Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 108

Name of Active Ingredient: AMG 108

Title of Study: A Randomized, Double-blind, Placebo-controlled, Multiple Dose Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Subcutaneous AMG 108 in Subjects With Rheumatoid Arthritis

Investigators and Study Centers: This was a multicenter study; 139 centers screened subjects and 132 centers enrolled subjects.

Publications: None

Study Period: 31 March 2006 (first subject enrolled) to 06 February 2008 (last subject visit)

Development Phase: 2

Introduction and Objectives: The primary objective was to determine whether AMG 108 at a monthly dose of 250 mg subcutaneous (SC) or less in combination with methotrexate (MTX) demonstrated a higher frequency in clinical response (American College of Rheumatology 20% response [ACR_{20}]) compared with placebo (MTX alone) in subjects with rheumatoid arthritis (RA) at week 24 of therapy.

The secondary objectives were to: (1) to determine whether AMG 108 at a monthly dose of 250 mg SC or less in combination with MTX demonstrated 20% or higher frequency in clinical response (ACR_{20}) above that observed with MTX alone at week 24; (2) to determine whether there was any improvement over MTX alone from baseline in subject reported outcomes measure Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 24; (3) to evaluate the short term safety profile of AMG 108 in combination with MTX in subjects with RA at doses up to 250 mg SC per month; (4) to determine whether the clinical response in subjects treated with AMG 108 at one or more doses with concomitant MTX, comparing week 24 with baseline, was superior to that of MTX alone based on: the proportion of subjects achieving an ACR_{50} and ACR_{70} responses; Disease Activity Score (DAS) 25 score and change in DAS 28 score from baseline (European league against rheumatism [EULAR28] response); ACR score ≥ n% (ACRn) measure and area under the curve (AUC) ACRn; (5) to determine AMG 108 pharmacokinetic parameters in subjects with RA after SC administration; (6) to determine whether there is any improvement over MTX along from baseline in subject reported outcomes measure SF-36 at week 24.

The exploratory objectives were to: [redacted]

Methodology: This was a double-blind, placebo-controlled, parallel dosing study in subjects with active RA on stable MTX therapy (15 to 25 mg weekly) who were biologic-naïve (ie, never treated with commercial or experimental biologic therapy for RA) and off all other disease modifying

anti-rheumatic drugs prior to randomization. Subjects were to be randomized equally to receive 50, 125, or 250 mg SC AMG 108 or placebo administered once every 4 weeks for 6 doses. After the initial dose of investigational product, subjects were to be monitored weekly up to week 12

and followed per the schedule of assessments from week 14 to week 34 (week 24 was the last study visit for subjects who were eligible and participated in the extension study [20060119]). The safety profile was based on adverse events; clinically significant changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests; and the presence of positive anti-AMG 108 antibodies.

Number of Subjects Planned: Approximately 784 subjects (196 subjects in each of the 4 treatment arms)

Number of Subjects Enrolled: A total of 813 subjects were enrolled and randomized in this study and 805 subjects received ≥ 1 dose of investigational product.

Sex: 250 mg AMG 108: 160 women (78.8%), 43 men (21.2%); 125 mg AMG 108: 163 (80.3%) women, 40 (19.7%) men; 50 mg AMG 108: 155 women (76.0%), 49 men (24.0%); placebo: 158 women (77.8%), 45 men (22.2%)

Age, Mean (SD): 250 mg AMG 108: 52.23 (9.78) years, range: 23.0 to 70.0 years; 125 mg AMG 108: 51.69 (11.18) years, range: 22.0 to 70.0 years; 50 mg AMG 108: 51.36 (11.97) years, range: 20.0 to 70.0 years; placebo: 52.13 (11.25) years, range: 20.0 to 70.0 years

Ethnicity/Race: 250 mg AMG 108: white (88.2%), Hispanic (8.4%), black (2.5%), Asian (0.5%), other (0.5%), American Indian or Alaska Native (0.0%), Native Hawaiian or Other Pacific Islander (0.0%);125 mg AMG 108: white (87.2%), Hispanic (8.9%), other (1.5%), black (1.0%), American Indian or Alaska Native (1.0%), Asian (0.5%); Native Hawaiian or Other Pacific Islander (0.0%); 50 mg AMG 108: white (82.8%), Hispanic (11.8%), black (2.9%), Asian (1.5%), American Indian or Alaska Native (0.5%), other (0.5%), Native Hawaiian or Other Pacific Islander (0.0%); placebo: white (82.8%), Hispanic (13.3%), black (2.0%), other (1.0%), American Indian or Alaska Native (0.5%), Native Hawaiian or Other Pacific Islander (0.5%), Asian (0.0%)

Diagnosis and Main Criteria for Eligibility: Men and women between the ages of 18 and 70 years, inclusive, at the time of screening and who had a diagnosis of active RA (as determined by meeting 1987 ACR classification criteria) for at least 6 months. Subjects must have been biologically naïve and receiving stable MTX for 4 weeks at the time of screening.

Investigational Product, Dose and Mode of Administration: Subjects received 50, 125, or 250 mg of AMG 108 administered once every 4 weeks subcutaneously for a total of 6 doses.

Duration of Treatment: 24 weeks of treatment (once every 4 weeks dosing)

Reference Therapy, Dose and Mode of Administration: The placebo formulation was identical to AMG 108 with the exception of the protein content.

Study Endpoints:

Primary Endpoint: The ACR_{20} response at week 24.

Secondary Endpoints: Change from baseline in the following measures at week 24: HAQ-DI, ACR_{50} and ACR_{70}, DAS28 score (EULAR28 response), SF-36, ACRn, and AUC ACRn.

Pharmacokinetic Endpoints: AMG 108 pharmacokinetic parameters (such as maximum AMG 108 concentration [C_{max}], time to reach maximum serum AMG 108 concentration [t_{max}], and AUC from time 0 to the time of the last measurable concentration [AUC_{0-t}]) after the first dose (on day 1) and after the sixth dose for the intensive sampling group.

Exploratory Endpoints: [redacted]

Safety Endpoints: The safety endpoints included treatment-emergent adverse events and infectious adverse events; serious adverse events and serious infectious events; frequency and severity of injection site reactions; significant changes in laboratory values and vital signs; and change in anti-AMG 108 antibody status.

Statistical Methods: The primary endpoint at week 24 compared the ACR_{20} response rate of 250 mg AMG 108 with placebo. All the secondary endpoints were tested sequentially in a prespecified order to control the overall family wise type 1 error rate at 5% (2-sided). The comparisons of proportions (for dichotomous variables) among treatment arms were performed using the Fisher's exact test. The comparisons of distribution location parameters (for continuous and ordinal variables) among treatments arms were to be compared using the Wilcoxon rank-sum test.

For the primary analysis of the primary endpoint, the missing data were imputed using the non-responder method of imputation.

Summary of Results:

Subject Disposition: Of the 813 subjects who were randomized and were analyzed for efficacy, 99% (805 of 813 subjects) received ≥ 1 dose of investigational product and were analyzed for safety; the number of subjects randomized to each dose group was well balanced.

Study completion at week 24 was similar across all dose groups (range: 85.3% to 89.2% [AMG 108 groups], 91.1% [placebo]). Per the protocol, subjects who completed 24 weeks of Study 20050168 could enroll into the extension study (20060119). A total of 96% (690 out of 718) of subjects who completed Study 20050168 at week 24 enrolled into the extension study. An additional eleven subjects who completed 24 weeks of Study 20050168 did not elect to enroll in the extension study; these subjects completed their 34 week visit. A total of 10.2% (83 of 813 subjects) subjects discontinued from Study 20050168 by week 34; among these subjects, 10.3% (21 of 203 subjects), 11.8% (24 of 203 subjects), and 11.3% (23 of 204 subjects) subjects received 250, 125, and 50 mg AMG 108, respectively, and 7.4% (15 of 203 subjects) received placebo.

Efficacy Results: After 24 weeks of AMG 108 treatment, AMG 108 provided clinically significant improvements in subjects with RA, as shown by ACR_{20} and ACR_{50} responses. The rate of ACR_{20} response was higher in the AMG 108 groups (40.4% [250 mg], 36.0% [125 mg], 31.0% [50 mg]) compared with placebo (29.1%); similar results were reported for ACR_{50} (20.2% [250 mg], 13.8% [125 mg], 11.8% [50 mg] versus 8.4% [placebo]). For ACR_{20} and ACR_{50}, statistical significance from placebo was achieved in the 250 mg AMG 108 group ($p < 0.05$). For ACR_{70}, none of the comparisons among any AMG 108 groups and placebo group were significant ($p < 0.05$).

Safety Results: AMG 108 was generally well tolerated at all doses (50 to 250 mg SC) administered during this study. The incidence of adverse events did not appear to increase with increasing AMG 108 dose. No deaths were reported and, with the exception of injection site reactions, the rates of adverse events, infectious episodes, serious adverse events, and withdrawals from study due to adverse events were no higher in the AMG 108 groups than the placebo group. Injection site reactions were more frequent with AMG 108 groups (4.5% [250 mg], 5.0% [125 mg], 4.0% [50 mg]) than placebo (2.5%). Injection site reactions were mild to moderate in severity. The duration of injection site reactions ranged from 1 to 141 days among subjects who had this data recorded, with the majority of cases lasting less than 5 days. Adverse events occurring in ≥ 5% of subject in all dose groups were (AMG 108 group [range], placebo): headache (5.4% to 7.5%, 8.0%), diarrhea (5.0% to 7.5%, 6.5%), nasopharyngitis

(5.4% to 6.5%, 9.0%), and upper respiratory tract infection (5.0% to 6.5%, 7.5%). No serious adverse event was reported by more than 1 subject in the AMG 108 groups.

No clinically significant changes in laboratory values were observed with the exception of expected decreases in ANC and platelet counts; these decreases recovered approximately to baseline for the AMG 108 groups. No clinically significant changes in vital signs were reported with the exception of 3 subjects with clinically significant changes in ECG; these changes in ECG were not considered to be related to investigational product and the subjects remained on study.

Antibody Results: A total of 13.7% of subjects in the AMG 108 groups were positive for binding antibodies at some time point postdose and 4.0% were positive for neutralizing antibodies. At the 2 highest doses (250 and 125 mg), a decreased incidence of anti-AMG 108 antibodies was seen,

which may have been a result of interference in the assay due to high levels of circulating AMG 108.

Pharmacokinetic Results: Following single- and multiple-dose administration, AMG 108 was slowly absorbed with median t_{max} ranging from 3.8 to 3.9 days (50 mg), 3.9 to 4.0 days (125 mg), and 5.9 to 7.0 days (250 mg) with an overall range in individual t_{max} from 1 to 14 days. C_{max} and AUC_{0-t} increased higher than dose-proportionally between 50 and 125 mg SC, and approximately dose proportionally from 125 to 250 mg.

Exploratory Endpoint Results: [redacted]