

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	Volume: Page:	
Name of Active Ingredient: Apremilast		
Title of Study: A Phase 2B, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate-to-Severe Plaque-Type Psoriasis (PSOR-005) and Two Extension Studies (PSOR-005E & PSOR-005LTE)		
Principal Investigator: <span style="background-color: gray; color: gray;">XXXXXXXXXX</span> Investigators: Refer to <a href="#">Appendix 16.1.4</a>		
Study center(s): This study included 20 active sites in the US and 15 active sites in Canada.		
Publications (reference): Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, Hu CC, Day RM; Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomized controlled trial. The Lancet, Volumen 380, Issue 9843, pp 735-746, 25 August 2012.		
Studied period (years): Date first subject enrolled: Date last subject completed:	Phase of development: 2b	
Objectives: Primary: The primary objective of the core study was to evaluate the clinical efficacy of three oral doses of apremilast (10 mg BID, 20 mg BID, and 30 mg BID) in subjects with moderate to severe plaque psoriasis. The primary objective of the extension studies was to evaluate the clinical safety of up to 5 years of therapy (28 weeks in CC-10004-PSOR-005E and up to 4 years in CC-10004-PSOR-005LTE) with 3 oral doses of apremilast (10 mg BID, 20 mg BID, and 30 mg BID) in subjects with moderate to severe plaque psoriasis who completed the core study and first extension study. Secondary: The secondary objectives of the core study were: To evaluate the safety of 3 oral doses of apremilast (10 mg BID, 20 mg BID and 30 mg BID) in subjects with moderate to severe plaque psoriasis To evaluate the effects of 3 oral doses of apremilast (10 mg BID, 20 mg BID, and 30 mg BID) on the quality of life in subjects with moderate to severe plaque psoriasis		

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	Volume: Page:	
Name of Active Ingredient: Apremilast		
<p>To determine a dose-response relationship for 3 oral doses of apremilast (10 mg BID, 20 mg BID and 30 mg BID) using percent reduction of PASI scores in subjects with moderate to severe plaque psoriasis</p> <p>To characterize the pharmacokinetics (PK) of apremilast in subjects with moderate to severe plaque psoriasis</p> <p>The secondary objectives of the extension studies were:</p> <p>To determine a dose-response relationship up to 52 weeks in 3 oral doses of apremilast using the percent reduction of PASI scores in subjects with moderate to severe plaque psoriasis who completed the treatment phase of the core study</p> <p>To evaluate the clinical efficacy of up to 5 years of therapy with 3 oral doses of apremilast in subjects with moderate to severe plaque psoriasis who completed the treatment phase of the core study</p> <p>To evaluate the effect on quality of life of up to 5 years of therapy with 3 oral doses of apremilast in subjects with moderate to severe plaque psoriasis who completed the treatment phase of the core study</p>		
<p>Methodology:</p> <p>This combined report includes a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study designed to characterize the efficacy and safety of three active doses of apremilast compared with placebo in subjects with moderate to severe plaque psoriasis and its two subsequent extension studies. The core study included several phases: a pre-randomization phase for up to 4 weeks, a 16-week placebo-controlled phase, an 8-week active treatment phase, and a 4-week observational follow-up. The extension studies included only the active treatment phases and a 4-week observational follow-up. Subjects meeting eligibility criteria at baseline were randomized 1:1:1:1 to placebo, apremilast 10 mg BID, apremilast 20 mg BID, or apremilast 30 mg BID.</p> <p>After 16 weeks of the study, all subjects originally randomized to the placebo group at the Baseline Visit were to be re-randomized 1:1 to receive 20 or 30 mg BID apremilast. At the Week 24 Visit (baseline of the extension study), subjects who entered the extension study continued the same treatment that they were receiving at the end of the core study. At the Week 52 Visit (baseline of the long-term extension study), subjects who had received 20 or 30 mg BID apremilast during the extension study continued treatment at the same dose level. Subjects who had received 10 mg BID during the extension study were randomized 1:1 to receive 20 or 30 mg apremilast BID, using a centralized IVRS. Once the final dose of apremilast for Phase 3 studies was selected, all subjects were to be switched to open-label apremilast at the selected dose starting at the Month 6 visit of the long-term extension study, or a subsequent visit if they had already completed Month 6 prior to the Phase 3 dose selection.</p>		

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	Volume: Page:	
Name of Active Ingredient: Apremilast		
<p>Safety data was to be monitored by the sponsor on an ongoing basis, additionally an independent Data Monitoring Committee (DMC) was to be convened to evaluate the relevant safety data after 20%, 40% and 80% of enrolled subjects either completed the 24-Week treatment period or prematurely discontinued from the core study.</p> <p>Efficacy and safety assessments performed during the study are outlined in the Schedule of Study Assessments in <a href="#">Table 2</a> (core study), <a href="#">Table 3</a> (extension study), and <a href="#">Table 4</a> (long-term extension study).</p>		
<p>Number of subjects (planned and analyzed): Planned: 348; Analyzed: 352</p>		
<p>Diagnosis and main criteria for inclusion: Males and females <math>\geq 18</math> years of age who were able to understand, consent to, and adhere to the study protocol if they met all eligibility criteria including the following diagnostic criteria: A <math>\geq 6</math>-month history of moderate to severe plaque psoriasis immediately prior to enrollment. Psoriasis Area and Severity Index (PASI) score <math>\geq 12</math> and body surface area (BSA) involvement <math>\geq 10\%</math> at screening. Detailed inclusion and exclusion criteria are provided in <a href="#">Section 9.3</a>.</p>		
<p>Test product, dose and mode of administration, batch number: Apremilast 10 mg tablets: 07B0035, 08B0032, 07B0060 Apremilast 20 mg tablets: 07B0064, 08B0022, 08B0023, 07B0063, 07B0065, 08B0033, 09B0124 Apremilast 30 mg tablets: 08B0024, 08B0034, 09B0075, 10B0272, 11B0198, 08B0013</p>		
<p>Duration of treatment: 88 Weeks</p>		
<p>Reference therapy, dose and mode of administration, batch number: Placebo 10 mg tablets: 07B0038, 08B0006, 08B0028 Placebo 20 mg tablets: 07B0039, 08B0019, 08B0007, 08B0029, 08B0020, 09B0073 Placebo 30 mg tablets: 09B0074, 08B0030</p>		
<p>Criteria for evaluation: Efficacy:</p> <ul style="list-style-type: none"> <li>- Proportion of subjects who achieve at least a PASI-75</li> <li>- Proportion of subjects who achieve PASI-50, PASI-90 and PASI-100</li> <li>- Time to achieve PASI-50, PASI-75, PASI-90 and PASI-100 during the treatment phase</li> <li>- Mean percent change from baseline PASI</li> <li>- Shift change (1 or more points on a 0 to 5 point scale) in static Physician Global Assessment (sPGA)</li> <li>- Percent change from baseline in percent of affected body surface area (BSA)</li> </ul>		

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	Volume: Page:	
Name of Active Ingredient: Apremilast		
<ul style="list-style-type: none"> <li>- Change from baseline in Dermatology Life Quality Index (DLQI) and Medical Outcome Study Short Form 36-Item Health Survey (SF-36), Version 2</li> <li>- Time to relapse (50% loss of maximal improvement in subjects who achieved <math>\geq</math> PASI-50 during the treatment phase) during the observational follow-up phase</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>- Adverse events (TEAE)</li> <li>- Death</li> <li>- Pregnancy</li> <li>- Laboratory Evaluations</li> <li>- Vital Signs and Weight</li> <li>- ECG</li> </ul> <p>Pharmacokinetic:</p> <ul style="list-style-type: none"> <li>- Systemic exposure of apremilast at Weeks 16 and 24 of the core study</li> <li>- Area under the plasma concentration-time curve (<math>AUC_{0-8}</math>)</li> <li>- Peak (maximum) plasma concentration of drug (<math>C_{max}</math>)</li> <li>- Time to maximum plasma concentration of drug (<math>t_{max}</math>)</li> </ul> <p>The pharmacokinetic endpoints will be addressed in a separate report (<a href="#">CC-10004-PSOR-005-PK</a>).</p>		
<p>Statistical methods:</p> <p>The efficacy analyses for the placebo-controlled period was based on the ITT population. Analyses for the apremilast-exposure period was based on all subjects who are randomized (at the randomization visit) or re-randomized at Week 16/Visit 11) to an apremilast dose and entered the extensions studies. The summaries at the observational follow-up visit only included subjects who entered the observational follow-up period. Supportive analyses using the PP population were conducted for the primary endpoint, PASI-75 response at Week 16.</p> <p>Treatment differences were evaluated only between each apremilast dose (30 mg BID, 20 mg BID, and 10 mg BID) and placebo and were calculated as apremilast minus placebo.</p> <p>Efficacy results were considered statistically significant after consideration of the strategy for controlling the Type 1 error rate. All statistical tests were conducted at the <math>\alpha = 0.05</math> (2-sided) level, and 2-sided p-values were reported.</p> <p>Continuous variables were summarized using descriptive statistics. Qualitative variables are presented as category frequencies and percentages. The denominator for calculating percentages is either the number of subjects in the analysis population, the number of non-missing observations in the treatment group for the particular variable presented or the number of evaluable subjects included in the analysis if there are certain conditions that must be met for evaluability, i.e., subjects must have a positive score at baseline for the variable under consideration.</p> <p>All AEs as well as treatment-emergent AEs were summarized by system organ class, preferred term, severity, and relationship to study medication.</p>		

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	Volume: Page:	
Name of Active Ingredient: Apremilast		
<p>Laboratory data were summarized by visit descriptively (mean, median, mode, standard deviation, minimum, and maximum). 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.</p> <p>Vital sign measurements and weight were summarized by visit descriptively (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.</p>		
<p><b>SUMMARY – CONCLUSIONS</b></p> <p><b>EFFICACY RESULTS:</b></p> <p>Apremilast demonstrated clinical efficacy at doses of 20 mg BID and 30 mg BID in subjects with moderate to severe plaque psoriasis; 28.7% of subjects on APR 20 mg BID and 40.9% of subjects on APR 30 mg BID achieving a PASI-75 response at Week 16 compared to 5.7% of subjects on placebo (<math>p &lt; 0.0001</math> for both treatment groups).</p> <p>In addition, the treatment difference for these two dose groups was also significantly greater than placebo for PASI-50 (47.1% on APR 20 BID and 60.2% on APR 30 BID versus 25.0% on placebo) and PASI-90 (9.2% on APR 20 BID and 11.4% on APR 30 BID versus 1.1% on placebo; <math>p &lt; 0.02</math> for all comparisons).</p> <p>While there was a decrease in the number of subjects in both groups with a PASI-50 and PASI-75 at Week 52 compared to Week 24, for those subjects who were able to remain on IP, the median change in PASI for subjects on APR 30 BID was generally maintained around -65% to -70% through Week 52, with the change in the APR 20 BID group being slightly lower.</p> <p>A significantly greater proportion of subjects on APR 20 BID and APR 30 BID had improvement in sPGA scores; 25.0% (<math>p = 0.0402</math>) and 33.7% (<math>p = 0.0011</math>) of subjects who had a baseline score <math>\geq 3</math> achieving a 0 (clear) or 1 (minimal) score at Week 16 (LOCF) compared to 12.6% of subjects on placebo.</p> <p>Subjects on all doses of apremilast had significant improvement (reduction) in their BSA at Week 16 (<math>p = 0.0020</math> for APR 10 BID, and <math>&lt; 0.0001</math> for APR 20 BID and APR 30 BID treatment difference versus placebo). For those subjects remaining in the study, this improvement in BSA tended to be maintained or improved through Week 52.</p> <p>With regards to quality of life measurements, subjects on APR 20 BID and APR 30 BID derived significant clinical benefit versus placebo based upon several measures. Both the absolute mean change in DLQI, as well as the proportion of subjects achieving a 5-point change (basis for clinically meaningful response), were significantly greater for the higher apremilast dose groups versus placebo (<math>p &lt; 0.008</math> for all differences). Subjects on all three doses of apremilast had significant improvement in the SF-36 MCS versus placebo (<math>p &lt; 0.008</math> for all differences), as well as various individual domain scores.</p> <p>Evaluation of exploratory efficacy endpoints supports the clinical benefit of apremilast in several different manifestations of psoriasis. Significant differences between the APR 20 BID and APR 30 BID groups versus placebo were found for nail psoriasis, scalp psoriasis, pruritus (which was significantly different at 1 week), and palmoplantar psoriasis.</p>		

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	Volume: Page:	
Name of Active Ingredient: Apremilast		

Based on other studies with apremilast, APR 10 BID was not expected to be a clinically efficacious dose. A small percentage of subjects on this dose did appear to derive clinical benefit. While both APR 20 BID and APR 30 BID demonstrated significant clinical benefit, subjects on the higher dose generally experienced greater benefit across the parameters measured.

**SAFETY RESULTS:**

Apremilast was generally well tolerated in the 334 subjects who received APR 10 BID, APR 20 BID, or APR 30 BID over the course of up to 88 weeks. Most adverse events were mild to moderate in severity. The most frequently reported AEs were diarrhea, nausea, and headache.

Few subjects (27/352; 7.7%) discontinued due to TEAEs, but there was a dose-dependent increase in the number of subjects citing this reason for discontinuation with increasing dose of apremilast. Nausea, headache, psoriasis, and vomiting were the only TEAEs leading to discontinuation reported in more than one subject each.

Sixteen subjects had SAEs during the course of the studies, 15 of which were on apremilast at time of onset (15/334 subjects on apremilast at any time during the studies; 4.5%). The overall distribution of SAEs was similar across the apremilast treatment groups.

A dose response for GI-related TEAEs was observed, with more events occurring in subjects with a higher dose of apremilast. In analyzing the onset of these events by time period, it appears that part of the reason for this difference between treatment groups lies in the first week of treatment, during the dose titration period when subjects randomized to apremilast may not have reached their targeted dose at the time of onset of the TEAE. While there was a still a dose response seen after titration for some TEAEs, the difference in incidence rate for these TEAEs through 52 weeks was smaller between treatment groups.

Two malignancies (prostate cancer) were reported in subjects on APR 30 BID. Neither case was considered to be related to apremilast by the investigator. The date of diagnosis for one subject was 36 days after first dose of apremilast, while the other was after 58 days of apremilast treatment. These subjects were [REDACTED] and had a history of elevated PSA values prior to screening.

As seen in other studies with apremilast, upper respiratory tract infection, viral upper respiratory tract infection, nasopharyngitis, and gastroenteritis were among the most frequently reported TEAEs. However, only one event of cellulitis was reported as an SAE. There were no cases of tuberculosis.

Two serious cardiac TEAEs were reported: angina pectoris in a subject on APR 20 BID and myocardial infarction in a subject on APR 30 BID. Both of these subjects had underlying risk factors for cardiac disease.

There were no reported cases of suicide, attempted suicide, or suicidal ideation.

One placebo subject died of unknown causes, and the Investigator considered the death to be likely due to a cardiovascular event.

Changes in hematology or clinical chemistry laboratory parameters were transient and no clinically meaningful trends were observed. Few laboratory abnormalities met the criteria of clinically meaningful. One subject treated with apremilast prematurely discontinued from the study due to an abnormal laboratory evaluation (Subject [REDACTED], elevated AST/ALT). Laboratory parameters showed no specific organ-related toxicities or trends that may require specific monitoring or interventions.

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	Volume: Page:	
Name of Active Ingredient: Apremilast		
<p>Most changes in body weight were minor (<math>\pm 5</math> kg) and were not associated with GI TEAEs. Few subjects experienced clinically relevant change in body weight. While no formal analysis was completed, by inspection, most subjects with at least a moderate weight loss did not appear to have an associated GI TEAE such as nausea or diarrhea.</p> <p>CONCLUSION:</p> <p>This combined report includes a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study designed to characterize the efficacy and safety of three active doses of apremilast compared with placebo in subjects with moderate to severe plaque psoriasis and its two subsequent extension studies. A total of 352 subjects were randomized 1:1:1 to receive placebo, apremilast 10 mg BID (APR 10 BID), apremilast 20 mg BID (APR 20 BID), or apremilast 30 mg BID (APR 30 BID). Of these subjects, 209 entered the extension study and 33 entered the LTE study. All four groups appeared to be balanced at baseline with respect to demographic and disease characteristics.</p> <p>Apremilast demonstrated clinical efficacy at doses of 20 BID and 30 BID in subjects with moderate to severe plaque psoriasis. The primary endpoint of a PASI-75 response was met by 28.7% of subjects on APR 20 BID and 40.9% of subjects on APR 30 BID achieving PASI-75 response at Week 16 compared with 5.7% of subjects on placebo (<math>p &lt; 0.0001</math> for both treatment groups).</p> <p>Subjects on APR 20 mg BID and APR 30 mg BID also experienced significant clinical benefit in regard to multiple secondary endpoints such as sPGA and BSA involvement, as well as in quality-of-life evaluations such as DLQI and SF-36 (mental component). Exploratory analyses of specific clinical manifestations of disease, including nail psoriasis, scalp psoriasis, palmoplantar psoriasis, and pruritus, also showed a significant benefit of treatment with APR 20 mg BID and APR 30 mg BID versus placebo.</p> <p>Apremilast was generally well tolerated in the 334 subjects who received APR 10 BID, APR 20 BID, or APR 30 BID over the course of up to 88 weeks. Most adverse events were mild to moderate in severity. The most frequently reported AEs were diarrhea, nausea, and headache. There were few study withdrawals due to TEAEs. There were a small number of SAEs in this study.</p> <p>Changes in hematology or clinical chemistry laboratory parameters were transient and no trend was observed. Few laboratory abnormalities were reported as TEAEs, and most subjects continued in the study. Only one subject treated with apremilast prematurely discontinued from the study due to an abnormal laboratory evaluation (elevated AST/ALT).</p> <p>Some patients experienced weight loss; however, most were mild to moderate and, for the most part, did not appear to be related to GI TEAEs. Weight changes will be analyzed in larger studies with apremilast in psoriasis subjects.</p> <p>Overall, the safety profile of both APR 20 BID and APR 30 BID were comparable and acceptable in the treated population, while the efficacy of APR 30 BID was consistently better than APR 20 BID.</p> <p>Date of the report: 21 December 2012</p>		