

CELGENE PROPRIETARY INFORMATION

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
<b>Title of Study:</b> A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacodynamics, Pharmacokinetics and Efficacy of CC-10004 in Subjects with Recalcitrant Plaque-Type Psoriasis		
<b>Investigators:</b> [REDACTED]		
<b>Study Centers:</b> [REDACTED]		
<b>Publications (reference):</b> None		
<b>Studied period (years):</b> Date first patient enrolled: 20 August 2007 Date last patient completed: 12 May 2009	<b>Phase of development:</b> 2	
<b>Objectives:</b> <b>Primary:</b> Treatment Phase: <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of apremilast (20 mg PO BID) for 84 days in subjects with recalcitrant plaque-type psoriasis</li> </ul> Extension Phase: <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of apremilast (20 mg PO BID) for a an additional 84 days (12 weeks) or apremilast (30 mg PO BID) for 84 days (12 weeks) in subjects with recalcitrant plaque-type psoriasis</li> </ul>		

CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
<p><b>Secondary:</b></p> <p>Treatment Phase:</p> <ul style="list-style-type: none"> <li>To evaluate the pharmacodynamic effects of apremilast in subjects with plaque-type psoriasis by evaluation of:                             <ul style="list-style-type: none"> <li>Peripheral blood T cell, B cell, and NK cell subsets using flow cytometry</li> <li>Psoriatic skin biopsies for epidermal thickness and inflammatory markers using immunohistochemistry and reverse transcriptase polymerase chain reaction (RT-PCR)</li> </ul> </li> <li>To characterize the pharmacokinetics (PK) of apremilast in subjects with recalcitrant plaque-type psoriasis</li> <li>To evaluate the clinical efficacy of apremilast when taken for 84 days in subjects with recalcitrant plaque-type psoriasis</li> <li>To determine the effect of apremilast on quality-of-life</li> </ul> <p>Extension Phase:</p> <ul style="list-style-type: none"> <li>To characterize the pharmacokinetics of 30 mg BID apremilast in subjects with recalcitrant plaque-type psoriasis</li> <li>To evaluate the clinical efficacy of apremilast when taken for 24 weeks in subjects with recalcitrant plaque-type psoriasis</li> <li>To determine the effect of apremilast on quality-of-life</li> </ul>		
<p><b>Methodology:</b> This was a phase 2, open-label, multicenter study to evaluate the safety, tolerability, pharmacodynamics, pharmacokinetics, and efficacy of apremilast 20 mg PO BID in subjects with recalcitrant plaque-type psoriasis. There were 4 study phases: a Pre-treatment Phase, an 84-day Treatment Phase, an 84-day Extension Phase, and a 28-day Observational Follow-up Phase.</p> <p>Screening procedures were performed no more than 35 days prior to start of study medication (Pre-treatment Phase). All prospective subjects provided signed informed consent before any study-related procedures or assessments were performed.</p> <p>Eligible subjects entered the Treatment Phase and began treatment with apremilast (20 mg PO BID) on Day 1. If subjects were unable to tolerate the study medication, dose reduction to 20 mg per day was permitted based on the investigator's clinical judgment. Subjects returned for clinic visits weekly to Day 15, and every 2 weeks thereafter to assess safety, tolerability and temporal onset of response. Skin biopsies of normal (Day 1 only) and psoriatic skin (Days 1, 29, and 85) were obtained at all study sites. Blood samples for PK measurements of apremilast were collected on Days 1, 8, 15, 29, 43, 57, 71, and 85. Subject participation in skin biopsy and PK testing was optional.</p> <p>Subjects who participated in the Treatment Phase of the study could continue in the optional 12-week Extension Phase. Subject's deemed responders (achieving a Psoriasis Area and Severity Index [PASI]-75) in the Treatment Phase, continued to receive apremilast 20 mg BID. Subjects deemed nonresponders (not achieving a PASI-75) in the Treatment Phase had the option to dose-escalate to apremilast 30 mg BID in the Extension Phase. If subjects were unable to tolerate the escalated dose, dose reduction to 20 mg BID</p>		

CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
<p>was permitted based on the investigator's clinical judgment. Subjects who were dose reduced to 20 mg QD in the Treatment Phase and failed to achieve a PASI-75 had the option to dose-escalate to 20 mg BID or continue on the 20 mg QD dose in the treatment Extension Phase. If at anytime subjects experienced overt study medication related adverse effects, dose reduction to 20 mg QD was permitted based on the investigator's clinical judgment. Blood samples for PK measurements of apremilast were collected on Day 169. Subject participation in PK testing was optional.</p> <p>All subjects (including those who prematurely discontinued from the Treatment Phase) were asked to participate in the 28-day Observational Follow-up Phase of the study to assess safety and monitor for worsening of the signs and symptoms of psoriasis and psoriatic arthritis (relapse/flare) off study medication. During the Observational Follow-up Phase, investigators were asked to refrain from prescribing concomitant psoriatic treatments prior to the occurrence of a relapse or flare in order to monitor these events free of the confounding effects of psoriatic therapy.</p>		
<p><b>Number of patients (planned and analyzed):</b></p> <p><i>Planned:</i> Approximately 20 subjects</p> <p><i>Analyzed:</i> Treatment Phase: 30 subjects                  Extension Phase: 11 subjects (4 subjects, 20 mg BID; 7 subjects, 30 mg BID)                  Observational Follow-up Phase: 22 subjects</p>		
<p><b>Diagnosis and main criteria for inclusion:</b></p> <ul style="list-style-type: none"> <li>• Male or female subject of any ethnic origin or race who was <math>\geq 18</math> years at time of consent</li> <li>• Documented history of plaque-type psoriasis for at least 6 months prior to screening visit</li> <li>• Met criteria for at least one of the following clinical categories:                         <ul style="list-style-type: none"> <li>– Unresponsive to standard systemic therapy, as defined by clinical history, in the investigator's opinion, i.e., inadequate response to one or more adequate treatment course(s) of standard systemic therapy including but not limited to: acitretin, cyclosporine, methotrexate, biologics, ultraviolet light A [UVA], narrowband ultraviolet B (NB-UVB), psoralen plus UVA photochemotherapy (PUVA)</li> <li>– Intolerant to or could not receive (e.g., contraindication to prescribe) standard systemic therapy or biological interventions for psoriasis</li> </ul> </li> <li>• Static Physician's Global Assessment (sPGA) score of at least 3 and body surface area (BSA) involvement <math>\geq 10\%</math> at screening</li> </ul>		
<p><b>Test product, dose and mode of administration, batch number:</b></p> <p>Treatment Phase:</p> <ul style="list-style-type: none"> <li>• Apremilast 20 mg capsules</li> <li>• 20 mg twice daily orally: one 20 mg capsule in the AM and one 20 mg capsule in the PM</li> </ul> <p>Extension Phase:</p> <ul style="list-style-type: none"> <li>• Apremilast 10 mg and 20 mg capsules</li> <li>• 20 mg twice daily orally: one 20 mg capsule in the AM and one 20 mg capsule in the PM</li> </ul>		

CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
or <ul style="list-style-type: none"> <li>30 mg twice daily orally: one 20 mg and one 10 mg capsule in the AM and one 20 mg and one 10 mg capsule in the PM</li> </ul> Batch numbers: <ul style="list-style-type: none"> <li>Apremilast 10 mg capsules: 08F0059</li> <li>Apremilast 20 mg capsules: 07F0045; 08F0281</li> </ul>		
<b>Duration of treatment:</b> Treatment Phase: 84 days (12 weeks) Extension Phase: 84 days (12 weeks) Subjects could receive apremilast (Treatment Phase + Extension Phase) for up to 24 weeks.		
<b>Reference therapy, dose and mode of administration, batch number:</b> None		
<b>Criteria for evaluation:</b> <b>Safety and Tolerability:</b> <ul style="list-style-type: none"> <li>Adverse events (AEs)</li> <li>Physical examinations</li> <li>Vital signs</li> <li>Clinical laboratory variables</li> <li>Centralized manual 12-lead ECG over-reading by external cardiologist</li> <li>Assessment of psoriasis and psoriatic arthritis flare</li> </ul> <b>Pharmacokinetics:</b> <ul style="list-style-type: none"> <li>Area under the plasma concentration time-curve (AUC)</li> <li>Peak (maximum) plasma concentration of drug (C<sub>max</sub>)</li> <li>Trough plasma concentration (C<sub>min</sub>)</li> <li>Time to maximum plasma concentration (t<sub>max</sub>)</li> <li>Terminal phase elimination half-life (t<sub>1/2</sub>)</li> <li>Apparent clearance of drug from plasma after extravascular administration (CL/F)</li> <li>Apparent volume of distribution during the terminal phase after extravascular administration (V<sub>z</sub>/F)</li> <li>Accumulation Index (R)</li> <li>Mean Residence Time (MRT)</li> </ul> <b>Pharmacodynamics:</b> <ul style="list-style-type: none"> <li>Change in peripheral blood T cell, B cell, and NK subsets at Day 85 (Visit 9.1) in reference to Day 1 (Baseline Visit)</li> </ul>		

CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
<ul style="list-style-type: none"> <li>• Change in epidermal thickness and change in inflammatory markers in psoriatic skin biopsies at Day 85 (Visit 9.1) in reference to Day 1 (Baseline Visit)</li> </ul> <p><b>Clinical Efficacy:</b></p> <ul style="list-style-type: none"> <li>• Shift change (<math>\geq 1</math> point reduction on a 0 to 5 point scale) in sPGA at Day 85 in reference to Day 1 (baseline)</li> <li>• Change in PASI score at Day 85 in reference to Day 1</li> <li>• Proportion of subjects who achieved PASI-75 at Day 85 in reference to Day 1</li> <li>• Proportion of subjects who achieved PASI-50 at Day 85 in reference to Day 1</li> <li>• Maximal PASI response documented for each subject during the Treatment Phase in reference to Day 1</li> <li>• Change in BSA involvement at Day 85 in reference to Day 1</li> <li>• Time to clinically relevant response (time to achieve PASI-50) during the Treatment Phase</li> <li>• Time to achieve PASI-75 during the Treatment Phase</li> <li>• Time to relapse of psoriasis (50% loss of maximal PASI score improvement in subjects who achieved at least PASI-50 during the Treatment/Extension Phase) during the Observational Follow-up Phase</li> <li>• Global assessment (sPGA) at Day 85</li> <li>• Proportion of subjects with psoriatic arthritis who achieve American College of Rheumatology criteria for 20% improvement (ACR 20) at Day 85 in reference to Day 1</li> <li>• Time to relapse of psoriatic arthritis (50% loss of maximal ACR score improvement in subjects with psoriatic arthritis who achieved at least ACR 20 during the Treatment/Extension Phase) during the Observational Follow-up Phase.</li> <li>• Quality-of-life: Change in Dermatology Life Quality Index (DLQI) and Medical Outcome Study Short Form 36-item Health Survey (SF-36), Version 2 at Day 169 (Final Treatment Visit) /Early Termination Visit in reference to Day 1 (Baseline Visit)</li> </ul>		
<p><b>Statistical methods:</b></p> <p><b>Safety:</b></p> <p>Adverse event reports, clinical laboratory assessments, vital sign measurements, and ECG findings were summarized and tabulated. Adverse events were summarized by frequency, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 3.0) grade, and relationship to study medication (suspected, not suspected). Psoriasis and psoriatic arthritis flare were listed by subject. Clinically significant physical examination abnormalities were reported as AEs.</p> <p><b>Pharmacokinetics:</b></p> <p>The pharmacokinetic analyses are provided in a separate report (<a href="#">CC-10004-PSOR-004-PK</a>).</p> <p><b>Pharmacodynamics:</b></p> <p>Skin biopsies were analyzed as follows:</p> <ul style="list-style-type: none"> <li>• A histological analysis of response was assessed in H&amp;E stained sections of skin biopsies and after staining frozen sections of skin biopsies with antibodies to keratin 16 (K16), CD3, CD11c, intercellular</li> </ul>		

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
<p>adhesion molecule 1 (ICAM-1), Langerin, CD56, Foxp3, and human leukocyte antigen-DR (HLA DR). This analysis thus included an assessment of epidermal growth/differentiation, skin infiltration by T-cells and dendritic cell (DC) subsets, presence of regulatory T-cells, and presence of inflammation-regulating molecules in skin lesions.</p> <ul style="list-style-type: none"> <li>mRNA abundance for a variety of inflammatory molecules was measured by real-time reverse transcriptase polymerase chain reaction (RT-PCR) and expression was normalized to the house-keeping gene human acidic ribosomal protein (HARP).</li> </ul> <p><b>Clinical Efficacy:</b>                  Clinical response to apremilast (treatment effect) in this study was defined as <math>\geq 20\%</math> of completed subjects with a shift change reduction of <math>\geq 1</math> in sPGA score at Day 85 (Final Visit/Treatment Phase) compared to baseline. Each subject's clinical response at the last post-baseline visit in the Treatment Phase was calculated. For subjects terminated early, clinical response was derived using the last observation carried forward (LOCF) approach. Clinical response was tabulated and a 2-sided 95% confidence interval (CI) for the proportion achieving clinical response was calculated.</p> <p>The proportions of subjects achieving PASI-50 (<math>\geq 50\%</math> reduction from baseline in total PASI score), PASI-75 (<math>\geq 75\%</math> reduction from baseline in total PASI score), and PASI-90 (<math>\geq 90\%</math> reduction from baseline in total PASI score) at Final Visit/Treatment Phase was calculated and the associated 95% CIs were provided. The proportion of subjects who experienced a relapse of psoriasis was summarized. The proportion of subjects with psoriatic arthritis who achieved ACR 20 at Day 85 compared to Day 1 was summarized. The Kaplan-Meier method was used to estimate time-to-event variables.</p>		
<p><b>SUMMARY – CONCLUSIONS</b></p> <p><b>SAFETY RESULTS:</b></p> <p>Apremilast was generally well tolerated in the 30 subjects in this study of subjects with recalcitrant plaque psoriasis regardless of phase of the study or dose of apremilast (20 or 30 mg BID). The tolerability profile showed that if subjects did experience an AE, it was mild to moderate in severity, and the most frequently reported AEs (diarrhea, nausea, and headache) are consistent with what has been seen in prior apremilast trials and the GI events are common with PDE4 inhibitors.</p> <p>Four subjects discontinued treatment due to AEs; all four occurred during the Treatment Phase. Discontinuations were generally for lack of efficacy of gastrointestinal AEs, which can be managed well and are self-limited.</p> <p>Four severe (NCI CTCAE Grade 3) AEs were reported in 3 subjects in the Treatment Phase. In the Extension Phase, one subject in each treatment group had severe AEs.</p> <p>There were no cases of opportunistic infection during the study. Of the six subjects who did have infections requiring antibiotics, none required intravenous treatment, and there were no unexpected outcomes from treatment.</p> <p>One subject receiving apremilast 30 mg BID in the Extension Phase had an unwitnessed, sudden death. The SAEs concurrent to the subject's death (potential arrhythmia, myocardial infarction, and hypertensive heart disease) were not suspected of being related to study drug. Results of the autopsy were not made</p>		

CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b> <b>Volume:</b> <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		

available to the investigator. There were no other SAEs reported during the study.

Laboratory parameters showed no specific organ-related toxicities or trends that require specific monitoring or interventions.

**PHARMACOKINETIC RESULTS:** The pharmacokinetic analyses are provided in a separate report ([CC-10004-PSOR-004-PK](#)).

**PHARMACODYNAMIC RESULTS:**

The results of the pharmacodynamic analysis provide evidence of the biological activity of apremilast in plaque psoriasis. At the cellular level, pathologic epidermal hyperplasia and production of K16 by epidermal keratinocytes were reduced in Day 29 and Day 85 biopsies. The reduction in K16 mRNA was of higher magnitude than reductions in epidermal thickness, as expected from known biology. The results of this study showed an important reduction in inflammatory DCs in psoriasis. CD11c+ DCs in psoriasis have also been referred to as TIP-DCs (TNF- $\alpha$  and iNOS-producing DCs) and it is believed that TNF is the major molecule regulating iNOS and p40 synthesis by this DC subset. Apremilast reduced overall numbers of CD11c+ DCs and, in particular, pathologic infiltration of psoriatic epidermis by this cell set. The reductions in iNOS mRNA and p40 mRNA, along with reductions in Th17 and Th22 T-cell pathways are consistent with decreased TNF bioactivity in psoriasis lesions. Overall, the analysis supports the concept that pro-inflammatory mediator signaling is reduced by apremilast in psoriasis. From the reductions in MX-1 levels, it is also likely that interferon levels are reduced as a direct or indirect affect of apremilast.

**EFFICACY RESULTS:**

The protocol-specified criteria for treatment effect was to have  $\geq 20\%$  of subjects achieved at least a 1-point reduction (improvement) in their sPGA score at Week 12 compared to Baseline). Apremilast met this criterion as 20 (66.7%) subjects had at least a 1-point reduction (improvement) in the sPGA compared with the baseline assessment, with a meaningful reduction in mean sPGA seen as early as Week 4 of treatment. During the Extension Phase, all 4 subjects who maintained their dose of apremilast 20 mg BID had a  $\geq 1$  point reduction in sPGA at Week 12, and all 4 maintained to Week 24, suggesting durability of response. The number of missing values for the subjects who increased their dose to 30 mg BID (4 subjects) precludes drawing meaningful conclusions for these subjects in the Extension Phase.

Having met the objective of the study, PASI response was looked at more closely as this is the endpoint required for further trials in apremilast. Subjects achieving at least a PASI-75 response independent of sPGA score were considered “responders” for these evaluations.

During the Treatment Phase, 9 subjects achieved PASI-75, and 4 subjects achieved a 90% improvement (PASI-90) in 12 weeks of therapy. During the Extension Phase, all 4 subjects who remained on apremilast 20 mg BID, who by definition had a PASI-75 response at Week 12, maintained at least a PASI-75 response at Week 24, suggesting durability of response. By definition, the 7 subjects who dose-escalated to 30 mg BID at Week 12 were not PASI-75 responders. Between Week 12 and Week 24, 3 of these subjects had substantial continued improvement (one reaching a maximum change in PASI of -74.4%), 2 had minor decreases (<5%) (improvement), and 2 has slight (< 1 point out of 72) increases (worsening).

The subjects on this trial had recalcitrant psoriasis and in order to meet eligibility criteria had to have failed

CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b> <b>Volume:</b> <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		

or been intolerant to at least 1 prior systemic therapy. Many subjects had multiple systemic treatment failures, including multiple biologic therapies. Nine subjects achieved at least PASI-75 response during the study and there did not seem to be a difference between responders and non-responders in terms of prior psoriasis therapy. In the 18 subjects with prior biologic therapy, 11 had some improvement in the PASI response, with 6 achieving PASI-50, 1 achieving PASI-75, and 4 achieving PASI-90.

It is important to note that the proportion of subjects achieving PASI-75 (30%) is similar to the 24.4% seen in [Study CC-10004-PSOR-003](#), where subjects could not enter if they had failed therapy with cyclosporine or biologic therapy. In addition, the subjects in this study had a mean and median baseline PASI of 17.0 and 14.5, respectively, with a range of 7.4 to 38.2. This low overall baseline score made a 75% reduction difficult to achieve for many subjects due to a floor effect in PASI scoring.

There did not seem to be an effect on PASI-75 response in relation to BMI, sex, age, smoking status, number of failed prior therapies, type of prior therapies, or concurrent psoriatic arthritis.

The ACR score was evaluated since approximately 20% of patients with psoriasis have concurrent psoriatic arthritis ([Radtke, 2009](#)). Two of the 8 subjects (25.0%) who entered the study with psoriatic arthritis achieved 20% improvement in their ACR score (ACR 20) during the Treatment Phase. Three subjects with psoriatic arthritis entered the Extension Phase and all 3 were dose escalated to apremilast 30 mg BID. Of these 3 subjects, 1 (33.3%) subject achieved ACR 20 during the Extension Phase.

Subject-reported outcomes suggest apremilast had a positive effect on QoL. Mean and median values for the DLQI decreased from baseline at both Week 12 and Week 24, indicating that the impact of skin disease on QoL was reduced (ie, improved) following treatment with apremilast. In addition, 72.2% of subjects who had both a baseline DLQI  $\geq 5$  and a follow-up assessment had a clinically meaningful improvement in their psoriasis skin involvement (reduction of  $\geq 5$  points). However, the general measure of QoL, the SF-36, showed minor worsening.

Overall, results during the Extension Phase suggested that continued exposure to apremilast either at the 20 mg BID dose or the higher 30 mg BID dose had continued benefit for subjects. However, these results should be interpreted as exploratory only. Due to the timing of the protocol amendment that introduced the Extension Phase, not all subjects had the same opportunity to continue into the Extension Phase. In addition, the 20 mg BID group was self-selected for subjects who had good response and tolerability while the 30 mg BID group was by definition selecting for subjects who were poor responders (did not achieve PASI-75 during the Treatment Phase).

**CONCLUSIONS:**

The medical history profile of these subjects was typical to psoriasis patients. Forty percent had a history of hypertension, 10% had some form of diabetes, and while only 10% had a medical history of obesity, by BMI calculations, 16.7% (5/30) were obese (BMI = 30 to 34.9), and 33% (10/30) of subjects were morbidly obese (BMI =  $\geq 35$ ). Given these comorbidities, apremilast was generally well tolerated regardless of phase of the study or dose of apremilast (20 or 30 mg BID). The safety profile showed that if subjects did experience an AE, it was mild to moderate in severity, and the most frequently reported AEs (diarrhea, nausea, and headache) are consistent with what has been seen in prior apremilast trials and the GI events are common with PDE4 inhibitors. Exacerbations of comorbid conditions were rare. There were no cases of opportunistic infection during the study. Of the six subjects who did have infections



CELGENE PROPRIETARY INFORMATION

<b>Name of Sponsor/Company:</b> Celgene Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Apremilast 10 mg and 20 mg capsules		
<b>Name of Active Ingredient:</b> Apremilast (formerly, CC-10004)		
requiring antibiotics, none required intravenous treatment.  Apremilast was generally well tolerated in this study. The results of the pharmacodynamic analysis provide evidence of the biological activity of apremilast in psoriasis. Apremilast met the protocol-specified criteria for treatment effect in that more than 20% of subjects achieved at least a 1-point improvement in their sPGA score at Week 12 compared to baseline. Subject-reported outcomes suggest apremilast had a positive effect on quality of life. Limitations of this study include: it was an open-label study with no control group, which introduces bias into the study measurements; the number of subjects evaluated was small (N=30); due to the timing of the protocol amendment that introduced the Extension Phase, not all subjects had the opportunity to continue past Week 12, introducing a potential selection bias for subjects who continued into the Extension Phase; and several subjects (4) dropped out early (on or prior to Week 4) due to intolerability (gastrointestinal effects) or withdrawn consent.  <b>Date of the report:</b> 14 December 2012		