

CELGENE PROPRIETARY INFORMATION

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Apremilast tablets	Volume: Page:	
Name of Active Ingredient: Apremilast (formerly CC-10004)		
<ul style="list-style-type: none"> • Randomized Treatment Withdrawal Phase – Weeks 32 to 52 To evaluate the durability of response, relapse, rebound (per European Medicines Agency [EMA] guidelines), and time to relapse/loss of effect, at Week 32 subjects were assessed for PASI response and managed as follows: <ul style="list-style-type: none"> – Subjects originally randomized to apremilast at baseline (Week 0): <ul style="list-style-type: none"> o At Week 32, responders (\geq PASI-75) were to be re-randomized 1:1 to maintain APR 30 BID dosing or switch to placebo (treatment withdrawal). If subjects experienced loss of response (ie, loss of PASI-75), they were to resume APR 30 BID treatment. This resumption of APR 30 BID treatment was to occur no later than Week 52, regardless of whether or not the subject lost PASI-75. o At Week 32, partial responders (PASI-50 to PASI-74) and nonresponders ($<$ PASI-50) had the option of adding topical therapies and/or UVB phototherapy to their APR 30 BID treatment. The decision to add these treatments during this phase could only be made at the Week 32 visit, and was based on the discretion of the investigator. – Subjects originally randomized to placebo at baseline (Week 0) and switched to APR 30 BID at Week 16: <ul style="list-style-type: none"> o At Week 32, all subjects were to maintain APR 30 BID dosing. Nonresponders ($<$ PASI-50) and partial responders (PASI-50 to PASI-74) had the option of adding topical therapies and/or UVB phototherapy to their treatment regimen. The decision to add these treatments during this phase could only be made at the Week 32 visit, and was based on the discretion of the investigator. Subjects originally randomized to placebo with a PASI-75 response were also included in this group, but were maintained on APR 30 BID. • Long-term Extension Phase – Weeks 52 to 260 Subjects are being followed and evaluated for safety and efficacy for up to an additional 4 years (years 2 through 5). • Observational Follow-up Phase Subjects who complete the study, or those subjects who discontinue investigational product (IP) prior to the completion of the study, are asked to participate in the 4-week Observational Follow-up Phase. 		
Number of patients (planned and analyzed): Planned: Approximately 825 Analyzed: Full analysis set: 844 Per protocol: 831 Safety population: 842		
Diagnosis and main criteria for inclusion: Subjects must have satisfied the following criteria in order to be enrolled in the study.		

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<ol style="list-style-type: none"> 1. Males or females, ≥ 18 years of age at the time of signing the informed consent document 2. Understood and voluntarily signed an informed consent document prior to any study related assessments/procedures being conducted 3. Able to adhere to the study visit schedule and other protocol requirements 4. Diagnosis of chronic plaque psoriasis for at least 12 months prior to screening 5. Had moderate to severe plaque psoriasis at screening and baseline as defined by: <ol style="list-style-type: none"> a. PASI score ≥ 12; and b. Body surface area (BSA) $\geq 10\%$; and c. sPGA ≥ 3 (moderate) 6. Was a candidate for phototherapy and/or systemic therapy 7. Was in good health (except for psoriasis) as judged by the investigator, based on medical history, physical examination, 12-lead ECG, clinical laboratories, and urinalysis 8. Met the following laboratory criteria: <ol style="list-style-type: none"> a. White blood cell count $\geq 3000/\text{mm}^3$ ($\geq 3.0 \times 10^9/\text{L}$) and $< 14,000/\text{mm}^3$ ($< 14 \times 10^9/\text{L}$) b. Platelet count $\geq 100,000/\mu\text{L}$ ($\geq 100 \times 10^9/\text{L}$) c. Serum creatinine $\leq 1.5 \text{ mg/dL}$ ($\leq 132.6 \mu\text{mol/L}$) d. Aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 2 \times$ upper limit of normal (ULN) e. Total bilirubin $\leq 2 \text{ mg/dL}$ ($34 \mu\text{mol/L}$) f. Hemoglobin $\geq 9 \text{ g/dL}$ ($\geq 5.6 \text{ mmol/L}$) g. Hemoglobin A1c (HbA1c) $\leq 9.0 \%$ 9. Females of childbearing potential (FCBP) must have had a negative pregnancy test at screening and baseline. FCBP who engaged in activity in which conception was possible had to use contraception while on IP and for at least 28 days after taking the last dose of IP, where contraception was one of the following: <ol style="list-style-type: none"> a. One highly effective form (nonoral hormonal, intrauterine device [IUD], tubal ligation, vasectomized partner); or b. An oral hormonal contraceptive PLUS one additional form of barrier contraception (male or female latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane], diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide); or c. Two forms of barrier contraception (male or female latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) PLUS one of the following (diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide) 		

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<p>Notes:</p> <p>A female of childbearing potential was defined as a sexually mature female who: 1) had not undergone a hysterectomy (surgical removal of the uterus) or bilateral oophorectomy (surgical removal of both ovaries) or 2) had not been postmenopausal for at least 24 consecutive months (that is, had menses at any time during the preceding 24 consecutive months).</p> <p>The female subject's chosen form of contraception must have been effective by the time the female subject was randomized into the study (for example, hormonal contraception was to be initiated at least 28 days before randomization).</p> <p>10. Male subjects (including those who had a vasectomy) who engaged in activity in which conception was possible must have used barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on IP and for at least 28 days after the last dose of IP</p> <p>The presence of any of the following excluded a subject from enrollment.</p> <ol style="list-style-type: none"> 1. Other than psoriasis, history of any 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, which would have placed the subject at unacceptable risk if he/she were to have participated in the study 3. Any condition that confounded the ability to interpret data from the study 4. Pregnant or breast feeding 5. History of allergy to any component of the IP 6. Hepatitis B surface antigen positive at screening 7. Anti-hepatitis C antibody positive at screening 8. AST or ALT > 1.5 X ULN and total bilirubin > ULN and/or albumin < LLN 9. Active tuberculosis (TB) or a history of incompletely treated TB 10. Clinically significant abnormality on 12-lead ECG at screening 11. Clinically significant abnormality based upon chest radiograph with at least posterior/anterior (PA) 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. History of positive human immunodeficiency virus (HIV), or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease) 13. Active substance abuse or a history of substance abuse within 6 months prior to screening 14. 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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<ol style="list-style-type: none"> 15. 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 [CIN] or carcinoma in situ of the cervix with no evidence of recurrence) 16. Psoriasis flare or rebound within 4 weeks prior to screening 17. Evidence of skin conditions that would interfere with clinical assessments 18. Topical therapy within 2 weeks of randomization (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). Exceptions: low-potency corticosteroids (Class 6 or 7) were allowed as background therapy for treatment of 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. An unmedicated skin moisturizer (eg, Eucerin®) was permitted for body lesions only. Subjects should not have used these topical treatments within 24 hours prior to the clinic visit. 19. Systemic therapy for psoriasis within 4 weeks prior to randomization (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters) 20. Use of phototherapy within 4 weeks prior to randomization (ie, ultraviolet B light [UVB], PUVA) 21. Adalimumab, etanercept, efalizumab, infliximab, or certolizumab pegol within 12 weeks prior to randomization 22. Alefacept, briakinumab, or ustekinumab within 24 weeks prior to randomization 23. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever was longer) 24. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources 25. Prior treatment with apremilast 		
<p>Test product, dose and mode of administration, batch number: Apremilast administered orally as 10-, 20-, or 30-mg tablets Batch numbers: Apremilast 10-mg tablets: 10B0036, 10B0200, 10B0353 Apremilast 20-mg tablets: 10B0037, 10B0201, 10B0202 Apremilast 30-mg tablets: 10B0041, 10B0039, 10B0210, 10B0357, 10B0358, 11B0099, 10B0211, 10B0204, 10B0206, 10B0239, 11B0104, 11B0107</p>		
<p>Duration of treatment: The study was designed as a 52-week study with an active-treatment, long-term extension of up to an additional 4 years.</p>		

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This report presents an analysis of the study results through Week 52 (or early termination). During the 52 weeks, subjects were to be treated with placebo or APR 30 BID for the first 16 weeks. From Weeks 16 to 32, all subjects were to receive APR 30 BID. From Week 32 up to Week 52, re-randomized subjects received placebo or APR 30 BID and non-re-randomized subjects continued to receive APR 30 BID. Subjects re-randomized to placebo at Week 32 could resume APR 30 BID prior to Week 52 if they lost response.		
Reference therapy, dose and mode of administration, batch number: Placebo administered orally as tablets identical in appearance to apremilast tablets Batch numbers: Placebo 10-mg tablets: 10B0005, 10B0207, 10B0348, 11B0170, 11B0220 Placebo 20-mg tablets: 10B0006, 10B0053, 10B0044, 10B0058, 10B0349, 11B0103, 10B0052, 10B0059, 10B0270, 10B0060, 10B0350, 11B0111, 10B0241, 11B0165 Placebo 30-mg tablets: 10B0010, 10B0045, 10B0055, 10B0062, 10B0063, 10B0081, 10B0351, 10B0352, 10B0363, 10B0054, 10B0209, 11B0157		
Criteria for evaluation: Efficacy: The primary endpoint was the proportion of subjects treated with either apremilast 30 mg BID or placebo who achieved at least a 75% reduction in Psoriasis Area and Severity Index (PASI-75) at Week 16 from baseline. The major secondary endpoint was the proportion of subjects treated with either apremilast 30 mg BID or placebo with a static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) with at least 2 points reduction from baseline at Week 16. Secondary endpoints in this study were: <ul style="list-style-type: none"> • Percent change from baseline in psoriasis affected BSA (%) at Week 16 • Percent change from baseline in the PASI score at Week 16 • Proportion of subjects who achieve PASI-50 at Week 16 • Change from baseline in the Pruritus Visual Analog Scale (VAS) at Week 16 • Change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 16 • Change from baseline in the Mental Component Summary (MCS) score of Medical Outcome Study Short Form 36-Item Health Survey (SF-36) at Week 16 • Proportion of subjects who achieved both PASI-75 and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction from Baseline at Week 16 • Time to loss of PASI-75 response (loss of effect) during the Randomized Treatment Withdrawal Phase The exploratory endpoints in this study were:		

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<ul style="list-style-type: none"> • PASI <ul style="list-style-type: none"> – Time to achieve PASI-50 and PASI-75 during Placebo-controlled Phase – Proportion of subjects who achieved PASI-75 at Weeks 24, 32, and 52 – Proportion of subjects who achieved PASI-50 at Weeks 24, 32, and 52 – Proportion of subjects who achieved PASI-90 at Weeks 16, 24, 32, and 52 – Percent change from baseline in the PASI score at Weeks 24, 32, and 52 • Proportion of subjects with a sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Weeks 24, 32, and 52 • Percent change from baseline in percent of psoriasis affected BSA at Weeks 24, 32, and 52 • DLQI <ul style="list-style-type: none"> – Proportion of subjects who achieved a decrease of at least 5 in DLQI total score at Weeks 16, 24, 32, and 52 – Proportion of subjects who achieved PASI-50 with a decrease of at least 5 in DLQI total score at Weeks 16, 24, 32, and 52 – Change from baseline in DLQI total score at Weeks 24, 32, and 52 • VAS <ul style="list-style-type: none"> – Change from baseline in the Pruritus VAS at Weeks 24, 32, and 52 – Proportion of subjects who achieved at least a 10-mm decrease in Pruritus VAS score at Weeks 16, 24, 32, and 52 – Change from baseline in the Psoriatic Arthritis Disease Activity VAS at Weeks 16, 24, 32, and 52 – Change from baseline in the Skin Discomfort/Pain VAS at Weeks 16, 24, 32, and 52 – Change from baseline in the Subject’s Global Assessment of Psoriasis Disease Activity VAS at Weeks 16, 24, 32, and 52 • Health-related Quality of Life <ul style="list-style-type: none"> – Change from baseline in SF-36 scores at Weeks 16, 24, 32, and 52 – Change from baseline in European Quality of Life-5 Dimensions Questionnaire (EQ-5D) scores at Weeks 16, 32 and 52 – Change from baseline in Patient Health Questionnaire-8 (PHQ-8) scores at Weeks 16, 24, 32, and 52 – Change from baseline in Work Limitations Questionnaire-25 (WLQ-25) scores at Weeks 16, 32 and 52 • Nail Assessments <ul style="list-style-type: none"> – Percent change from baseline in the Nail Psoriasis Severity Index (NAPSI) score at Weeks 		

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<p style="text-align: center;">16, 24, 32, and 52</p> <ul style="list-style-type: none"> – Proportion of subjects who achieve a 50% reduction in NAPSI score from the baseline visit at Weeks 16, 24, 32, and 52 – Change from baseline in the number of involved nails in subjects with nail psoriasis • Scalp Psoriasis <ul style="list-style-type: none"> – Proportion of subjects with scalp psoriasis with improvement of Scalp Physician Global Assessment (ScPGA) scores to 0 and 1 at Weeks 16, 24, 32, and 52 – Proportion of subjects with scalp psoriasis with improvement of ScPGA scores to 0, 1, and 2 at Weeks 16, 24, 32, and 52 • Palmoplantar Psoriasis <ul style="list-style-type: none"> – Proportion of subjects with palmoplantar psoriasis with improvement of Palmoplantar Psoriasis Physician Global Assessment (PPPGA) scores to 0 and 1 at Weeks 16, 24, 32, and 52 – Proportion of subjects with palmoplantar psoriasis with improvement of PPPGA scores to 0, 1, and 2 at Weeks 16, 24, 32, and 52 <p>The pharmacokinetic (PK) endpoints in this study were:</p> <ul style="list-style-type: none"> • Population-based PK estimate of systemic exposure of apremilast • Explore the relationship of apremilast exposure with efficacy and safety endpoints <p>The PK data collected during the study are summarized in a separate report (CC-10004-PSOR-008-PK).</p> <p>Safety: Safety assessments included:</p> <ul style="list-style-type: none"> • Adverse events (AE) • 12-lead electrocardiograms (ECG) • Chest radiographs (CXR) • Physical examinations • Vital signs • Pregnancy tests • Clinical laboratory tests • Evaluation of psoriasis flare or rebound 		
<p>Statistical methods:</p> <p>Analysis populations: The safety population analysis set included all subjects who were randomized and received at least 1 dose of IP.</p>		

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The full analysis set (FAS), defined all subjects who were randomized as specified in the protocol, was the primary population for the efficacy analyses for the Placebo controlled Phase. The per protocol (PP) population analysis set included all subjects included in the safety population who had at least 1 posttreatment PASI evaluation and no protocol violations. Supportive analyses using the per-protocol (PP) population were conducted for the primary endpoint and the major secondary endpoint.

Efficacy:

The primary efficacy analysis compared the proportions of subjects in the 2 treatment groups (APR 30 BID or placebo) who achieved at least a PASI-75 at Week 16 in reference to the baseline visit, using a 2-sided chi-square test at the 0.05 level. The primary analysis was based on the FAS. Missing values at Week 16 were imputed using the last observation carried forward (LOCF) method.

To control the overall type I error rate at the 2-sided 0.05 significance, a step-down procedure was used to claim statistical significance for the primary, the major secondary, the 8 other secondary, and 3 additional endpoints. Statistical significance for an endpoint was claimed only if its 2-sided p-value was < 0.05 and all previous tests were significant at the 2-sided 0.05 level. The test sequence for efficacy endpoints was as follows:

- Proportion of subjects treated with either APR 30 BID or placebo who achieved at least a 75% reduction in PASI (PASI-75) at Week 16 from baseline
- Proportion of subjects treated with either APR 30 BID or placebo with a sPGA score of clear (0) or almost clear (1) with at least 2-points reduction from baseline at Week 16
- Percent change from baseline in the psoriasis affected BSA (%) at Week 16
- Percent change in the PASI score from the Baseline Visit at Week 16
- Proportion of subjects who achieve PASI-50 at Week 16
- Change from baseline in the Pruritus VAS at Week 16
- Change from baseline in the DLQI total score at Week 16
- Percent change from baseline in the NAPSI score at Weeks 16 for subjects with baseline nail psoriasis
- Proportion of subjects with improvement of ScPGA scores to clear (0) or minimal (1) with at least 2-point reduction from baseline at Weeks 16 for subjects with baseline ScPGA score moderate (3) or above
- Proportion of subjects with improvement of PPPGA scores to clear (0) or almost clear (1) with at least 2-point reduction from baseline at Weeks 16 (Pooled data from PSOR-008 and PSOR-009) for subjects with baseline PPPGA score moderate (3) or above
- Change from baseline in the MCS score of SF-36 at Week 16
- Proportion of subjects with improvement of PPPGA scores to clear (0) or almost clear (1) with at least 2-point reduction from baseline at Weeks 16 for subjects with baseline PPPGA score moderate (3) or above
- Proportion of subjects who achieve both PASI-75 and sPGA score of clear (0) or almost clear

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<p>(1) with at least 2-point reduction from baseline at Week 16</p> <ul style="list-style-type: none"> Time to loss of PASI-75 response (loss of effect) during the Randomized Treatment Withdrawal Phase <p>Endpoints that did not meet the hierarchical criteria were considered nominally statistically significant if their 2-sided p-value was < 0.05. Other efficacy analyses were considered supportive and/or explanatory.</p> <p>The analysis of the major secondary endpoint compared the proportions of subjects in the 2 treatment groups (APR 30 BID or placebo) who achieved at least an sPGA at Week 16 in reference to the baseline visit, using a 2-sided chi-square test at the 0.05 level, conditional on observing a statistically significant result for the primary analysis.</p> <p>Supportive analyses were conducted for the primary endpoint and the major secondary efficacy endpoint as follows: (1) FAS treating missing values as nonresponders (nonresponder imputation [NRI]), (2) FAS [REDACTED] using LOCF, (3) PP population using LOCF method for imputing missing values. In addition, analyses using CMH test [REDACTED] was performed for FAS using LOCF method for imputing missing values.</p> <p>The other endpoints in the hierarchical sequence were compared using the chi-square test for discrete variables, an analysis of covariance (ANCOVA) model for continuous variables, and the log-rank test for time-to-event variables. Data were summarized using descriptive summary statistics for continuous variables (n, mean, standard deviation, median, minimum, and maximum). Frequency and percentages were provided for categorical variables. The changes or percent changes from baseline between the 2 treatment groups (APR 30 BID and placebo) were to be compared using an ANCOVA model with treatment as the factor and the baseline score as the covariate.</p> <p>Statistical evaluation of time to loss of PASI-75 response (loss of effect) during the Randomized Treatment Withdrawal Phase was based on the re-randomized treatment groups, APR 30 BID or placebo, for those subjects who were originally randomized to APR 30 BID and achieved \geq PASI-75 at Week 32. The Kaplan-Meier procedure was to be used to estimate the median time to loss of effect and the log-rank test was to be used to compare the two treatment groups.</p> <p>Subgroup analyses for the primary endpoint and the major secondary efficacy endpoint based on baseline demographic (age, sex, race), baseline disease characteristics, as well as region were provided to determine the robustness of the treatment effect.</p> <p>Safety:</p> <p>For the analysis of safety, 3 phases and an Apremilast-exposure Period were used as follows: Placebo-controlled Phase (Weeks 0 to 16), Maintenance Phase (Weeks 16 to 32), Randomized Treatment Withdrawal Phase (Weeks 32 to 52) for subjects who were re-randomized and subjects who were not re-randomized, and Apremilast-exposure Period.</p> <p>The safety analyses for the 3 phase were performed using the safety population. 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).</p> <p>Adverse events were coded according to the Medical Dictionary for Drug Regulatory Activities,</p>		

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version 14.0. Adverse events were tabulated by phase/period. Treatment-emergent adverse events (TEAEs) were summarized by system organ class (SOC), preferred term (PT), severity, relationship to IP, and duration of treatment,. Adverse events leading to death or to discontinuation from treatment and SAEs were summarized.

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 posttreatment were provided. Hy's law criteria (AST/ALT $\geq 3 \times$ ULN plus total bilirubin $\geq 1.8 \times$ ULN) were assessed and summarized.

Vital sign measurements, including weight, were summarized by visit descriptively. Shift tables of shifts from baseline to postbaseline timepoints, and to the worst postbaseline value in terms of normal/abnormal, were provided for pulse and blood pressure.

The proportion of subjects in each treatment group who had a flare or rebound of their psoriasis during each study phase was provided.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

CC-10004-PSOR-008 is an ongoing Phase 3, double-blind, multicenter, placebo-controlled trial that comprises a 16-week Placebo-controlled Phase, a 16-week Maintenance Phase, and a 20 week Randomized Treatment Withdrawal phase, followed by an open-label, long-term safety extension phase of up to 4 additional years. This report presents an analysis of the study results through Week 52 (or early termination).

A total of 844 subjects with moderate to severe plaque psoriasis were enrolled in this study. The baseline disease characteristics and medical history were similar for the 2 treatment groups and reflect the patient populations typically enrolled in psoriasis clinical trials. Approximately 68% of the study population was male and more than 50% of the subjects were obese, with a mean weight of 93.38 kg and a mean BMI of 31.26. The mean baseline PASI score was 18.95, mean duration of disease was 19.4 years, and the mean BSA involvement was 24.71%. Approximately 30% of the population had severe psoriasis at baseline (PASI > 20 [29.0%] or sPGA=4 [29.6%]), and 49.2% of subjects had BSA involvement of greater than 20%. Approximately, 65% of subjects had been treated previously with phototherapy or systemic therapy (including approximately 30% who had used biologics).

The primary endpoint of the study was met, ie, a statistically significantly greater proportion of subjects treated with APR 30 BID achieved a PASI-75 at Week 16, compared with placebo-treated subjects (5.3% placebo; 33.1% APR 30 BID; $p < 0.0001$). The primary efficacy analysis was supported by multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (eg, LOCF, NRI). In addition, the primary endpoint analysis consistently demonstrated the treatment benefit of APR 30 BID, relative to placebo, across multiple demographic and disease characteristic subgroups, including baseline disease severity (moderate vs. severe psoriasis) and whether or not subjects had been treated previously with systemic (including biologics) psoriasis treatments. There were trends toward higher PASI-75 responses in subjects who were female, resided outside the US, had no history of palmoplantar psoriasis, or were not currently using tobacco products. There was a possible trend for higher responses in low body weight individuals; however, this trend was

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not observed when analyzing PASI-75 response rate by baseline BMI values. In addition, there may be an apparent association between moderate disease severity at baseline and better response rates following APR 30 BID treatment compared with those with severe disease at baseline.

The analysis of the major secondary endpoint further supported the primary efficacy analysis, ie, a statistically significantly greater proportion of subjects treated with APR 30 BID achieved an sPGA score of clear (0) or almost clear (1), with at least a 2-point reduction from baseline at Week 16, compared with placebo (3.9% placebo; 21.7% APR 30 BID; $p < 0.0001$). The major secondary endpoint analysis also consistently demonstrated the treatment benefit of APR 30 BID, compared with placebo, across multiple subgroups.

A nominally statistically significantly greater proportion of subjects treated with APR 30 BID achieved the composite endpoint, comprising both a PASI-75 response and an sPGA response, compared with placebo-treated subjects (nominal $p < 0.0001$). Note: For the primary, the major secondary, the 8 secondary, and 3 additional endpoints, a step-down procedure was used to claim statistical significance. Statistical significance for an endpoint was claimed only if its p value was < 0.05 and all previous tests were significant at $p < 0.05$. Endpoints that did not meet the hierarchical criteria were considered nominally statistically significant if their p-value was < 0.05 .

For the majority of secondary endpoints at Week 16, subjects treated with APR 30 BID showed clinically meaningful and statistically significant improvements, compared with placebo, demonstrating the effect of apremilast on a number of disease characteristics, including clinical signs, symptoms, and quality of life. Statistically significant ($p < 0.0001$) effects of APR 30 BID, compared with placebo, were observed in percent change from baseline in BSA involvement, percent change from baseline in PASI score, proportion of subjects achieving PASI-50, change from baseline in Pruritus VAS, and change from baseline in DLQI total score. A nominally statistically significant effect of APR 30 BID, compared with placebo, was observed in change from baseline in the SF-36 MCS (nominal $p < 0.0001$).

Meaningful treatment benefits of APR 30 BID, compared with placebo, at Week 16 were also observed in subject self-assessments, including change from baseline in Skin Discomfort/Pain VAS [nominal $p < 0.0001$], Subject's Global Assessment of Psoriasis Disease Activity VAS [nominal $p < 0.0001$], and Psoriatic Arthritis Disease Activity VAS [nominal $p = 0.0033$]; as well as HRQoL endpoints, such as change from baseline in PHQ-8 total score, EQ-5D Index Value score, and the following WLQ-25 domains, Productivity Loss Score, Index, Mental-Interpersonal, Output, and Time Management ($p = 0.0091$, $p < 0.0001$, $p = 0.0181$, $p = 0.0148$, $p = 0.0103$, $p = 0.0202$, and $p = 0.0020$, respectively).

Meaningful effects of APR 30 BID, compared with placebo, were observed in difficult to treat areas of psoriasis, such as nail psoriasis (change from baseline in NAPSI score [$p < 0.0001$]) and proportion of subjects with NAPSI-50 [nominal $p < 0.0001$]) and scalp psoriasis (proportion of subjects with ScPGA response [improvement of ScPGA scores to 0 and 1 at Week 16], $p < 0.0001$). Improvements were also observed in assessments of palmoplantar psoriasis lesions (PPPGA), but these did not reach statistical significance.

Meaningful APR 30 BID responses occurred by Week 2 in multiple assessments, including percent change from baseline in PASI score, proportion of subjects achieving PASI-50, and change from baseline in Pruritus VAS, Skin Discomfort/Pain VAS, and Subject's Global Assessment of Psoriasis Disease Activity VAS.

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During the Maintenance Phase (Weeks 16 to 32), response rates for PASI-75 and sPGA response reached a plateau at Week 16 and Week 24, respectively, for subjects originally randomized to APR 30 BID at baseline, and these responses were generally maintained throughout this phase of the study (Week 32). The PASI-75 and sPGA response rates for subjects who switched from placebo to APR 30 BID at Week 16 were similar to those observed in subjects originally randomized to APR 30 BID during the Placebo-controlled Phase. By Week 32, the responses for Placebo/APR 30 BID subjects following 16 weeks of active treatment were similar to those observed following 32 weeks of APR 30 BID treatment.

In the Randomized Treatment Withdrawal Phase, subjects who were originally randomized to APR 30 BID and were PASI-75 responders at Week 32 were re-randomized to APR 30 BID or placebo in order to evaluate loss of response. The analysis showed that loss of response occurred significantly faster in subjects re-randomized to placebo than subjects re-randomized to APR 30 BID, ie, Kaplan-Meier estimate of median time to first loss of PASI 75 was 5.1 and 17.7 weeks following the Week 32 re-randomization in the APR 30 BID/APR 30 BID/Placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively. For the APR 30 BID/APR 30 BID/Placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively, 81.8% and 51.9% lost PASI 75 response at some timepoint during the Randomized Treatment Withdrawal Phase. In the APR 30 BID/APR 30 BID/APR 30 BID treatment group, 61% of the PASI-75 responders at Week 32 demonstrated a PASI-75 response at Week 52; 75% of these subjects were PASI-70 responders. The mean percent change in PASI score in the APR 30 BID/APR 30 BID/APR 30 BID treatment group (PASI-75 responders) was generally maintained following re-randomization (Week 32) through Week 52 with mean changes during this interval ranging from 81% to 88%. Subjects originally randomized to APR 30 BID, who were not PASI-75 responders at Week 32 tended to maintain a clinically meaningful (> PASI-50) and stable mean percent change in PASI score through Week 52. In addition, of the 27 subjects originally randomized to placebo, who were not PASI-75 responders at Week 32, and achieved a PASI-75 response at Week 52 following continued treatment on APR 30 BID, a larger number added topical or phototherapy to their APR 30 BID treatment (21 subjects), compared with those who remained on APR 30 BID alone (6 subjects).

In summary, APR 30 BID was shown to be an efficacious treatment for moderate to severe plaque psoriasis, with a rapid onset of action and a sustained effect in most subjects. Subjects treated with APR 30 BID demonstrated significant clinical benefit, compared with placebo, across the multiple parameters measured.

SAFETY RESULTS:

During the 16-week Placebo-controlled Phase, the subject incidence of TEAEs was 69.3% in subjects treated with APR 30 BID, compared with 55.7% in subjects treated with placebo. The incidence of subjects with drug-related TEAEs was higher in the APR 30 BID treatment group (40.0%), compared with the placebo treatment group (20.6%). The proportions of subjects with severe TEAEs and SAEs were similar between the APR 30 BID and placebo treatment groups. The proportions of subjects with TEAEs leading to study drug interruption or discontinuation were higher in APR 30 BID treatment group (6.6% and 5.2%, respectively), compared with placebo treatment group (4.6% and 3.2%, respectively). The most frequently reported TEAEs during Weeks 0 to 16 that occurred at a higher

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subject incidence rate in the APR 30 BID treatment group than placebo group included diarrhea, nausea, upper respiratory tract infection, and headaches including tension headaches. However, the majority of these TEAEs were mild or moderate in severity, and most had a duration of less than 2 weeks. Diarrhea, nausea, headache, tension headache, and vomiting occurred at a reduced incidence after the first week of dosing. The incidence of upper respiratory tract infection and nasopharyngitis did not appear to increase with exposure during the Placebo-controlled Phase.

Two deaths were reported during the first 16 weeks of the study; 1 in the placebo group and 1 in the APR 30 BID group. A [REDACTED] subject in the APR 30 BID treatment group died on Study Day 111. An autopsy indicated diffuse lung congestion and bilateral edema consistent with acute cardiac failure. The investigator considered the event as suspected of being related to IP. A [REDACTED] subject in the placebo group committed suicide by gunshot wound on Study Day 55. This subject had a medical history of obesity, attempted suicide, bipolar disorder, depression, insomnia, and alcohol abuse. The investigator considered the event not suspected to be related to IP.

No new safety findings emerged during the Maintenance Phase or Randomized Treatment Withdrawal Phase. Subjects who were re-randomized to placebo during the Randomized Treatment Withdrawal and resumed APR 30 BID without titration did not appear to experience an increase in TEAEs.

Similar results were observed in the Apremilast-exposure Period, which comprised the entire duration of exposure to apremilast through Week 52. The most frequently reported TEAEs observed during apremilast exposure were diarrhea, upper respiratory tract infection, nausea, nasopharyngitis, tension headache, and headache. Comparable to the findings from the Placebo-controlled Phase, nausea and diarrhea occurred more frequently during the first week of apremilast exposure, tension headache and headache occurred more frequently during the first 8 weeks of exposure, and upper respiratory tract infection and nasopharyngitis did not appear to increase at a specific exposure interval during the 52 weeks. No new deaths other than the 2 deaths reported in the Placebo-controlled Phase were reported through Week 52. The rate of SAEs through Week 52 remained low at 4.2%.

In general, for apremilast-treated subjects, rates of flare and rebound, were comparable or lower throughout the study compared with the rates observed for placebo-treated subjects in the Placebo-controlled Phase (Weeks 0 to 16).

The safety analysis of TEAEs of special interest, which included infections, MACE, malignancies, suicidal ideation and behavior, GI events, and vasculitis, revealed no new findings during the study. There was no apparent treatment-effect observed in the proportion of subjects reporting any infection (29.1% of placebo subjects versus 32.0% of APR 30 BID subjects) during the Placebo-controlled Phase. Upper respiratory tract infection and nasopharyngitis were the only TEAEs that occurred in more than 5% of subjects in any treatment group during the Placebo-controlled Phase. Four serious infections were recorded in the Apremilast-exposure Period, including urinary tract infection (n=2), diverticulitis (n=1), and pneumonia (n=1). Gastrointestinal events, particularly diarrhea and nausea, accounted for the most frequently reported TEAEs during the Placebo-controlled Phase, and were also the most frequently considered by the investigator to be drug-related. However, in the APR 30 BID treatment group, diarrhea and nausea were predominantly mild in severity and had the highest incidence rate during the first week of dosing, and generally resolved within 1 month. Severe diarrhea and nausea were each reported by 1 subject in the placebo and 2 subjects in the APR 30 BID treatment groups

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<p>during the Placebo-controlled Phase. Serious GI TEAEs (inguinal hernia and abdominal pain) were reported in 2 subjects receiving APR 30 BID. Four possible MACE were recorded in the Apremilast-exposure period (myocardial infarction [n=3] and cardiac failure [1]). One solid-tumor malignancy of ductal breast cancer was reported in a subject receiving APR 30 BID. Eleven nonserious events of skin malignancy (5 squamous cell carcinomas and 6 basal cell carcinomas) were reported in 10 subjects receiving APR 30 BID. Systemic vasculitis was not reported by any subject during the study.</p> <p>Although there was no age effect observed with overall TEAEs, diarrhea was reported at a higher frequency in >65 years age group whereas upper respiratory tract infection and tension headaches were more frequency reported in < 65 years age group. Overall, a higher frequency of TEAEs was observed among female subjects compared with males.</p> <p>No clinically meaningful changes in hematology and clinical chemistry parameters were observed except associated with co morbidities. No cases meeting Hy's Law were reported.</p> <p>The majority of subjects originally randomized to APR 30 BID maintained their weight within \pm 5% of baseline in all phases of the study. Weight loss of 5% to 10% at Week 16 was observed in 11.7% and 5.8% in subjects who received APR 30 BID and placebo, respectively. At Week 32, weight loss of > 10% was observed in 5.6% of subjects who were randomized to APR 30 BID at Week 0 and in 4.2% of subjects who were switched to APR 30 BID at Week 16. At Week 52, weight loss of > 10% was reported in 9.6% subjects who were re-randomized to APR 30 BID and 7.7% subjects who were re-randomized to placebo who remained on placebo. For non-re-randomized subjects at Week 52, weight loss of > 10% was reported in 6.5% and 8.2% of the subjects originally randomized to APR 30 BID and placebo, respectively. Four subjects had > 20% of weight loss during the study.</p> <p>In summary, the profile of TEAEs reported in this study, including severe TEAEs, SAEs, AEs leading to drug withdrawal, and AEs of special interest, is consistent with the known safety profile of apremilast. There was no increase in the incidence of TEAEs over time, and no unusual or unexpected safety findings emerged during the 52-week study.</p> <p>CONCLUSION:</p> <p>Apremilast demonstrated a statistically significant and clinically meaningful improvement, compared with placebo, in clinical endpoints and patient-reported outcome measures. The profile of TEAEs reported in this study, including severe TEAEs, SAEs, AEs leading to drug withdrawal, and AEs of special interest, is consistent with the known safety profile of apremilast. Apremilast may therefore provide a novel therapeutic option for the treatment of patients with moderate to severe plaque psoriasis.</p> <p>Date of the report: 03 July 2013</p>		