptoms of active PsA and improvement in physical function in patients with active PsA who are DMARD-naïve.

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