


CELGENE PROPRIETARY INFORMATION

**2. SYNOPSIS**

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)		
Title of Study: A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY FOLLOWED BY AN ACTIVE-TREATMENT EXTENSION TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN THE TREATMENT OF BEHÇET DISEASE		
Principal Investigator: 		
Study Centers: Six centers: 3 in the US and 3 in Turkey		
Publications (reference): None		
Studied Period (years): 2.6 years Date first patient enrolled: 23 October 2009 Date last patient completed: 08 May 2012		Phase of Development: Phase 2
Objectives: Primary: <ul style="list-style-type: none"> <li>To evaluate the efficacy of apremilast in the treatment of oral ulcers after 84 days of treatment.</li> </ul> Secondary: <i>Treatment Phase</i> <ul style="list-style-type: none"> <li>To evaluate the safety of apremilast</li> <li>To evaluate the efficacy of apremilast in the treatment of genital ulcers</li> <li>To evaluate apremilast's efficacy over time in the treatment of oral and genital ulcers</li> <li>To evaluate the effect of apremilast on patient-reported outcomes (PROs)</li> <li>To evaluate the effect of apremilast on disease activity</li> </ul> <i>Extension and Observational Follow-up Phases</i> <ul style="list-style-type: none"> <li>To evaluate the safety of apremilast during the Extension Phase and the Follow-up Phase</li> <li>To evaluate the efficacy of apremilast in the treatment of oral and genital ulcers during the Extension Phase</li> </ul>		

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<ul style="list-style-type: none"> <li>To evaluate the effect of apremilast on the PROs during the Extension Phase</li> <li>To evaluate the effect of apremilast on disease activity during the Extension Phase</li> <li>To evaluate the durability of response after the treatment was stopped</li> </ul> <p>Exploratory:</p> <ul style="list-style-type: none"> <li>To evaluate the effect of apremilast on the skin lesions of Behçet’s disease (BD)</li> <li>To evaluate the effect of apremilast on the arthritis associated with BD</li> <li>To evaluate the effect of apremilast on uveitis</li> </ul>		
<p>Methodology:</p> <p>This was a Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group study of apremilast in the treatment of BD. The study consisted of 4 phases: a 3-month Prerandomization Phase; a 12-week, placebo-controlled Treatment Phase; a 12-week, blinded Extension Phase; and a 4-week posttreatment Observational Follow-up Phase.</p> <p><i>Prerandomization Phase (Days -90 to 1)</i></p> <p>Subjects were screened no more than 90 days prior to the start of study drug on Day 1.</p> <p><i>Treatment Phase (Days 1 to 85)</i></p> <p>Eligible subjects were randomized 1:1 to receive study drug (apremilast or placebo). Since the incidence and severity of BD differ between males and females, randomization was stratified by gender to minimize the imbalance between the two treatment groups.</p> <p>To optimize the gastrointestinal (GI) tolerability of apremilast and mitigate potential side effects (primarily mild-to-moderate nausea), dose titration was implemented during the first week of treatment. Subjects were dosed orally (PO) twice per day (BID) with 10 mg apremilast or identically appearing placebo on Days 1 and 2, followed by 20 mg BID apremilast or placebo on Days 3 and 4, and 30 mg BID apremilast or placebo on Days 5-7. Thereafter, subjects took apremilast 30 mg BID or matching placebo through Day 84.</p> <p>After the dose-titration period (ie, starting at Day 8), subjects who were unable to tolerate study drug were permitted to dose-reduce to 20 mg BID apremilast or matching placebo, after the investigator consulted with Celgene. Each subject was allowed to dose reduce only once during the study (all phases).</p> <p><i>Extension Phase (Days 85 to 169)</i></p> <p>Subjects who had received placebo during the Treatment Phase (including those who were “dose reduced” on placebo) were switched to apremilast 30 mg BID, following the titration scheme utilized for subjects randomized to apremilast in the Treatment Phase. Subjects who had been randomized to apremilast continued to receive apremilast at the same dosage at which they completed the Treatment Phase (30 mg BID or 20 mg BID). Study drug during the Extension Phase remained blinded to preserve the blind from the Treatment Phase.</p> <p><i>Observational Follow-up Phase (Days 169 to 197)</i></p> <p>All subjects, including those who discontinued study drug prematurely for any reason, were followed for 28 days after the last dose of study drug to monitor for AEs and worsening of disease after study drug was withdrawn.</p>		

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<p>The study was originally planned to randomize approximately 156 subjects. One interim and one final efficacy analysis were planned per protocol. The planned interim efficacy analysis was to be performed when approximately 70% of enrolled subjects had either completed Day 85 or had discontinued prematurely from the study. In the face of slow enrollment, when approximately 50% of subjects had been randomized, the investigators were informed that they would have an additional 6 months to randomize subjects before enrollment would end. With the additional 6 months of recruitment, approximately 70% of subjects (N=111) were randomized. A sample size of 111 subjects was sufficient to provide 80% power to detect a difference between treatment groups using the assumptions stated in the protocol. The result of the primary analysis met not only the 0.05 level of significance, but also achieved the boundary for declaring superiority for the planned interim analysis that was not performed.</p>		
<p>Number of patients (planned and analyzed):</p> <p>Planned: Approximately 156 subjects (78 subjects the Placebo group and 78 subjects in the apremilast 30 mg BID group [30 mg BID group])</p> <p>Analyzed: <i>Treatment Phase:</i> 111 subjects (56 subjects the Placebo group and 55 subjects in the 30 mg BID group)</p> <p><i>Extension Phase:</i> 95 subjects (45 subjects the Placebo/30 mg BID group and 50 subjects in the 30 mg BID/30 mg BID group)</p> <p><i>Observational Follow-up Phase:</i> 108 subjects (54 subjects the Placebo/30 mg BID group and 54 subjects in the 30 mg BID/30 mg BID group)</p>		
<p>Diagnosis and Main Criteria for Inclusion:</p> <ul style="list-style-type: none"> <li>• Male or female subjects <math>\geq</math> 18 years of age at the time of signing the informed consent form</li> <li>• Met the international study group criteria for BD at the time of diagnosis</li> <li>• Had active ulcer disease (oral and/or genital) in the 28-day period prior to screening, with or without current treatment</li> <li>• Had 2 or more oral ulcers at the time of randomization (Baseline; Day 1)</li> <li>• Without any active major organ involvement of BD, including ocular, central nervous system, lung, vascular, or gastrointestinal (GI) involvement. Subjects with mild BD-related inflammatory eye disease not requiring immunosuppressive therapy were allowed. Subjects with arthritis were allowed.</li> </ul>		
<p>Test Product, Dose and Mode of Administration, Batch Number:</p> <p>Apremilast 10-, 20-, and 30-mg tablets and matching placebo, taken orally twice daily (BID)</p> <p><i>Treatment Phase:</i> Apremilast or matching placebo. Dose titration, Days 1 to 7 (10 mg BID, Days 1 and 2; then 20 mg BID, Days 3 and 4; then 30 mg BID, Days 5 to 7), followed by apremilast 30 mg BID or matching placebo BID for 77 days.</p> <p><i>Extension Phase:</i> Subjects who were randomized to placebo during the Treatment Phase underwent blinded apremilast dose titration as described above plus an additional 77 days treatment with blinded apremilast 30 mg BID. Subjects who had been randomized to apremilast continued to receive blinded apremilast at the same dosage at which they completed the Treatment Phase (30 mg BID or 20 mg BID).</p>		

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<p>Subjects who were randomized to apremilast in the Treatment Phase received blinded “dose titration” cards followed by an additional 77 days’ treatment with blinded apremilast. (“Dose titration” cards for subjects who were treated with apremilast during the Treatment Phase contained 30 mg BID or 20 mg BID for the 7-day titration period.)</p> <p><i>Dose Reduction:</i> Subjects were allowed to dose reduce to 20 mg BID (or matching placebo during the Treatment Phase) if they were unable to tolerate the overt side effects of the study medication. Each subject was allowed to dose reduce only once during the entire study.</p> <p><i>Batch Numbers:</i> [REDACTED]</p>		
<p>Duration of Treatment:</p> <p><i>Treatment Phase:</i> 84 days (12 weeks)</p> <p><i>Extension Phase:</i> 84 days (12 weeks)</p> <p>Subjects randomized to apremilast could receive apremilast for up to 24 weeks (Treatment Phase + Extension Phase).</p>		
<p>Reference Therapy, Dose and Mode of Administration, Batch Number:</p> <p>None.</p>		
<p>Criteria for Evaluation:</p> <p>Efficacy:</p> <p><i>Primary Efficacy Endpoint – Treatment Phase</i></p> <ul style="list-style-type: none"> <li>• The number of oral ulcers at Day 85.</li> </ul> <p><i>Secondary Efficacy Endpoints – Treatment Phase</i></p> <ul style="list-style-type: none"> <li>• Ulcer response (proportion of subjects who were oral ulcer-free (complete response), or whose oral ulcers were reduced by <math>\geq 50\%</math> (partial response) from Day 1 to Day 85</li> <li>• Changes from baseline in the pain of oral ulcers, as measured by a visual analog scale (VAS) at Day 85</li> <li>• Area under the ulcer-time curve from Day 1 to Day 85 (AUC<sub>85</sub>) for the number of oral ulcers, genital ulcers, or oral + genital ulcers</li> <li>• Sum of the number of oral ulcers, genital ulcers, or oral + genital ulcers from Day 1 to Day 85</li> <li>• Number of genital ulcers at Day 85</li> <li>• Changes from baseline in the pain of genital ulcers, as measured by VAS at Day 85</li> <li>• Changes from baseline in Behçet’s Disease Current Activity Form scores at Day 85</li> </ul> <p><i>Secondary Efficacy Endpoints – Extension and Observational Follow-up Phases</i></p> <ul style="list-style-type: none"> <li>• Number of oral ulcers</li> <li>• Changes from baseline in the pain of oral ulcers, as measured by VAS</li> <li>• Number of genital ulcers</li> </ul>		

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<ul style="list-style-type: none"> <li>• Changes from baseline in the pain of genital ulcers, as measured by VAS</li> <li>• Changes from baseline in disease activity as measured by Behçet’s Disease Current Activity scores</li> <li>• Number of ulcers and pain for both oral and genital ulcers and Behçet’s Disease Current Activity score at the end of the 28-day observational follow-up as compared to Day 169</li> </ul> <p><i>Patient-reported Outcomes – Treatment Phase</i></p> <ul style="list-style-type: none"> <li>• Changes from baseline in Behçet’s Disease Quality of Life Questionnaire (BD QoL) score at Day 85</li> <li>• Changes from baseline in Behçet’s Disease Multidimensional Health Assessment Questionnaire (BD MDHAQ) score at Day 85; also known as the Behçet’s Syndrome Activity Score (BSAS)</li> <li>• Changes from baseline in the 8 domains and the 2 component scores (physical and mental) of the SF-36v2 at Day 85</li> </ul> <p><i>Patient-reported Outcomes – Extension and Observational Follow-up Phases</i></p> <ul style="list-style-type: none"> <li>• Changes from baseline in BD QoL score</li> <li>• Changes from baseline in BD MDHAQ score</li> <li>• Changes from baseline in the 8 domains and the 2 component scores (physical and mental) of the Medical Outcome Study Short Form 36-Item health Survey, version 2 (SF-36v2)</li> </ul> <p><i>Exploratory Endpoints</i></p> <ul style="list-style-type: none"> <li>• Response according to the Physician’s global assessment (PGA) of BD-related skin lesions</li> <li>• Percent change in the numbers of swollen and tender joints (66/68 joint counts, respectively)</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events (AEs)</li> <li>• Number of subjects who experienced new onset of uveitis or worsening of existing uveitis (defined as initiation of immunosuppressive therapy)</li> <li>• Number of new manifestations of BD that were not present at Day 1</li> <li>• Assessment of flare throughout the study</li> <li>• Laboratory evaluations, including immunology/inflammation panel</li> <li>• Vital signs and weight</li> <li>• ECG findings</li> </ul>		
<p>Statistical Methods:</p> <p>For purposes of data analysis and reporting two analysis periods were defined as follows: (1) placebo-controlled period, which included all data by treatment group (active, placebo) during the Treatment Phase, and (2) apremilast-exposure period, which included all data while subjects were exposed apremilast regardless of when the apremilast exposure started.</p> <p>The intent to treat (ITT) population, defined as all randomized subjects with at least one oral ulcer</p>		

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evaluation, was the primary population for all efficacy analyses for this study. Safety analyses for the placebo-controlled period were based on the safety population, which included all subjects who were randomized and received at least 1 dose of study drug. Safety analyses for the apremilast-exposure period were based on the apremilast subjects as treated (AAT) population, which included all subjects who were randomized or switched to apremilast 30 mg BID and received at least one dose of apremilast after the initial randomization or switch to 30 mg BID.

Efficacy and safety variables were summarized by treatment group/sequence unless otherwise specified. In the placebo-controlled period, treatment groups were Placebo and Apremilast 30 mg BID (abbreviated 30 mg BID). In the apremilast-exposure period, data were presented by treatment sequence, ie, Placebo/30 mg BID, for subjects whose treatment was switched to active therapy, and 30 mg BID/30 mg BID for subjects who remained on active therapy throughout the study.

Descriptive statistics (number of subjects with nonmissing values [n], mean, standard deviation [SD], median, minimum, and maximum) were used to summarize continuous variables. Frequency distributions (number and percentage of subjects) were used to summarize categorical variables.

*Primary Efficacy Analysis:*

The number of oral ulcers on Day 85 was compared between the placebo and active treatment arms using a 2-tailed parametric analysis of covariance (ANCOVA) test at the 0.05 level. The model included treatment, gender, and the number of oral ulcers at baseline as the covariate. A last observation carried forward (LOCF) approach was applied for subjects terminated early from the study. Analyses using the PP population and subjects who completed the Day 85 visit served as sensitivity analyses.

*Secondary Efficacy Analyses:*

The number of subjects who were oral ulcer-free (complete response) or whose oral ulcers were reduced by  $\geq 50\%$ , including ulcer-free (partial response) at Day 85 was determined. The proportions of subjects who had an ulcer response (oral ulcers were reduced at least by  $\geq 50\%$ ) in the 2 study groups were compared using a 2-sided Cochran-Mantel-Haenszel (CMH) test with significance level of 0.05, controlling for gender (male, female), using an LOCF approach. A sensitivity analysis with nonresponder imputation (NRI) was conducted using the ITT population. For this analysis, subjects without the Day 85 oral ulcer assessment were considered nonresponders. Analysis of the PP Population using the LOCF approach also served as a sensitivity analysis.

Descriptive statistics were presented for  $AUC_{85}$ , average daily AUC, and average of the number of oral ulcers from Day 1 to Day 85; number of genital ulcers, oral + genital ulcers, pain VAS of oral ulcers, Behçet's Disease Activity Index BD index score, patient and clinician's perception scores.

A parametric ANCOVA as described above was used to compare the number of oral + genital ulcers at the Day 85/ET between treatments, using an LOCF approach. Parametric ANCOVA was not performed for the number of genital ulcers, because the number of subjects enrolled with genital ulcers was small. Instead, for subjects with genital ulcers at baseline, the proportion of subjects whose genital ulcers were cleared at Day 85 and Day 169 was summarized, and the LOCF approach was used to impute missing data.

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<p><i>Patient-reported Outcome Analyses:</i> Descriptive statistics were presented for BD MDHAQ and BD QoL total scores and the SF-36v2 norm-based scale scores and component summary scores. An ANCOVA was used to compare PRO assessments at Day 85 between treatment groups.</p> <p><i>Exploratory Analyses:</i> A shift table from baseline to each applicable postbaseline visit for the PGA of each of the BD-related skin lesion was provided. Descriptive statistics for percent change in the numbers of swollen and tender joints were presented.</p> <p><i>Ad hoc Analyses:</i> Additional sensitivity analyses for the primary endpoint and nominal p-values for key secondary endpoints were provided as ad hoc analyses.</p> <p><i>Safety Analysis:</i> Treatment-emergent adverse events (TEAEs), clinical laboratory assessments, vital sign measurements, and ECG findings were summarized and tabulated. Adverse events were coded according to the Medical Dictionary for Drug Regulatory Activities (MedDRA), Version 14.0. TEAEs, abnormalities (laboratory, vital signs, and ECG measurements), disease flare, and new onset or worsening of uveitis were summarized using subject incidence rate. TEAEs were summarized by severity (Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe], Grade 4 [life-threatening], Grade 5 [death]) and relationship to study medication (suspected, not suspected). Descriptive statistics, including change from baseline values, were provided for vital signs, weight, laboratory values (continuous measurements) and ECG measurements.</p>		
<p>SUMMARY – CONCLUSIONS</p> <p>EFFICACY RESULTS:</p> <p>In the primary analysis (ITT population LOCF), there were statistically significantly fewer oral ulcers at Day 85 in the APR 30 BID group compared with the Placebo group. The mean oral ulcer counts at baseline were 2.7 and 2.9 in the APR 30 BID and Placebo groups, respectively. On Day 85 the LS mean oral ulcer counts were 0.4 in the APR 30 BID group and 2.0 in the Placebo group, yielding an LS mean difference (95% CI) of -1.6 (-2.4, -0.9) (<math>p &lt; 0.0001</math>). All sensitivity analyses for the primary endpoint showed statistically significantly fewer oral ulcers at Day 85 in the APR 30 BID group compared with the Placebo group.</p> <p>Secondary and PRO endpoints support the results of the primary analysis. A significantly greater proportion of subjects in the APR 30 BID group achieved complete (ulcer free) or partial (<math>\geq 50\%</math> reduction in ulcer number [including ulcer-free]) oral ulcer responses at Day 85 compared with the Placebo group (<math>p &lt; 0.0001</math>). Similar results were obtained in the sensitivity analyses (ITT population NRI and PP population LOCF).</p> <p>The <math>AUC_{85}</math> for oral ulcer count, average daily <math>AUC_{85}</math>, and average number of ulcers from Day 1 to Day 85 were more than 2-fold lower in the APR 30 BID group compared with the Placebo group. In an analysis that was not preplanned, the nominal p-value showed that <math>AUC_{85}</math> was significantly smaller in the APR 30 BID group compared with the Placebo group (<math>p &lt; 0.0001</math>).</p> <p>Oral ulcer counts in apremilast-treated subjects decreased sharply, reaching maximum reduction at the</p>		

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time of the first postbaseline assessment on Day 15, and remained reduced for up to 6 months on treatment. In subjects who received placebo, mean oral ulcer counts were consistently higher compared with subjects treated with apremilast during the placebo-controlled Treatment Phase. Placebo subjects who switched to apremilast in the Extension Phase experienced a reduction in ulcer counts that was similar to that observed in apremilast-treated subjects. When apremilast treatment was stopped at the end of the Extension Phase, oral ulcer counts increased.

Oral ulcer pain VAS scores in apremilast- and placebo-treated subjects showed a pattern of change over time that was similar to that of oral ulcer counts. At Day 85, there was a more than 2-fold greater decrease from baseline in VAS scores (indicating decreased pain) in the APR 30 BID group compared with the Placebo group. The nominal p-value showed that the oral ulcer pain was significantly improved in the APR 30 BID group compared with the Placebo group ( $p < 0.0001$ ). The mean oral ulcer pain VAS score in subjects treated with apremilast decreased sharply, reaching near maximum reduction at the time of the first postbaseline assessment on Day 15, and remained reduced for up to 6 months on treatment. Placebo subjects who switched to apremilast in the Extension Phase experienced a reduction in oral ulcer pain VAS score that was similar to that observed in the APR 30 BID group. Mean oral ulcer pain VAS scores increased sharply in both treatment groups when apremilast treatment was stopped.

The comparative effect of placebo versus apremilast on oral ulcer count and pain VAS over time was similar in male and female subjects.

Few subjects had genital ulcers at baseline (10 and 6 subjects in the apremilast and placebo groups, respectively), so statistical comparisons were not done. However, a complete genital ulcer response (genital ulcer-free, at Day 85) was achieved by all 10 (100%) subjects with baseline lesions in the APR 30 BID group versus 3 (50.0%) subjects with baseline lesions in the Placebo group. Further, 6 subjects in the Placebo group had an increase in number of genital ulcers at Day 85 relative to baseline; whereas, in the APR 30 BID group, there was only 1 subject with a single, new genital ulcer postbaseline.

All components of the Behçet's Disease Current Activity Index (patient's perception of disease activity, clinician's overall perception of disease activity, and Behçet's Disease Current Activity Index score) showed the same pattern of response to apremilast treatment, indicating improvement in disease activity. At the end of the placebo-controlled Treatment Phase (Day 85), there was a greater reduction (improvement) from baseline in mean scores in the APR 30 BID group compared with the Placebo group. At the end of the Extension Phase (Day 169), mean scores remained reduced in apremilast-treated subjects who continued in the Extension Phase. In subjects who received placebo during the Treatment Phase and switched to apremilast, the reduction from baseline in mean scores at the end of the Extension Phase was similar to that observed in the APR 30 BID group. In both treatment groups, mean component scores were increased on Day 197 compared to Day 169 when treatment was discontinued. The nominal p-value for change from baseline in the Behçet's Current Disease Activity Index showed significantly greater improvement in disease activity in the APR 30 BID group compared with the Placebo group ( $p = 0.0007$ ).

The health-related QoL endpoints BD QoL ( $p = 0.0397$ ), BD MDHAQ ( $p < 0.0001$ ), and the SF-36v2 Physical Component Summary ( $p = 0.0011$ ), all validated instruments, showed statistically significant improvements in the physical function and QoL in the APR 30 BID group compared with the Placebo group. The SF-36v2 is a standard measure of overall physical function with established criteria for



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clinical significance. Based on these criteria, the treatment effect of apremilast on physical function was shown to be clinically significant. For all of QoL measures, the improvement in apremilast-treated subjects was maintained in the Extension Phase, and placebo subjects who switched to apremilast in the Extension Phase achieved improvement similar to that in apremilast-treated subjects.

For the PGA of BD-related skin lesions, investigators graded acne-like lesions and folliculitis for severity as none (absent), mild, moderate, or severe. New nodular lesions were graded as present or absent. The majority of subjects did not have acne-like lesions or new nodular lesions during the study. The most common skin lesion type was folliculitis. With the exception of folliculitis in the Placebo group, there were fewer skin lesions present at Day 85 compared with baseline in both treatment groups. There were no apparent differences between treatment groups in the PGA assessment. At baseline, tender and swollen joints were present, respectively, in 12 and 6 subjects in the APR 30 BID group and 5 and 1 subject in the Placebo group. The numbers of subjects with tender and swollen joints were too small for a meaningful assessment of change from baseline over time, although there appeared to be better improvement (mean percent reduction in joint count) at Day 85 (LOCF) in the APR 30 BID group (tender joints, -97.92; swollen joints, -94.44) relative to the Placebo group (tender joints, -46.59; swollen joints, 200.00).

**SAFETY RESULTS:**

The proportion of subjects with at least 1 TEAE during the placebo-controlled period was similar in the two treatment groups, 89.3% of subjects in the Placebo group and 89.1% of subjects in the APR 30 BID group. The most common TEAEs in the APR 30 BID group in decreasing order of frequency were headache, nausea, Behçet’s syndrome/flare, and diarrhea. Note: The investigator’s verbatim term for all AEs coded to the MedDRA preferred term “Behçet’s syndrome” was Behçet’s flare. Gastrointestinal TEAEs (eg, nausea, diarrhea, and vomiting) occurred more frequently in the APR 30 BID group than the Placebo group, which is consistent with the apremilast safety profile. The majority of TEAEs in the placebo-controlled period were Grade 1 or 2 (mild or moderate). Grade 3/4 TEAEs were reported in less than 10% of subjects, 8.9% of subjects in the Placebo group and 9.1% of subjects in the APR 30 BID group. The most frequently reported Grade 3 TEAE was Behçet’s syndrome/flare; all cases of Behçet’s syndrome/flare were assessed by the investigator as not suspected of being related to study drug. The most common drug-related TEAEs were nausea and headache. No effects of sex on the frequency of TEAEs were observed.

During the apremilast-exposure period, 89.0% of subjects reported at least 1 TEAE. The most common TEAEs in decreasing order of frequency were headache, Behçet’s syndrome/flare, nausea, and diarrhea. Grade 3/4 TEAEs were reported in 12.0% of subjects. The most frequently reported Grade 3 TEAE was Behçet’s syndrome/flare; all cases of Behçet’s syndrome/flare were assessed by the investigator as not suspected of being related to study drug. The most common drug-related TEAEs were nausea and headache.

There were no deaths in this study. Nine subjects had one or more serious TEAEs other than death, 3 subjects while receiving placebo and 6 subjects while receiving apremilast. The most common serious TEAE was Behçet’s syndrome/flare. One serious TEAE (influenza) in an apremilast-treated subject was considered related to study drug. The event of influenza led to withdrawal of study drug and resolved within 3 days. There was one Grade 4 SAE (diplegia) in an apremilast-treated subject that was

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<p>considered not related to study drug. The event of diplegia (verbatim term: bilateral lower extremity paralysis) resolved within 6 days. Thirteen subjects had one or more TEAEs that led to discontinuation of study drug, 5 subjects while receiving placebo and 8 subjects while receiving apremilast. The most common TEAE leading to discontinuation of study drug was Behçet’s syndrome/flare. All cases of Behçet’s syndrome/flare leading to withdrawal of study drug in the placebo-controlled period occurred in the Placebo group.</p> <p>New onset or worsening of uveitis occurred infrequently, ie, 3 of 56 (5.4%) subjects receiving placebo in the placebo-controlled period and 3 of 100 (3.0%) subjects receiving apremilast in the apremilast-exposure period. BD flare was reported more frequently while subjects were receiving placebo (48.2%) than apremilast (34.0%) in the placebo-controlled period.</p> <p>Six categories of AEs of special interest have been identified based on the mechanism of action for apremilast (PDE4 inhibition), ie, gastrointestinal events, infections, major adverse cardiac events (defined as cardiac death, myocardial infarction, and stroke), malignances, suicidal ideation and behavior (including attempted suicide or suicide ideation), and vasculitis. No major adverse cardiac events, malignances, suicide, or system vasculitis were reported. The most frequently reported TEAEs in subjects receiving apremilast were in the gastrointestinal disorders SOC, with nausea and diarrhea being the most frequently reported GI events. The subject incidence of gastrointestinal disorders and individual GI TEAEs (primarily, nausea, diarrhea, and vomiting) during the placebo-controlled period was higher in apremilast-treated subjects than placebo subjects. Most GI TEAEs were considered by the investigator to be drug related; however, the majority of events were Grade 1 or 2. No serious, drug-related GI events were reported. Gastrointestinal events leading to drug withdrawal were infrequent. The percentage of subjects reporting infections in the placebo-controlled period was similar in the apremilast and placebo treatment groups. There was one serious infection (influenza) considered related to study drug in a subject receiving apremilast (see above). No other serious infections or infections leading to interruption or withdrawal of study drug were reported.</p> <p>Mean and median changes from baseline in laboratory parameters, vital signs, and ECG findings were generally small. There were few laboratory abnormalities during the study. Few subjects experienced a greater than 5% weight gain or loss during the placebo-controlled period, although 15% of subjects experienced a greater than 5% weight loss while receiving apremilast overall (apremilast-exposure period).</p> <p><b>CONCLUSION:</b></p> <p>Collective evidence in this study indicates that apremilast at a dose of 30 mg BID effectively reduces the number of oral and genital ulcers, decreases ulcer pain, and improves physical function and QoL in subjects with BD. Apremilast exhibited a safety profile in BD that is consistent with the known safety profile of the drug. Taken together, the data demonstrate that apremilast at the 30 mg BID dose has a favorable benefit/risk ratio in patients with BD.</p> <p>Date of the report: 21 December, 2012.</p>		