2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 761

Name of Active Ingredient: AMG 761

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 761 in Subjects with Asthma

Investigator(s) and Study Center(s): This study was conducted at 2 centers in the United States. The principal investigators were [redacted], MD ([redacted]) and [redacted], MD ([redacted]).

Publication(s): None

Study Period: 14 December 2011 (date first subject enrolled) to 08 January 2014 (last subject completed follow-up)

Development Phase: 1

Objectives: The primary objective was to evaluate the safety, tolerability and immunogenicity of AMG 761 following single-dose administration.

The secondary objectives were to evaluate the single-dose pharmacokinetics (PK) of AMG 761 and to characterize the relationship between AMG 761 dose/exposure, and reduction over time of circulating $CD4^+$ CC chemokine receptor type 4 ($CCR4^+$) T cell counts.

Methodology: This was a phase 1, randomized, double-blind, placebo-controlled, single-dose study in subjects with asthma who were otherwise healthy. Forty eight subjects with asthma were to be enrolled into 6 sequential cohorts. Within each cohort, 8 subjects were to be enrolled and randomized in a 3:1 ratio to receive a single dose of AMG 761 or placebo, respectively.

Number of Subjects Planned: 48

Diagnosis and Main Criteria for Eligibility: Men and women with asthma, between 18 and 60 years old, non-smokers at the time of screening. Subjects had to be clinically stable with a diagnosis of asthma for a minimum of 6 months before enrollment. At screening, subjects were required have a

- forced expiratory volume in the first second (FEV_1) of >70% of the predicted normal value (without the aid of a bronchodilator);
- spirometric evidence of reversibility (at least 12% or 200 mL increase in FEV_1) with bronchodilators;
- or documented history of such reversibility or spirometric evidence, or other documented history, of airway hyperreactivity to methacholine challenge within the 12 months before enrollment.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 761 was provided as a colorless to slightly yellow, sterile, protein solution in 10.0-mL glass vials containing approximately 5.5 mL AMG 761 (maximum withdrawal 5.0 mL) at a concentration of 4.0 mg/mL. AMG 761 was to be administered by the subcutaneous (SC) route as a single dose of 0.2, 0.6, 1.2, 2.5, 5.0, and 10.0 mg. The manufacturing batch number was [redacted].

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Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: A control group was included in each dosing cohort to receive a matching dose of placebo provided as an open-label, colorless to slightly yellow, sterile solution in 10-mL glass vials. The manufacturing batch number was [redacted].

Duration of Treatment: 141 days including a 113-day postdose follow-up period.

Study Endpoints: Primary endpoints included subject incidence of treatment emergent adverse events, including clinically significant changes in vital signs, physical examinations, laboratory safety tests, electrocardiograms (ECGs) and anti-AMG 761 antibodies determined in serum.

Secondary endpoints were AMG 761 PK parameters including, but not limited to maximum observed concentration (C_{max}), time to maximum concentration (t_{max}), and area under the serum concentration-time curve (AUC).

Statistical Methods: No efficacy or safety analyses as planned in the statistical analysis plan were done as the study was terminated early. Individual subject data listings were generated. Noncompartmental PK analyses were conducted for C_{max} value after SC administration, the t_{max} at which C_{max} occurred, and the area under the serum concentration-time curve from time zero to time of last quantifiable concentration (AUC_{last}), estimated using the linear trapezoidal method. Descriptive statistics were provided for pharmacodynamics data ($CD4^+$ $CCR4^+$ T-cells sub-populations in blood, and bronchial alveolar lavage [BAL]).

Summary of Results: [redacted]

Subject Disposition: A total of 8 subjects were enrolled in cohort 1: 4 subjects were randomized to receive 0.2 mg AMG 761, 2 subjects were randomized to receive placebo, and 2 subjects were withdrawn before randomization when the study was put on hold and then terminated, and did not receive study medication. None of the 6 subjects who received AMG 761 or placebo discontinued participation in the study prematurely.

Baseline Demographics: An [redacted] were enrolled in the study ([redacted]). All subjects were [redacted] with a mean age of 38.8 years (range [redacted] years).

Immunogenicity Results: A total of 6 subjects were tested for the presence (baseline) or development (posttreatment) of anti-AMG 761 antibodies. One subject was positive for anti-AMG 761 binding antibodies at day 57, but negative at the predose time point and every other time point tested, including end of study. No subjects developed neutralizing antibodies after administration of AMG 761.

Pharmacokinetic Results: In 4 subjects administered AMG 761 at a dose of 0.2 mg, the mean C_{max} and AUC were 16.5 ng/mL and 90.9 day·ng/mL, respectively. AMG 761 concentrations were only quantifiable through 7 days postdose and were below quantifiable limit (BQL) by 14 days postdose for subjects who had samples collected at that time point.

Pharmacodynamic Results: The mean $CD4^+$ $CCR4^+$ T-cell counts were reduced in subjects treated with AMG 761 compared with the placebo treated subjects. All subjects met $CD4^+$ $CCR4^+$ T-cell recovery criteria (counts returning to either within ± 2 standard deviation [SD], or ≥ 50%, of the subject's predose baseline mean) before discharge from the study.

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Safety Results: Treatment-emergent adverse events were more common with AMG 761 than with placebo (100% in AMG 761 [4 of 4 subjects] vs 50% in placebo [1 of 2 subjects]). Adverse events in both groups were mild or moderate in severity. In the AMG 761 group, adverse events were considered by the investigator to be related to the study medication in 2 (50%) subjects whereas none of the adverse events were considered by the investigator to be related to the study medication in the placebo group.

Treatment-related adverse events in the AMG 761 group included mild cutaneous events (a potential risk for AMG 761) of skin plaque and eczema ([elbow, antecubital fossa, unspecified location] in 1 subject (Subject [redacted]), and eczema ([face, trunk, extremities] and neurodermatitis in another subject (Subject [redacted]). Subject [redacted] also experienced treatment-related mild to moderate gastrointestinal disorders including anal pruritus, proctalgia, rectal fissure, rectal ulcers, and rectal hemorrhage. Adverse events of anal pruritus, proctalgia, rectal fissure, rectal hemorrhage and neurodermatitis were reported as ongoing at the end of the study for Subject [redacted]. This subject remained on study until stabilization of mild to moderate adverse events (for approximately 18 months after administration of AMG 761).

No deaths or serious adverse events occurred.

Vital signs including blood pressure, heart rate, respiratory rate and temperature remained stable throughout the study in all the subjects. No subjects had grade 3 or 4 laboratory abnormalities or a maximum absolute QTcF interval of ≥480 msec in the study.

Conclusions:

In this [redacted] study of the administration of AMG 761 at a single dose of 0.2 mg SC, no serious or fatal adverse events were observed. Mild cutaneous adverse events and mild to moderate gastrointestinal disorders were reported in the AMG 761 group but were absent in the placebo group. One subject (Subject [redacted]) in the AMG 761 group remained in follow-up until stabilization of mild to moderate adverse events of anal pruritus, proctalgia, rectal fissure, rectal hemorrhage and neurodermatitis, all assessed by the investigator as related to AMG 761. This subject was on study for approximately 18 months after administration of AMG 761, and was discharged from the study when the events stabilized. The mean C_{max} and AUC of AMG 761 were 16.5 ng/mL and 90.9 day·ng/mL, respectively. [redacted] No subjects developed neutralizing antibodies following administration of AMG 761. [redacted]

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