

CELGENE PROPRIETARY INFORMATION

2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Apremilast		
Name of Active Ingredient: CC-10004		
Title of Study: A phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two dose regimens of CC-10004 in subjects with active psoriatic arthritis		
Principal Investigator: 		
Investigators: Refer to Appendix 16.1.4 .		
Study center(s): 38 sites in Canada, Belgium, Germany, the Netherlands, and the United Kingdom		
Publications (reference): Not applicable		
Studied period (years): 1 Date first patient enrolled: 5 March 2007 Date last patient completed: 9 May 2009	Phase of development: 2	
Objectives: Primary: <ul style="list-style-type: none"> To evaluate the 84-day clinical efficacy of 2 dose regimens of apremilast (20 mg <i>per os</i> [PO] twice per day [BID, total daily dose of 40 mg] or 40 mg PO once per day [QD], subsequent to a 7-day dose titration), compared with placebo, for the treatment of active psoriatic arthritis Secondary: <ul style="list-style-type: none"> Evaluation of the safety and tolerability of 20 mg PO BID and 40 mg PO QD of apremilast, compared with placebo, in subjects with active psoriatic arthritis Examination of the effect of 20 mg PO BID and 40 mg PO QD of apremilast, compared with placebo, on quality of life in subjects with active psoriatic arthritis Examination of the pharmacokinetic/pharmacodynamic (PK/PD) relationship between 20 mg PO BID and 40 mg PO QD of apremilast and PD activity, as well as clinical outcomes, in subjects with active psoriatic arthritis to be reported in Report CC-10004-PSA-001-PK 		

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<p>Methodology:</p> <p>This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two dose regimens of CC-10004 in subjects with active psoriatic arthritis. Eligible subjects with a minimum of 6 months' history of psoriatic arthritis immediately prior to enrollment were randomized in a 1:1:1 fashion to either apremilast 40 mg QD, apremilast 20 mg BID, or placebo.</p> <p>After Amendment 1/UK 3, subjects who successfully completed the treatment phase were invited to participate in an 84-day (12 week) extension phase. Subjects receiving apremilast 40 mg QD or 20mg BID during the treatment phase remained on those doses, while subjects on placebo were re-randomized in a 1:1 fashion to either apremilast 40 mg QD or 20 mg BID.</p> <p>Subjects who either prematurely discontinued from the study (during either phase) completed the treatment phase but did not participate in the extension phase, or completed the extension phase were invited to participate in a 4-week observational follow-up phase.</p> <p>Efficacy and safety assessments performed during the study are outlined in the Schedule of Study Assessments in Table 3 and Table 4.</p>		
<p>Number of patients (planned and analyzed):</p> <p>Planned: Approximately 204</p> <p>Analyzed: 204</p>		
<p>Diagnosis and main criteria for inclusion:</p> <p>Males and females \geq 18 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:</p> <p>Diagnosis of psoriatic arthritis (Moll and Wright Criteria), including but not limited to symmetrical or asymmetrical peripheral joint involvement for at least 6 months</p> <p>Active psoriatic arthritis at the time of screening and baseline as defined by: 3 or more swollen joints AND 3 or more tender joints</p> <p>Negative rheumatoid factor (RF) (titer \leq 30 IU/ml)</p> <p>If using methotrexate, must have been on methotrexate for at least 168 days (24 weeks) and was on a stable dose for at least 56 days prior to screening and throughout the study</p> <p>If using oral corticosteroids, must have been on a stable dose of prednisone \leq 10 mg/day or equivalent for at least 28 days prior to screening and throughout the study</p> <p>If using nonsteroidal anti-inflammatory drug (NSAID) therapy, must have been on a stable dose for at least 14 days prior to screening and throughout the study</p> <p>Detailed inclusion and exclusion criteria are provided in Section 9.3</p>		
<p>Test product, dose and mode of administration, batch number:</p> <p>CC-10004 10 mg capsules: Lot numbers 05B0012.1 and 07B0006</p> <p>CC-10004 20 mg capsules: Lot numbers 05B0006, 07B0007, and 07B0053</p> <p>Matched placebo capsules: Lot numbers 06B0002, 07B0005, and 05B0054</p>		

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Duration of treatment: Pre randomization phase: up to 35 days Treatment phase: up to 12 weeks (84 days) Extension phase: up to 12 weeks (84 days) Observational follow-up phases: up to 4 weeks		
Reference therapy, dose and mode of administration, batch number: Not applicable		
Criteria for evaluation: Efficacy: <ul style="list-style-type: none"> • ACR20/50/70 • PsARC • Enthesitis • Dactylitis • DAS28 • PASI Safety: <ul style="list-style-type: none"> • Adverse events • Complete physical examinations including, height (at Visit 1 only), weight (at Visits 1 and 9 only), skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems • Vital signs, including blood pressure, pulse and temperature • Clinical laboratory evaluations, eg, serum chemistry, hematology (including absolute white blood cell count, erythrocyte sedimentation rate, and fibrinogen), urinalysis, C-reactive protein, antinuclear antibody, serum antineutrophilic cytoplasmic antibody, quantitative assessment of serum immunoglobulins (immunoglobulin A [IgA], immunoglobulin M [IgM], and immunoglobulin G [IgG]), CD3+, CD4+, CD8+ lymphocyte subsets (flow cytometry) • Centralized manual 12-lead ECG over-reading by external cardiologist • Assessment of flare as defined as a sudden intensification of psoriasis and/or psoriatic arthritis or a diagnosis of erythrodermic, guttate, or pustular psoriasis. • To determine a worsening of disease state, a retrospective analysis was done to calculate the proportion of subjects who achieved PASI-125 or greater during the study. PASI-125 was defined as a $\geq 25\%$ worsening of PASI in reference to the baseline. Other: HAQ-DI, FACIT-Fatigue, SF-36, DLQI		

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PK as reported in Study Report CC-10004-PSA-001-PK .		
Samples collected for PD analysis from qualified subjects included synovial biopsy, skin biopsy, and blood.		
<p>Statistical methods:</p> <p>The modified ACR20 criteria response, the primary efficacy endpoint consists of a 20 % improvement in the ACR components measured at the final treatment visit. The components include a 20% improvement in the tender and swollen joint count, and a 20% improvement in three out of five of ACR components including subject global assessment of disease (VAS), physician global assessment of disease (VAS), subject pain score (VAS) HAQ-DI, and CRP.</p> <p>Shift tables were provided for changes in the physician and subject global assessments of disease activity. The Kaplan-Meier procedure was used to characterize time to achieve clinically relevant responses (ACR 20, 50, 70, 90 or PASI-50, -75, -90, -100).</p> <p>Cochran-Mantel Haenszel tests controlling for methotrexate use were applied to compare each treatment group to placebo for categorical responses. Analyses of covariance (ANCOVA) with the treatment as factor and baseline as the covariate, blocking for methotrexate use, was applied for treatment comparisons to placebo for continuous measures. Results by center were provided to assess homogeneity as needed.</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> <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>SUMMARY – CONCLUSIONS</p> <p>EFFICACY RESULTS:</p> <p>A total of 204 subjects were enrolled in the Treatment Phase across 38 sites in Canada, Belgium, Germany, the Netherlands, and the United Kingdom. Of these 204 subjects, 165 (80.9%) completed treatment and 39 (19.1%) discontinued prematurely from the study. AEs and worsening or not responding to study medication were the most frequently reported primary reasons for discontinuation.</p> <p>The primary endpoint of the study was a 20% improvement in the ACR score (ACR 20). During the Treatment Phase a significantly greater proportion of subjects achieved an ACR20 on apremilast 40 mg QD (35.8%) and on 20 mg BID (43.5%) versus placebo (11.8%) (p = 0.002 and p < 0.001, respectively).</p> <p>A significantly greater proportion of subjects on apremilast 20 mg BID (17.4%) achieved ACR 50 versus placebo (2.9%) (p = 0.012). While statistically significant, this level of response is considered a</p>		

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minimally important clinical difference.

Improvements in other secondary endpoints such as PsARC, SF-36, HAQ-DI, and FACIT-Fatigue were consistent with the observed ACR20 response.

PASI results were confounded by limited skin involvement in the subjects at baseline. However, there was improvement in the active treatment groups compared to placebo, which was consistent with other completed studies of apremilast in psoriasis.

The PsA patient population in this study exhibited low CRP values at baseline. This, plus the lack of effect that apremilast has on drivers of CRP, such as IL-6, may confound interpretation of the effect of apremilast on CRP. In addition, since CRP is an element of the ACR evaluation, overall clinical response may be under-estimated by the ACR score.

Response rates based on EULAR criteria did not correlate with observed ACR20 response. This may be due to 2 potential confounding factors. The first is that the DAS28 only measures larger joints that may not be representative of active disease in this study population. The second factor may be that CRP has a disproportionate influence on DAS28 and apremilast did not demonstrate an effect on CRP levels in this study.

Of the 165 subjects that completed treatment in the Treatment Phase, 126 chose to enter the Extension Phase and 103 completed the Extension Phase.

During the Extension Phase more than 40% of subjects in each treatment group achieved and ACR20 by Week 24, and response rates in subjects originally treated with placebo who were re-randomized to apremilast were similar to those who were treated with apremilast during both phases of the study.

SAFETY RESULTS:

The majority of subjects (84.3% overall) during the Treatment Phase and more than half of subjects (68.3% overall) in the Extension Phase reported at least 1 AE with a similar proportion of subjects across treatment groups. Overall, no new safety signals were observed during this trial.

During the Treatment Phase, the most frequently reported AEs were diarrhea, headache, nausea, fatigue, and nasopharyngitis. During the Extension Phase, nasopharyngitis was the most common AE reported, followed by nausea, diarrhea, headache, and hypertension.

Most subjects reported AEs that were mild or moderate in severity; no Grade 4 AEs were reported. Fifteen subjects experienced SAEs during either the Treatment or Extension Phases of the study. Most events were mild to moderate in severity (NCI CTCAE Grade 1 or 2) and only one was suspected to be related to the study drug (abdominal abscess). There were no deaths reported in this study.

Twenty-eight subjects experienced AEs that led to dose reduction or interruption, and 31 subjects experienced AEs that led to premature discontinuation from the study (23 during the Treatment Phase and 8 during the Extension Phase).

Apremilast is a small molecule that is mainly metabolized through the CYP 3A4 system. The safety analyses have been focused on related liver laboratory parameters, specifically liver enzymes and total bilirubin. There was no meaningful clinical shift in these parameters observed. Only 1 subject had a liver enzyme elevation 3 x ULN, and no subject had total bilirubin elevations greater than 2 x ULN. No subjects had concomitant elevations in transaminases and abnormalities of hepatic production (bilirubin

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and/or albumin). In addition there were no meaningful shifts detected within each treatment arm.

Apremilast has 4% renal excretion and its metabolites have 50% renal excretion. Renal functions were monitored throughout the study. No subjects had serum creatinine more than 2 x ULN. Two subjects (one each on apremilast 20 mg BID and 40 mg QD) had elevation of serum creatinine that was reported as AEs, but these mild elevations returned to normal. There were no clinically meaningful shifts in renal panel within each treatment arm. An AE of hematuria was reported for one subject (Subject [REDACTED]), but the subject had no recorded abnormal central laboratory urinalysis values during the study. The laboratory AE for the [REDACTED] subject, on 20 mg BID was based on an outside laboratory test.

In general, mean and median changes in laboratory parameters were small and did not show a consistent trend of liver or renal impairment, cytopenias, or heightened autoimmunity over time. Laboratory findings from apremilast clinical studies reveal no consistent pattern of changes suggesting toxicity or a subclinical inflammatory process. These results are consistent with results from other clinical studies with apremilast.

Pharmacologically, apremilast blocks the degradation of cyclic adenosine monophosphate (cAMP) via inhibition of the PDE4 enzyme, resulting in an increase of cAMP in PDE4- expressing cells. Results from various in vitro cellular assays demonstrated that apremilast potently inhibits production of cytokines and chemokines produced by a variety of cells involved in psoriatic pathophysiology, including monocytes, synoviocytes, T cells, neutrophils, keratinocytes, dendritic cells, and endothelial cells. As an immunomodulator, infections, malignancies, and autoimmune disorders are looked at as potential safety concerns.

Treatment with apremilast was not associated with increased overall incidence of infection or serious infection in this study. Nasopharyngitis was the most frequently reported infection, although its incidence was similar between active treatment (11.9% of subjects on 40 mg QD and 11.6% of subjects on 20 mg BID) and placebo (17.6%). Of note, upper respiratory tract infection was reported with a higher frequency in subjects on 40 mg QD (6.0%) than in those on 20 mg BID or placebo (1.4% and 0.0%, respectively) All of the nasopharyngitis and upper respiratory tract infections were mild to moderate in severity. There were only 2 severe infections reported: 1 severe bronchitis and 1 gastrointestinal infection; both of which were in the 40mg QD group. No infections resulted in study discontinuation. No opportunistic infections were reported.

Three subjects treated with apremilast reported malignancies; Subject [REDACTED] had a squamous cell carcinoma of the skin, which was not considered to be related to the investigational drug; Subject [REDACTED] had prostate cancer, which was also not considered to be related to the investigational drug. Subject [REDACTED] had a bronchoalveolar carcinoma, which was reported four months after the subject's completion of the study, and was considered by the investigator to be related to the investigational drug. The sponsor disagreed with the investigator's opinion, as the subject was a smoker, and had a previous history of breast cancer. Narratives are provided for all three events in Section 14.3.3.

Seven subjects treated with apremilast 40 mg QD, 3 subjects on 20 mg BID, and 4 subjects on Placebo tested positive for ANA during the study. Only one subject (on 40 mg QD) tested positive for anti-dsDNA. However, there was an absence of the signs and symptoms of drug-induced lupus-like syndrome.

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As a PDE4 inhibitor, apremilast has been associated with increased GI intolerability and inflammatory diseases. Diarrhea was more frequently reported in the two apremilast groups compared with placebo. Nausea was slightly more frequent in the 40 mg QD and similar between 20 mg BID and placebo groups. Abdominal pain upper was slightly more frequent in the 20 mg BID group and similar between 40 mg QD and placebo groups. Vomiting was similar across all three groups. All of the above GI Disorders were mild-to-moderate in severity. Only a few of these adverse events led to study discontinuation: 1 subject in the 40 mg QD group discontinued due to diarrhea; 2 subjects in the 40 mg QD and 1 in the placebo group discontinued due to nausea; 1 subject in the 40 mg QD and 1 in the 20 mg BID group discontinued due to abdominal pain or abdominal pain upper.

The proportion of subjects reporting any AE that was suspected to be related to the study drug was similar across treatment groups during the Treatment Phase. Drug-related AEs indicative of GI intolerability such as nausea, diarrhea, and vomiting, were more frequently reported in subjects with 40 mg QD dosing than 20 mg BID.

In general, the proportion of subjects treated with concomitant methotrexate who experienced AEs was higher than for those who were not (87.6% versus 81.7%).

In addition, there were no reports of vasculitis or drug-induced lupus-like syndrome, and no consistent findings to suggest end organ toxicity or cumulative toxicity.

The ECG findings in this study were consistent with findings in previous studies including a thorough QT study. Apremilast did not have any important adverse effect on the ECG.

CONCLUSION:

Apremilast at doses of both 40 mg QD and 20 mg BID showed superior efficacy versus placebo in the treatment of PsA. The 20 mg BID regimen exhibited an increased ACR20 of 43.5% at 12 weeks, compared to the 40 mg QD regimen which demonstrated an ACR20 of 35.8%. Both results were statistically significant. A significantly greater number of subjects in the 20 mg BID regimen achieved ACR50, though statistically significant, the rate was of marginal clinical significance. No statistically significant differences were noted in the ACR50 rate in the 40 mg QD group. Thus, the 20 mg BID dose is considered to be the minimal effective dose for apremilast, and suggests that an increased dose regimen be utilized in future studies. Also implied is that twice daily dosing is more efficacious than single dosing. Decreases in each of the components of the ACR20 were observed, including tender and swollen joint counts, HAQ-DI, subject and physician global assessments, and pain assessments, indicating that the effects of apremilast are effective in the sub-types of psoriatic arthritis. Efficacious results were observed in both methotrexate treated and non-methotrexate subjects. The safety profile was favorable; few adverse events remained ongoing at the time of study completion.

While there are some issues of tolerability seen with apremilast, these are seen with the class of PDE4 inhibitors and do not pose a risk to patient safety. This benefit to risk ratio for apremilast in PsA appears favorable and justifies further studies.

Date of the report: 3 May 2010