2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>Celgene Corporation</th>
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<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>CC-10004 10-mg capsules</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>CC-1004</td>
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Title of Study:
Open-label, single-arm pilot study to evaluate the pharmacodynamics, pharmacokinetics, safety, and preliminary efficacy of CC-10004 in subjects with severe plaque type psoriasis

Principal Investigator

The study was conducted at 3 study sites in the United States.

Publications (reference):

Studied Period (years):
Date first subject enrolled: 11 Jan 2005
Date last subject completed: 17 Oct 2005

Phase of Development:
2

Objectives:
Primary:
- To evaluate the pharmacodynamic effect of orally administered CC-10004 (2 x 10 mg once daily [20 mg QD] upon awakening fasted) when taken for 29 days in reducing epidermal thickness in subjects with severe plaque-type psoriasis

Secondary:
- To evaluate the safety of orally administered CC-10004 in subjects with severe plaque-type psoriasis during the study treatment and follow-up phases
- To explore the clinical efficacy of orally administered CC-10004 when taken for 29 days in subjects with severe plaque-type psoriasis
- To explore the clinical efficacy of orally administered CC-10004 when taken for 29 days in the subset of subjects with psoriatic arthritis
- To evaluate the pharmacodynamic effect of CC-10004 using an \textit{ex vivo} whole blood lipopolysaccharide (LPS)-stimulated tumor necrosis factor-alpha (TNF-\alpha) assay
CC-10004
Clinical Study Report: CC-10004-PSOR-001
Celgene Corporation

Individual Study Table
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- To evaluate the pharmacodynamic effects of CC-10004 on a skin biopsy using immunochemistry and reverse transcriptase polymerase chain reaction to assess markers of inflammation
- To explore the pharmacodynamic effects of CC-10004 on T cell, B cell, and natural killer (NK) cell subsets by flow cytometry
- To describe the steady-state pharmacokinetics (PK) of CC-10004 and explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship between CC-10004 and pharmacodynamic activity in subjects with severe plaque-type psoriasis

Methodology:
This was a multicenter, open-label, single-arm study. Subjects with severe plaque-type psoriasis who were candidates for photo/systemic therapy were enrolled in the study. CC-10004 was administered at an oral dose of 2 x 10 mg once daily (20 mg QD) upon awakening fasted. Treatment duration was 29 days. Screening procedures were performed 4 to 28 days prior to the start of the study medication. Subjects who met the entry criteria began the 29-day treatment phase with CC-10004 at Visit 2. Subsequent study visits were scheduled at 8, 15, 22, and 29 days of treatment for assessments of safety and efficacy (pharmacodynamic and clinical). Blood samples in select subjects were collected on Day 29 at 0, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 (Day 30) hours postdose for the determination of CC-10004 concentrations at steady state. If a site was unable to house subjects overnight, blood samples were collected on Day 29 at 0, 0.5, 1, 2, 3, 4, 8, and 24 (Day 30) hours postdose. Two follow-up visits were scheduled for 2 and 4 weeks after the last dose of study medication to assess the frequency of psoriasis relapse and flare and overall safety following the completion of the study drug medication.

Number of subjects (planned and analyzed):
Planned: Approximately 21 enrolled to achieve 17 evaluable
Enrolled: 19
Analyzed: 19

Diagnosis and main criteria for inclusion:
- Male and female subjects ≥ 18 to 65 years of age
- History of severe plaque-type psoriasis for at least 6 months affecting at least 15% of the total body surface area (BSA)
- Clinical laboratory criteria:
  - White blood cell count ≥ 3000/mm$^3$ and < 20,000/mm$^3$
  - Platelet count ≥ 100,000/μL
  - Serum creatinine ≤ 1.5 mg/dL
  - Total bilirubin ≤ 2.0 mg/dL
  - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) and alanine aminotransferase (serum glutamate pyruvic transaminase) (ALT [SGPT]) ≤ 1.5 x the upper limit of the reference range
- Candidate for photo/systemic therapy. A subject was considered to be a candidate for photo/systemic therapy, if in the judgment of a clinician, the subject required any systemic therapy (e.g., ultraviolet light A [UVA], ultraviolet light B [UVB], psoralens and long-wave ultraviolet radiation [PUVA], cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate

Confidential and Proprietary 3
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mofetil, thioguanine, hydroxyurea, sirolimus, tacrolimus, azathioprine) to control psoriasis whether or not that subject had a history of receiving systemic therapy

- At least 1 psoriatic plaque ≥ 2.5 cm in diameter for biopsy

**Test product, dose and mode of administration, batch number:**

CC-10004 10-mg capsules
2 x 10 mg once daily orally (20 mg QD) upon awakening fasted
Batch numbers: 0293X; 0129U

**Duration of treatment:**
29 days

**Reference therapy, dose and mode of administration, batch number:**
None

**Criteria for evaluation:**

**Pharmacodynamic:**

- Skin biopsy
  - Immunohistochemistry: epidermal thickness, quantitative total T cells in epidermis and dermis, qualitative K16, intercellular adhesion molecule-1 (ICAM-1), human leukocyte antigen-DR (HLA-DR), filaggrin, CD83, CD11c
  - Reverse transcriptase polymerase chain reaction (RT-PCR) for psoriasis-associated inflammatory markers: TNF-α, encoding p40 subunit of human IL12 (p40-IL12), interleukin-10 (IL-10), interferon gamma (IFN-γ), interferon gamma-inducible protein-10 (IFN γ-IP10), interleukin-2 (IL-2), interleukin-8 (IL-8), inducible nitric oxide synthase (iNOS), encoding p19 subunit of human IL23 (p19-IL23), K16, CD83, heparin affin regulatory peptide (hARP)

- Blood
  - TNF-α levels following *ex vivo* whole blood LPS stimulation
  - Phenotype for memory CD4+ T cells (CD4+/45RO+), phenotype for memory CD8+ T cells (CD8+/45RO+), human B lymphocyte cluster of differentiation antigen 19 (CD19+), and phenotype for NK cells (CD16/56+) by flow cytometry

**Clinical Efficacy:**

- Psoriasis Area and Severity Index (PASI)
- Static Physician Global Assessment (sPGA)
- Body surface area (BSA)

**Pharmacokinetic (PK):**

- Pharmacokinetic parameter estimates from steady-state plasma levels: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve (AUC_{t} and AUC_{24}), apparent elimination rate constant (λ_{z}), apparent total body clearance (CL/F), apparent volume of distribution (Vz/F), and terminal half-life (t_{1/2,z})

**Safety:**

- Adverse event reporting
Clinical laboratory evaluations (e.g., hematology, chemistry, and urinalysis, including absolute white blood cell counts, fibrinogen, erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibody)

- Physical examination findings
- Vital sign measurements
- 12-lead electrocardiogram (ECG) recordings
- Total number of T lymphocytes (CD3+), T helper cluster of differentiation antigen 4 (CD4+), and T suppressor cluster of differentiation antigen 8 (CD8+) lymphocytes
- Chest x-ray
- Purified protein derivative (PPD)
- Psoriasis relapse and flare assessments during follow-up

Exploratory:
- Photographic documentation of lesions
- American College of Rheumatology 20 (ACR 20) response for subjects with psoriatic arthritis

Statistical Methods:
Sample size:
The sample size of 17 evaluable subjects was based on an exact single-stage design to test the null hypothesis that the true epidermal thickness response rate is ≤ 20% versus the alternative hypothesis that the true rate is ≥ 50%. The sample size and corresponding decision rule were selected so that the probability of rejecting the null hypothesis was less than 0.05 if the null hypothesis was true and the probability of rejecting the alternative hypothesis was less than 0.20 if the alternative hypothesis was true. Seven or more responses among 17 evaluable subjects would be considered strong evidence that the medication be studied further. Assuming a 20% dropout rate, the total sample size needed to obtain 17 evaluable subjects for this study was 21 subjects. With a sample size of 21 subjects and for any adverse event with a true occurrence rate of at least 5%, the probability of observing an adverse event in at least 1 subject was ≥ 0.66. Likewise, for adverse event with true occurrence rate of at least 10%, the probability of observing the adverse event in at least 1 subject was 0.89. Note that this hypothesis-testing model was used primarily to estimate an appropriate sample size. Ultimately, assessment was based on the observed proportion of subjects who respond according to epidermal thickness and the associated confidence interval, together with results obtained for other efficacy variables and the safety profile.

Study endpoints:
Primary
- 20% reduction in epidermal thickness from baseline to Final Visit/Day 29

Secondary
- Change from baseline in PASI at Final Visit/Day 29
- Static Physician Global Assessment (sPGA) at Final Visit/Day 29
- Safety (type, frequency, severity and relationship of adverse events to CC-10004). Physical examination findings, laboratory abnormalities, and ECG changes were captured as adverse events
when deemed medically significant by the investigator.

- Systemic exposure of CC-10004 (AUC and $C_{max}$)
- Pharmacodynamic assessments (skin biopsy and blood)
  - \textit{Ex vivo} TNF-\(\alpha\) levels in LPS-stimulated whole blood
  - Skin biopsy measurements and RT-PCR for psoriasis-associated inflammatory markers
  - Lymphocyte safety subtypes by flow cytometry

\textit{Exploratory}

- Photographic assessment at Final Visit/Day 29
- ACR 20 response at Final Visit/Day 29 for subjects with psoriatic arthritis

\textbf{Analyses:}

\textit{Primary Endpoint}

Epidermal thickness reduction was summarized as a response rate defined as the proportion of subjects whose epidermal thickness was reduced by at least 20\% from baseline to Visit 6/Day 29. The number and percentage of epidermal thickness responders with 95\% exact confidence intervals, calculated using Fisher’s exact test, were summarized by visit. Percent change from baseline in epidermal thickness was summarized by visit using descriptive statistics. \textit{P} values for change from baseline to postbaseline assessment were calculated using 2-sided paired \textit{t}-tests.

\textit{Pharmacodynamic Variables}

Pharmacodynamic variables derived from skin biopsy and blood samples were summarized using descriptive statistics. For TNF-\(\alpha\) levels, percent TNF-\(\alpha\) inhibition was calculated.

\textit{Clinical Efficacy Variables}

Clinical efficacy parameters, PASI and sPGA Average Overall Lesions Scale score were summarized by visit using descriptive statistics. The number and percentage of subjects with more than 50\% and more than 75\% reduction from baseline in PASI score (PASI-50 and PASI-75, respectively) with corresponding 95\% exact confidence intervals were presented by visit. A shift table for sPGA Average Overall Lesions Scale by score and visit was provided. A shift table for psoriasis BSA by severity category (mild [0 to \(<10\%\)], moderate [10\% to \(<15\%\)], and severe [\(\geq15\%\)]) was provided.

\textit{Pharmacokinetic and PK/PD Relationship}

Pharmacokinetic parameters were estimated by noncompartmental methods using software.

The PK/PD relationship between CC-10004 exposure and percent inhibition of \textit{ex vivo} whole blood LPS-stimulated TNF-\(\alpha\) levels was explored using a graphical approach: 2-hour postdose TNF-\(\alpha\) levels and % inhibition of TNF-\(\alpha\) levels on Day 29 plotted against CC-10004 $C_{max}$ and AUC$_{24}$.

\textit{Safety}

Adverse event reports, vital sign measurements, clinical laboratory assessments, ECG measurement, and psoriasis relapse and flare during the follow-up period were tabulated and summarized. All adverse events were summarized by frequency, severity, and relationship to study medication. Serious adverse events and
SUMMARY – CONCLUSIONS

Pharmacodynamic and Preliminary Efficacy Results:
Eight (53.3%; 95% CI [26.6, 78.7]) of the 15 subjects with evaluable skin biopsies demonstrated a ≥ 20% reduction in epidermal thickness at Day 29. Thus, the prespecified protocol-defined definition of a pharmacodynamic response was met.

Mean reduction from baseline in epidermal and dermal T cells at Day 29 was 18.6% and 23.4%, respectively. Similar changes from baseline in epidermal and dermal CD83 and CD11c cells were observed, although the mean change from baseline was not statistically significant for most parameters. Several subjects with biomarkers present in psoriatic lesional biopsies at baseline showed an absence of these markers at Day 29 (as would be expected in normal, non-psoriatic skin): ICAM-1 and filaggrin, 3 subjects; HLA-DR, 2 subjects; quantitative K16, 1 subject. Mean mRNA gene expression of most psoriasis-related inflammatory markers, including iNOS (P < 0.0001) and K16+, was decreased at Day 29 relative to baseline.

CC-10004 had a statistically significant inhibitory effect on ex vivo whole blood LPS-stimulated TNF-α production 2 hours after the first dose. Inhibition of TNF-α production was also noted after 2 hours postdose at Day 29 but was not statistically significant, most likely because TNF-α levels were already suppressed from the prior 29 days of therapy. Mean changes in CD19+, CD3+, CD4+, CD8+, and RO±/RA± T-cell subtypes were small with no consistent pattern over time. Interestingly, 12 of 15 subjects experienced a decrease from baseline in the NK (CD16/56+) lymphocyte population at the end of the study drug treatment period compared with pretreatment (baseline) values. Recent experimental evidence suggests that NK and NK T cells are involved in the pathogenesis of psoriasis as these cells produce INF-γ, which is the only cytokine identified thus far to play a role in psoriasis keratinocyte proliferation (Bos, 2005).

Fourteen of the 19 subjects (73.7%) enrolled in the study demonstrated an improvement in their psoriasis symptoms, and 3 (17.6%) of the 17 subjects with data at Day 29 had a > 50% reduction from baseline in their total PASI score (PASI-50). Nine (52.9%) of the 17 subjects with an assessment at Day 29 had at least a 1-category improvement in the sPGA Average Overall Lesions Scale score relative to baseline. Ten (58.8%) of the 17 subjects with a psoriasis BSA assessment at Day 29 showed an improvement relative to baseline.

Pharmacokinetic and PK/PD Relationship:
On Day 29, mean steady-state CC-10004 exposure, expressed as Cₘₐₓ and AUC₂₄, in subjects with severe plaque-type psoriasis was 207.07 ng/mL and 1799 ng·h/mL, respectively. Tₘₐₓ occurred at a median of 2 hours, and mean t₁/₂, CL/F, and Vz/F were 8.2 hours, 10.4 L/hr, and 128 L, respectively.

No significant correlation between percent inhibition of LPS-stimulated TNF-α production and CC-10004 exposure was observed in the sample population (6 subjects had both PK and PD data available for exposure-response analysis). Interpretation of these results was limited by the small sample size.

Safety Results:
Fourteen (73.7%) subjects reported at least 1 AE during the study. The most common AEs were headache (5 subjects) and nausea (3 subjects). Most AEs were judged by the investigator as mild in severity and were not suspected of having a causal relationship to study drug. The most common AEs with a suspected relationship to study medication were nausea (3 subjects) and dizziness (2 subjects). One subject experienced a severe AE (pharyngitis) that was not suspected of having a causal relationship to study drug.
There were no deaths during treatment or within 30 days of the end of treatment. One serious adverse event (nonaccidental injury) occurred 25 days after the subject stopped treatment with study drug. The event was not suspected of having a causal relationship to study drug as judged by the investigator. No subject prematurely discontinued the study due to adverse events.

Mean changes from baseline in clinical laboratory parameters were small (usually ≤ 10%), with no consistent pattern over time. There were no individual subject shifts from normal at baseline to abnormal posttreatment for albumin, WBC count, neutrophil count, or sedimentation rate during the 29-day treatment phase. Subject shifts from normal at baseline to high posttreatment for C-reactive protein (3 subjects) and fibrinogen (1 subject) were thought to be reflective of these subjects’ underlying psoriatic disease. One subject had an elevated lipase test result on Day 8 of treatment that was considered clinically significant and was reported as an adverse event. Lipase values for this subject returned to normal on Day 10 and remained normal during the remainder of the 29-day treatment phase. The elevated lipase was rated by the investigator as mild in severity and was not suspected of having a causal relationship to treatment with CC-10004. None of the other observed clinical laboratory parameter changes were considered clinically significant by the investigator.

There were no clinically relevant changes in vital sign measurements or ECG findings during the study. Two subjects converted from ANA titer negative at screening to weakly positive (1:40) at Day 29. The investigator determined that no further follow-up was required.

Of the 18 subjects who participated in the 28-day follow-up phase of the study, none had a flare in their psoriasis symptoms. Seven (38.9%) subjects relapsed and required the use of antipsoriatic medication.

Conclusions:
The primary endpoint of this phase 2 pilot study was met. Eight (53.3%; 95% CI [26.6, 78.7]) of the 15 subjects with evaluable skin biopsies had a ≥ 20% reduction in epidermal thickness, which was the protocol-specified definition of a pharmacodynamic response. These data are interpreted as evidence of a positive biological treatment effect of CC-10004 in subjects with severe plaque-type psoriasis. Other pharmacodynamic data and preliminary clinical efficacy results support this interpretation of the primary endpoint results.

Overall, treatment with CC-10004 20 mg QD for up to 29 days was safe in subjects with severe plaque-type psoriasis in this study.

Date of the report: 10 Aug 2006