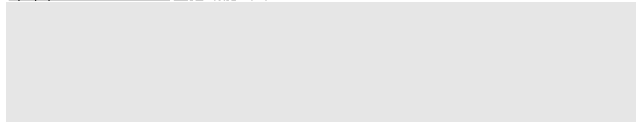


2. SYNOPSIS

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: CC-10004 10-mg capsules		
Name of Active Ingredient: CC-10004		
Title of Study: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Comparison, Parallel-Group, Exercise Challenge Study of CC-10004 in Subjects With Mild Asthma		
Principal Investigators: See below.		
Study centers: This study was conducted at 4 study sites (2 United Kingdom, 1 Germany, and 1 Republic of South Africa). Principal investigators: <div style="background-color: #cccccc; height: 150px; width: 100%; margin-top: 10px;"></div>		
Publications (reference): None		
Studied period: Date first subject enrolled: 21 Jul 2004 Date last subject completed: 07 Mar 2005		Phase of development: 2
Objectives: <u>Primary:</u> <ul style="list-style-type: none"> • To compare the efficacy of 2 doses of oral CC-10004 (2 x 10 mg [20 mg] once daily [QD] or 2 x 10 mg [20 mg] twice daily [BID]) to placebo when taken for 29 days, in improving (i.e., reducing) the percentage fall in forced expiratory volume in 1 second (FEV₁) following exercise-challenge testing in subjects with mild asthma <u>Secondary:</u> <ul style="list-style-type: none"> • To determine the safety of an oral administration of 2 doses of CC-10004 x 29 days in subjects with mild asthma • To determine the pharmacokinetics of an oral administration of 2 doses of CC-10004 x 29 days in subjects with mild asthma • To evaluate the pharmacodynamic effects of CC-10004 using an <i>ex vivo</i> whole blood lipopolysaccharide (LPS)-stimulated tumor necrosis factor-alpha (TNF-α) assay, gene expression analyses, and exhaled nitric oxide (NO) measurements in subjects with mild asthma • To explore the pharmacokinetic/pharmacodynamic relationship between CC-10004 and the percentage fall index (%FI), TNF-α levels, gene expression, and NO measurements in subjects with mild asthma 		

CELGENE PROPRIETARY INFORMATION



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Name of Active Ingredient: CC-10004	Volume: Page:	
<p>Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, exercise-challenge study of CC-10004 comparing 2 oral doses of CC-10004 to placebo administered for 29 days in subjects with mild asthma. The study consisted of 2 phases:</p> <p><u>Pre-randomization Phase:</u> Screening procedures were performed 4 to 28 days prior to the start of study medication. One screening and 1 baseline exercise-challenge test took place during the 28-day pre-randomization phase.</p> <p><u>Treatment Phase:</u> Subjects who met criteria for study entry began the 29-day treatment phase (CC-10004 or placebo) at Visit 2. Subjects were randomized to 1 of 3 arms: CC-10004 20 mg QD, CC-10004 20 mg BID, or placebo. All subjects received 2 bottles of capsules, one for a morning dose and one for an evening dose. The bottles contained either active drug or placebo as appropriate for the randomization arm to which each subject was assigned. Morning doses were taken upon awakening fasted (between 7 AM and 9 AM). Evening doses were taken 12 hours later (\pm 30 minutes), > 1 hour after the evening meal. Salbutamol metered dose inhaler (MDI), 2 puffs every 4 to 6 hours (100 μg/puff), was permitted as needed, for the treatment of asthma symptoms. On-treatment study visits occurred every 7 days for assessments of efficacy and safety. At Visits 2 through 6, a subset of 15 subjects (5 subjects per treatment group) from 1 study site had blood and urine samples collected at protocol-specified times for the determination of CC-10004 concentrations. Of these 15 subjects, 8 subjects had additional blood and urine samples collected at specified times at Visit 6 for the analysis of CC-10004, CC-10007, and M7 metabolites. Subjects at 2 study sites had blood samples drawn for pharmacodynamic assessments at Visits 2, 4, and 6.</p>		
<p>Number of subjects (planned and analyzed): Planned: Approximately 72 subjects (24 subjects per treatment arm) Analyzed: 73 subjects (26 subjects received CC-10004 20 mg QD; 23 subjects received CC-10004 20 mg BID; 24 subjects received placebo)</p>		
<p>Diagnosis and main criteria for inclusion: Male subjects \geq 18 and \leq 45 years of age with a history of exercise-induced asthma and a history of at least 1 year of mild stable asthma ($FEV_1 \geq$ 70% predicted normal value) who required only short-acting β-agonists for routine asthma control</p>		
<p>Test product, dose, mode of administration, and batch number:</p> <ul style="list-style-type: none"> • CC-10004 20 mg QD administered orally: 2 x 10-mg capsules every morning (2 identical appearing placebo capsule in the evening) • CC-10004 20 mg BID administered orally: 2 x 10-mg capsules morning and evening Lot number: 0129U		
<p>Duration of treatment: 29 days</p>		
<p>Reference therapy, dose, mode of administration, and batch number: Placebo capsules (identical in appearance to CC-10004 10-mg capsules) administered orally</p> <ul style="list-style-type: none"> • 2 capsules morning and evening Lot number: 0108U		

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Name of Active Ingredient: CC-10004		
Criteria for evaluation:		
Efficacy:		
<i>Primary efficacy variable</i>		
<ul style="list-style-type: none"> Maximum postexercise percentage fall index (%FI) at Day 29 		
<i>Secondary efficacy variables</i>		
<ul style="list-style-type: none"> Maximum postexercise %FI at Days 1 and 15 Time to recovery (i.e., FEV₁ within 5% of pre-exercise baseline value) after exercise-challenge testing Maximum absolute change in FEV₁, forced expiratory flow between 25% and 75% of the forced vital capacity (FEF 25-75%), and forced vital capacity (FVC) compared with pre-exercise baseline Time average of FEV₁ during 30 minutes after end of exercise referenced to pre-exercise baseline ([AUC_{FEV₁ 0-30 min}/30 min] / pre-exercise baseline) Absolute change in resting lung function (AM FEV₁, FEF 25-75%, and FVC) from predose to 1, 2, and 3 hours after study medication on Days 1, 15, and 29 		
Safety:		
<ul style="list-style-type: none"> Adverse events Clinical laboratory evaluations, e.g., urinalysis, chemistry, hematology, including absolute white blood cell counts and anti-nuclear antibody Physical examination findings Vital sign measurements 12-lead electrocardiogram recordings Investigator's Global Assessment of Atopic Dermatitis (for subjects with atopic dermatitis at screening) 		
Pharmacodynamics:		
<ul style="list-style-type: none"> <i>Ex vivo</i> LPS-stimulated TNF-α levels in whole blood on Days 1 and 29 Whole blood gene expression (mRNA) analysis of inflammatory mediators on Days 1 and 29. Absolute change in resting AM online measurements of exhaled NO on Days 1, 15, and 29. 		
Pharmacokinetics:		
<ul style="list-style-type: none"> Area under the concentration versus time curve (AUC) Maximum concentration (C_{max}) Terminal elimination half-life (t_{1/2}) Time to maximum concentration (T_{max}) Apparent clearance (CL/F) Volume of distribution (V_d) Relative accumulation rate (RA) CC-10004 (S-enantiomer), CC-10007 (R-enantiomer), and M7 (an active metabolite of CC-10004 identified <i>in vitro</i>) at steady state 		

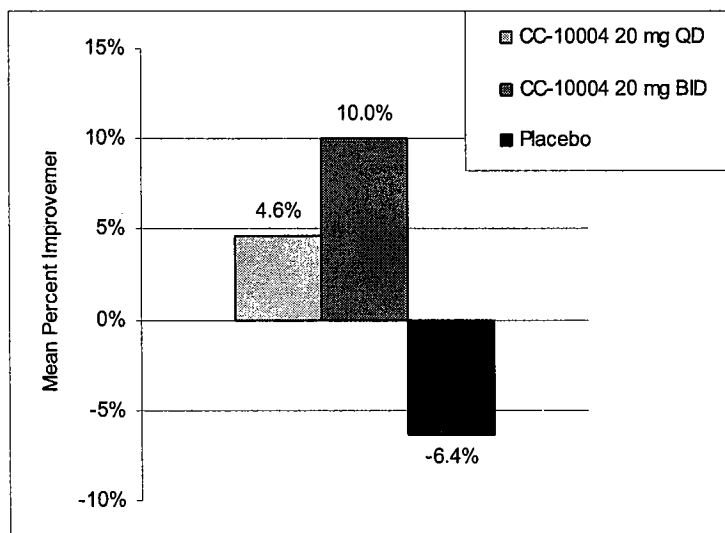
CELGENE PROPRIETARY INFORMATION

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: CC-10004 10-mg capsules	Volume:	
Name of Active Ingredient: CC-10004	Page:	
<p>Statistical Methods:</p> <p>Data were summarized using descriptive statistics: 1) for categorical variables, frequency count and percent; 2) for continuous variables, mean and mean change from baseline, standard deviation, median, and range.</p> <p>Efficacy analyses:</p> <p>The primary efficacy variable was maximum postexercise %FI at Day 29 and was calculated as follows:</p> $\% \text{ FI} = \frac{\text{preexercise FEV}_1 - \text{lowest FEV}_1 \text{ (after exercise)}}{\text{preexercise FEV}_1} \times 100$ <p>The primary treatment comparisons were: 1) CC-10004 20 mg BID versus placebo and 2) CC-10004 20 mg QD versus placebo tested at the 0.025 significance level. Analysis of covariance (ANCOVA) with change from baseline %FI at Day 29 as the response variable and baseline %FI as a covariate was used to compare each of the active treatments to placebo. Pairwise treatment comparisons were considered statistically significant at the 0.025 significance level.</p> <p>Safety:</p> <p>Adverse event reports, vital sign measurements, clinical laboratory assessments, Investigator's Global Assessment of Atopic Dermatitis, and 12-lead ECG measurements were summarized and/or listed. All treatment-emergent adverse events were summarized by frequency, severity, and relationship to study medication. Serious adverse events and adverse events leading to discontinuation were listed separately.</p> <p>Sample size:</p> <p>For this 3-arm, parallel-group design, 21 subjects per treatment arm were sufficient for a 2-sample t-test at the 0.025 2-tailed significance level (to adjust for 2 multiple comparisons) to detect with 80% power an absolute difference of 8% (10% for active and 18% for placebo), with a standard deviation of 8.0% in maximum postexercise %FI at Study Day 29. Assuming that at least 10% of randomized subjects would be nonevaluable, the total sample size for the study was projected to be 72 (24 per treatment arm).</p>		
<p>SUMMARY – CONCLUSIONS</p> <p>Efficacy Results:</p> <p>CC-10004 at doses of 20 mg QD and 20 mg BID showed a trend for a small improvement in the primary efficacy variable, mean change in maximum postexercise %FI from study baseline to Day 29 (see figure below). The comparative analyses (CC-10004 20 mg QD vs. placebo and CC-10004 20 mg BID vs. placebo) were not statistically significant. Both doses of CC-10004 fell short of the WHO suggested standard, i.e., > 50% improvement in %FI in more than 60% of patients (WHO, 1985), as only 4 (15.4%) subjects in the CC-10004 20 mg QD group and 2 (8.7%) subjects in the CC-10004 20 mg BID group experienced a ≥ 50% improvement in %FI.</p>		

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Name of Active Ingredient: CC-10004		

Percent Improvement in Maximum Postexercise Percent Fall Index (%FI) at Day 29 Compared With Baseline by Treatment (ITT Population)



BID = twice daily; ITT = intent to treat; QD = once daily.

$\% \text{ FI} = \frac{([\text{pre-exercise FEV}_1 - \text{lowest postexercise FEV}_1] / [\text{pre-exercise FEV}_1]) \times 100}{}$

Percent improvement based on change from baseline adjusting for %FI at pre-randomization visit.

Source: Table 14.2.1.1

Selected secondary variables supported a pharmacodynamic effect of CC-10004 in subjects with mild asthma.

- Subjects treated with CC-10004 had a numerically greater mean reduction from baseline in exhaled nitric oxide than placebo. A dose-dependent effect was not observed.
- CC-10004 inhibited whole blood LPS-stimulated TNF- α production *ex vivo*, whereas placebo caused an apparent stimulation of LPS-stimulated TNF- α production. A dose-dependent effect of CC-10004 was not observed. These results confirm a positive correlation between LPS-stimulated TNF- α inhibition and CC-10004 exposure that was observed in pharmacokinetic/pharmacodynamic modeling studies.
- There was a suggestion of a dose effect in the use of rescue medication; i.e., use was lowest in the CC-10004 20 mg BID group, higher in the CC-10004 20 mg QD group, and highest in the placebo group.

Clinically meaningful differences between treatment groups for other secondary variables were not observed: time to recovery, maximum absolute change from pre-exercise to postexercise in lung function parameters (FEV₁, FEF 25-75%, and FVC) and resting morning lung function parameter changes (from predose baseline to subsequent visit and predose to 1, 2, or 3 hours postdose within each visit).

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<p>Safety Results:</p> <p>Fifty-two (71.2%) subjects reported at least 1 AE during the study, with no clinically meaningful difference across treatment groups (CC-10004 20 mg QD, 76.9%; CC-10004 20 mg BID, 60.9%; placebo, 75.0%). Overall, the most frequently reported AEs were headache (22 subjects; 30.1%), nausea (17 subjects; 23.3%), nasopharyngitis (8 subjects; 11.0%), and loose stools (5 subjects; 6.8%). Of these, headache, nausea, and loose stools occurred more frequently in the CC-10004 treatment groups compared with the placebo group, although a dose-related effect was not observed for headache or nausea.</p> <p>The proportion of subjects with AEs suspected of having a relationship to treatment was higher in the CC-10004 groups (20 mg QD, 57.7%; 20 mg BID, 43.5%) relative to the placebo group (16.7%), although a dose-related effect in the active treatment groups was not observed. Of the frequently reported AEs suspected of having a relationship to treatment, a dose-related effect was not observed for nausea (30.8% and 21.7% of subjects in the CC-10004 20 mg QD and CC-10004 20 mg BID groups, respectively) and there was only a slight increase in the proportion of subjects with drug-related headache in the higher CC-10004 dose group (20 mg BID, 21.7%) relative to the lower dose group (20 mg QD, 19.2%). There was a suggestion of a dose effect for loose stools (7.7% and 13.0% of subjects in the CC-10004 20 mg QD and CC-10004 20 mg BID groups, respectively). Most AEs were judged by the investigator to be mild in intensity. Three subjects experienced 5 severe AEs: 2 subjects who received CC-10004 20 mg QD (vasovagal attack in 1 subject; compartment syndrome and hematoma not otherwise specified (NOS) in 1 subject) and 1 subject who received placebo (aggression and depression). None of the severe AEs were judged by the investigator to be related to study drug.</p> <p>There were no deaths during treatment or within 30 days of the end of treatment. Three subjects experienced 4 serious adverse events (nephrolithiasis, compartment syndrome, hematoma NOS, and thumb amputation). The thumb amputation occurred 4 days before the first dose of study medication. The subject with serious compartment syndrome and hematoma NOS discontinued study drug due to these events. One additional subject discontinued study drug due to a nonserious AE (chest infection). None of the SAEs or AEs leading to premature discontinuation were rated by the investigator as having a suspected relationship to study drug.</p> <p>Small mean decreases (-0.1 10⁹/L) from screening in white blood cell counts were observed for the 20 mg CC-10004 QD and BID groups at Day 29. A small mean increase (+0.3 10⁹/L) from screening in white blood cell counts was noted in the placebo group at Day 29. None of these changes were considered to be clinically relevant. Overall, mean changes from baseline in clinical laboratory parameters were small (usually ≤ 10%) with no evidence of a treatment effect relative to placebo. None of the observed clinical laboratory parameter changes were considered to be clinically significant by the investigator.</p> <p>There were no clinically relevant changes in vital sign measurements, or ECG findings during the study. No clinically significant ventricular arrhythmias occurred during the study, and there were no incidences of <i>torsades de pointes</i>. Small nonsignificant changes in heart rate, PR interval, and QRS duration were documented, but these were not associated with any potential adverse effect. There was no QTc interval prolongation during the treatment period (no QTc values exceeded 450 msec), and no QT or QTc changes exceeded 60 msec.</p> <p>Overall, doses of 20 mg QD and 20 mg BID CC-10004 were safe. There were no unusual or unexpected safety findings.</p>		

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Name of Active Ingredient: CC-10004	Volume: Page:	
Pharmacokinetic/Pharmacodynamic Results:		
<p>The pharmacokinetics of CC-10004 in subjects with mild asthma were characterized by rapid absorption following both QD and BID dosing at daily dose levels of 20 and 40 mg, with C_{max} occurring at a median T_{max} of 1.5 to 3.0 hours following both the first dose administration on Day 1 and the last dose on Day 29, at the end of the multiple dosing. The mean $t_{1/2}$ of CC-10004 was approximately 4 to 5 hours, and was similar across dosing days for both dose regimens and after single and multiple doses. The urinary excretion of CC-10004 on each dosing day was low, with < 4% eliminated as unchanged drug over the dosing interval. There was no accumulation of CC-10004 following QD multiple dosing at the 20-mg dose level, but approximately a 1.8-fold accumulation following the 40-mg daily dose administered as 20 mg BID. The mean steady-state pharmacokinetic parameters of CC-10004, $AUC_{0-24 (ss)}$ and $C_{min (ss)}$, were approximately 2.6- and 13-fold greater for the BID dose regimen compared with the QD dose regimen, respectively.</p> <p>Based on the 9 subjects in the pharmacokinetic population, a significant correlation was found between the systemic exposure to CC-10004 and LPS stimulated TNF-α production (% inhibition) at 2 hours postdose on Day 1, but there was no apparent correlation on Day 29. There was no apparent relationship between the systemic exposure to CC-10004 and the pharmacodynamic variables of maximum postexercise %FI and exhaled nitric oxide (difference from baseline).</p> <p>In addition, CC-10004 was not converted to CC-10007 in humans, and CC-10055 (M7) was present in both human plasma and urine after oral administration of CC-10004.</p> <p>Conclusions:</p> <p>The results of this phase 2 pharmacodynamic study showed a trend suggesting a treatment effect of CC-10004 at the doses studied (20 mg QD and 20 mg BID). The primary efficacy variable, mean change in maximum postexercise %FI from baseline to Day 29, improved in the CC-10004 groups relative to the placebo group, although the comparative analyses (CC-10004 20 mg QD vs. placebo and CC-10004 20 mg BID vs. placebo) were not statistically significant. Data from some secondary pharmacodynamic variables support the results of the primary efficacy variable. For example, subjects treated with CC-10004 showed a numerically greater mean reduction from baseline in exhaled nitric oxide than subjects receiving placebo. These results confirm a positive correlation between LPS-stimulated TNF-α inhibition and CC-10004 exposure that was observed in pharmacokinetic/pharmacodynamic modeling studies.</p> <p>CC-10004, at doses of 20 mg QD and 20 mg BID, was safe in this study. Dose-limiting adverse events were not observed. In particular, there was no dose-limiting nausea and no reported incidences of vomiting.</p> <p>Taken together, the results of this study showed a trend suggesting a treatment effect of CC-10004 in subjects with mild asthma, although, at the doses studied (20 mg QD and 20 mg BID), CC-10004 did not achieve the degree of protection expected to be clinically meaningful. The data suggest that evaluation of the efficacy and safety of CC-10004 at higher doses is warranted.</p>		
Date of the report: 13 Feb 2006		