2. SYNOPSIS

Name of Sponsor: Amgen, Inc, Thousand Oaks, California, USA

Name of Finished Product: AMG 827

Name of Active Ingredient: AMG 827

Title of Study: A Randomized, Double-blind, Placebo-controlled, Ascending Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 827 in Healthy Subjects and Subjects with Moderate to Severe Psoriasis

Investigators and Study Centers: This study was conducted at 3 sites; 2 in Australia and 1 in Canada.

Publication: Russell CB, Kerkof K, Bigler, et al. Blockade of the IL-17R with AMG 827 leads to rapid reversal of gene expression and histopathologic abnormalities in human psoriatic skin. *Soc Invest Derm.* In press.

Study Period: 07 December 2007 (first subject enrolled) to 02 September 2009 (last subject visit)

Development Phase: 1

Introduction and Objectives

AMG 827 is a fully human, Chinese hamster ovary cell-derived immunoglobulin G_2 (IgG_2) monoclonal antibody that binds with high affinity to the human interleukin (IL)-17 receptor, blocking the biological activity of IL-17, IL-17F, and IL-25. IL-17 is an innate cytokine that, in synergy with other pro-inflammatory mediators, leads to local tissue inflammation. Increased levels of IL-17 have been detected in the synovial fluid of patients with rheumatoid arthritis (RA), suggesting that IL-17 receptor blockade may provide therapeutic benefit to patients with RA. In addition, IL-17 receptor blockade may down-modulate features of RA unique from those induced by the IL-1 and tumor necrosis factor (TNF) pathways of disease. Recent studies suggest that IL-17 and IL-17-positive T-cells play an important role in psoriasis. IL-17 mRNA levels are elevated in psoriasis lesional tissue, and these levels decrease following effective treatments such as anti-TNF agents and cyclosporine. Disease remission in psoriasis at 2 weeks after treatment with cyclosporine correlates most strongly with changes in the levels of IL-17 in skin tissue, suggesting a prominent and proximal role for this inflammatory cytokine, and supporting the hypothesis that blockade of IL-17 receptor signaling will lead to improvements in the signs and symptoms of psoriasis.

The primary objective of this study was to assess the safety and tolerability of AMG 827 following single dose subcutaneous (SC) or intravenous (IV) administration in healthy subjects and subjects with moderate to severe psoriasis.

The secondary objective of this study was to characterize the pharmacokinetics of AMG 827 following single dose SC or IV administration in healthy subjects and subjects with moderate to severe psoriasis.

The exploratory objectives of this study were: [redacted]

[redacted]

Methodology

This first-in-human study was a multi-center, randomized, double-blind, placebo-controlled, single-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 827 in healthy subjects and subjects with moderate to severe psoriasis. This study consisted of 2 parts. In Part A, healthy subjects were randomized 6:2 (cohorts 1, 2, 4, 5, 7, 8) or 3:1 (cohorts 3, 6) to receive a single dose of placebo or AMG 827 administered by SC (7, 21, 70, 210, 420 mg) or IV (21, 210, 700 mg) injection. In Part B, subjects with moderate to severe psoriasis were randomized 8:2 (cohorts 9 and 11) or 4:1 (cohort 10) to receive a single dose of placebo or AMG 827 at 700 mg IV or 140 or 350 mg SC. Each subject participated in only 1 part of the study. In Part A, dose escalation occurred at approximately 21-day intervals and only after review of 14 days of safety data (ie, adverse events, electrocardiogram [ECG], laboratory safety data, and vital signs) from all subjects in the preceding cohort(s) by the principal investigator and Amgen clinical safety physicians, with agreement that AMG 827 was safe and well tolerated. The enrollment of Part B occurred after review of a minimum of 21 days of safety data from the 700 mg IV dose in healthy subjects (cohort 8).

Clinical assessments were evaluated at predefined times and included safety assessments and blood collections for laboratory safety tests, and pharmacokinetic and pharmacodynamic analyses.

Number of Subjects Planned: 56 healthy subjects and up to 30 subjects with moderate to severe psoriasis

Number of Subjects Enrolled

In Part A, a total of 58 healthy subjects enrolled in this study and 57 subjects received the planned dose of investigational product. In Part B, a total of 26 subjects with psoriasis enrolled in this study and 25 subjects received the planned dose of investigational product.

Sex: In Part A, all subjects were men. In Part B, 76% of subjects were men and 24% were women.

Age: In Part A, the mean (SD) age was 24.5 (5.7) years. In Part B, the mean (SD) age was 41.0 (11.4) years.

Ethnicity (Race): In Parts A and B, ≥ 67% of subjects were white regardless of treatment assignment.

Diagnosis and Main Criteria for Eligibility: In Part A, healthy men and surgically sterilized or postmenopausal women between 18 to 45 years old with a body mass index between 18 and 30 kg/m^2 were deemed eligible. In Part B, eligibility criteria for subjects with psoriasis included men and women between 18 and 55 years old with active but clinically stable plaque psoriasis that involved ≥ 10% of their body surface area and a PASI score of ≥ 10 during the screening period. Subjects were also required to have received at least 1 phototherapy or systemic psoriasis therapy or have been a candidate for phototherapy or systemic therapy.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Healthy subjects received a single SC (7, 21, 70, 210, 420 mg) or IV (21, 210, 700 mg) dose of AMG 827. Subjects with psoriasis received a single SC (140 or 350 mg) or IV (700 mg) dose of AMG 827. The lot numbers used were [redacted], and [redacted].

Duration of Treatment: Single dose

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Subjects randomized to the placebo group received a single SC or IV dose of matching placebo. The lot number was [redacted].

Study Endpoints

Primary Endpoints: The primary endpoints of this study were the number (percent) of subjects who reported treatment-emergent adverse events; the number of subjects who experienced clinically significant changes in safety laboratory tests, physical examination findings, vital signs, or ECGs and; the number of subjects who developed anti-AMG 827 antibodies.

Secondary Endpoint: The secondary endpoints of this study were pharmacokinetic parameters (area under the drug concentration-time curve [AUC] from time 0 to the time of the last quantifiable sample [AUC_{last}], maximum observed serum concentration [C_{max}], time of maximum concentration [t_{max}]) for AMG 827 after single SC and IV (short infusion) dose administration. Other pharmacokinetic parameters were derived based on the pharmacokinetic data obtained.

Exploratory Endpoints: [redacted].

Statistical Methods

Descriptive statistics were provided for selected demographic, safety, pharmacokinetic, and pharmacodynamic marker data for each dose and route of administration. After review, safety data for subjects who received placebo were combined across all cohorts. Descriptive statistics on continuous measurements included means, medians, standard deviations, and ranges. Categorical data were summarized using frequency counts and percentages. Graphical summaries of the data were also presented.

The number and percentage of subjects reporting any treatment-emergent adverse event were tabulated by system organ class and preferred term, and were further classified by relationship to treatment. Summaries of serious adverse event(s), clinical laboratory test values, ECG, or vital signs were tabulated.

The number and percentage of subjects achieving a 50/75/90% reduction in PASI (PASI 50/75/90) were tabulated by treatment group. The percent improvement in PASI from baseline through Day 85 was summarized by treatment groups. The PGA scores through Day 85 were also summarized. Subjects who received placebo were combined across all cohorts in Part B.

Summary of Results

Subject Disposition

In Part A, of the 58 healthy subjects who were enrolled in the study, 57 subjects (98%) received a single dose of investigational product and were analyzed for safety (1 subject did not receive investigational product because of ineligibility), and 56 subjects (97%) completed the study

(1 subject [redacted] who received 210 mg IV AMG 827 discontinued from the study on Day 42 due to other reasons [unable to attend subsequent study visits; moved interstate]).

In Part B, of the 26 subjects with psoriasis who were enrolled in the study, 25 (96%) received a single dose of investigational product and were analyzed for safety and efficacy; 1 subject did not receive investigational product because of ineligibility. All 25 subjects who received investigational product completed the study.

Efficacy Results: The exploratory efficacy endpoint of this study was only assessed in subjects with psoriasis enrolled in Part B.

Psoriasis Area Severity Index (PASI): There was a positive relationship between AMG 827 dose and PASI 50/75/90 response among the AMG 827-treated subjects. No subjects who received placebo achieved a PASI 50 response or greater at any postdose time point. The mean percent improvement in PASI score increased with increasing AMG 827 dose through Day 29. The 700 mg IV and 350 mg SC groups had higher mean percent improvement in PASI scores than the placebo group at all postdose time points. A total of 7 of 8 (88%) and 5 of 8 (63%) subjects in the 700 mg IV and 350 mg SC groups, respectively, achieved a PASI 75 score or greater response. The 140 mg SC group had higher mean percent improvement in PASI scores than the placebo group up to Day 29, with 2 of 4 subjects (50%) achieving a PASI 50 response at any postdose time point.

Physician Global Assessment (PGA): The mean PGA improvement from baseline scores was higher in the 700 mg IV group compared with the placebo group at all time points; these differences were statistically significant ($\alpha = 0.05$) at all time points based on post hoc analyses, an exception was the mean PGA improvement score on Day 85 ($p = 0.0510$). Based on post hoc analyses, the mean PGA improvement scores from baseline were significantly ($\alpha = 0.05$) higher in the 350 mg SC group compared with placebo on Days 15 and 43; similar results were observed for the 140 mg SC group on Day 15 ($\alpha = 0.05$).

Pharmacokinetic Results: AMG 827 exhibited nonlinear pharmacokinetics in healthy subjects. Serum AMG 827 exposure, as measured by AUC, increased greater than dose proportionally across the dose range of 21 to 700 mg IV and 70 to 420 mg SC. The median time to C_{max} (t_{max}) ranged from 2 to 7 days after SC administration. Bioavailability after SC dosing was estimated to be 0.576 (standard error [SE] = 8.9%) based on simultaneous compartmental modeling of SC and IV cohort data. Pharmacokinetics parameters for AMG 827 were similar between healthy subjects and subjects with psoriasis.

Exploratory Endpoint Results

Pharmacodynamic Results

[redacted]

[redacted]

[redacted]

Safety Results

In Part A, AMG 827 was well tolerated among healthy subjects at all doses tested (up to 700 mg IV and 420 mg SC). No deaths, serious adverse events, dose-limiting toxicities, or withdrawals due to adverse events were reported. The incidence of treatment-emergent adverse events was similar between the AMG 827 subjects (range: 83% to 100%) and the placebo subjects (100%). Treatment-emergent adverse events were all mild or moderate in severity. Treatment-emergent adverse events reported for ≥ 5 subjects in any treatment group were injection site erythema, headache, and upper respiratory tract infection; no dose-related trends in any of these adverse events were observed in subjects treated with AMG 827. With the exception of the 700 mg IV group (33%), most subjects (≥ 67%) in each treatment group including the placebo group had an adverse event that was considered treatment related by the investigator. The incidence of adverse events considered treatment related did not appear to increase with increasing AMG 827 dose.

In Part B, the safety profile among the psoriasis cohorts was similar to that seen in healthy subjects.

In both parts of the study, no clinically significant abnormalities in ECGs, physical examinations, safety laboratory values, or vital signs were observed.

Antibody Results

In Part A, of the 43 healthy subjects who received AMG 827, 3 subjects (7%) tested positive for anti-AMG 827 binding antibodies. One subject (21 mg IV) tested positive at Days 29 and 43, and 2 subjects (1 subject each in the 210 and 420 mg SC groups) tested positive at Day 64 only. No healthy subjects who received placebo tested positive for anti-AMG 827 binding antibodies.

In Part B, of the 20 subjects with psoriasis who received AMG 827, 2 subjects (10%) tested positive for anti-AMG 827 binding antibodies. Two subjects with psoriasis (1 subject each in the 350 mg SC and 700 mg IV groups) tested positive for anti-AMG 827 binding antibodies on Day 85 only. No subjects with psoriasis who received placebo tested positive for anti-AMG 827 binding antibodies.

All subjects in Parts A and B who tested positive for anti-AMG 827 binding antibodies tested negative for the presence of neutralizing anti-AMG 827 antibodies.

Conclusions: This study demonstrated that a single dose of AMG 827 at ≤ 420 mg SC or ≤ 700 mg IV was well tolerated in healthy subjects and subjects with psoriasis, provided desirable systemic exposures, and provided early evidence of clinical efficacy in subjects with moderate to severe psoriasis. [redacted]