2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA

Name of Finished Product: AMG 827

Name of Active Ingredient: AMG 827

Title of Study: A Randomized, Double-blind, Placebo-controlled, Multiple-dose Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 827 in Subjects with Psoriasis

Investigator(s) and Study Center(s): Coordinating investigator: [redacted], MD, PhD, [redacted]

This study was conducted at 23 sites in the United States, Canada, Denmark, Australia, and France. A list of investigators is provided in Appendix 4.

Publication(s): Papp K, Leonardi C, Menter A, et al. Efficacy and safety of AMG 827 in patients with moderate to severe plaque psoriasis: results of a phase 2, randomized, double-blind, placebo-controlled study. Abstract presented at: World Congress of Dermatology; 24 to 29 May 2011; Seoul, South Korea.

Study Period: 09 December 2009 (first subject enrolled) to 27 September 2010 (last subject completed follow-up)

Development Phase: Phase 2

Introduction and Objectives:

AMG 827 is a human, Chinese Hamster Ovary cell-derived IgG2 anti-interleukin-17A receptor (IL-17RA) monoclonal antibody that selectively targets human IL-17RA and antagonizes the IL-17 pathway. It binds with high affinity to human IL-17RA and blocks the biological activity of IL-17A, IL-17F, and the IL-17 AF heterodimer. Recent studies have revealed that AMG 827 also blocks IL-25 (or IL-17E) in a dose-dependent manner. Recent studies suggest that IL-17A and IL-17A-positive T-cells play an important role in psoriasis. Interleukin-17A stimulates production of inflammatory mediators and anti-microbial peptides that are commonly observed in psoriasis lesions, and induces autocrine IL-22 production, leading to epidermal inflammation and thickening. Interleukin-17A mRNA is elevated in psoriasis lesional tissue and decreases following effective treatments, including anti-TNF agents and cyclosporine. Disease response in psoriasis at 2 weeks following treatment with cyclosporine correlates most strongly with changes in the skin levels of IL-17A mRNA, suggesting a prominent and proximal role for this inflammatory cytokine.

The primary objectives of the study were to establish a dose-response efficacy profile of AMG 827 compared with placebo as measured by the percent improvement from baseline in Psoriasis Area and Severity Index (PASI) score at week 12 and to identify an appropriate dose regimen for future studies.

The secondary objectives of the study were:

- To evaluate the efficacy of AMG 827 as measured by the following:
    - The proportion of subjects with a PASI 75 at week 12
    - The proportion of subjects with a PASI 50, 90, and 100 at week 12
    - The proportion of subjects with a static physician's global assessment (sPGA) of clear (0) or clear/almost clear (0 or 1) at week 12
    - Body surface area (BSA) involvement at week 12
- To evaluate the short term safety profile of AMG 827 in subjects with moderate to severe psoriasis
- To characterize the pharmacokinetics (PK) of AMG 827 in subjects with moderate to severe psoriasis

Exploratory objectives are discussed in Section 6.3.

Methodology: This was a randomized, double-blind, placebo-controlled study in subjects with moderate to severe plaque psoriasis. This study evaluated the efficacy of AMG 827 compared with placebo as measured by the percent improvement in PASI score at week 12. After signing

the informed consent form and then completing all screening assessments and meeting all eligibility criteria, approximately 175 subjects were to be randomized in a 1:1:1:1:1 ratio. Subjects received AMG 827 (70, 140, or 210 mg) and/or placebo at day 1 and weeks 1, 2, 4, 6, 8, and 10 or 280 mg AMG 827 on day 1 and weeks 4 and 8. Subjects randomized to active drug received additional placebo injections as necessary to maintain the blind.

For a small subset of subjects (n = 68), additional samples at additional timepoints for pharmacokinetic analysis were collected as a substudy. For the subjects (n = 198) in the main study, pharmacokinetic assessments with sparse sampling were performed. Randomization was to be stratified to assure treatment balance in the pharmacokinetic substudy and by body mass index (BMI), above and below 35. Enrollment for subjects with prior use of biologic psoriasis therapies was capped at 50% of the planned study population.

Skin samples were collected from a subset of subjects (n = 26 consented, 24 had data available) at day 1 (1 each, lesional and nonlesional), week 2 (lesional only), and week 12 (lesional only). Serum, plasma, and blood RNA were collected from all subjects; pharmacogenetic analysis was performed only on those subjects who consented to it.

Subjects were to first enter a screening period of up to 30 days. Starting with the first dose of investigational product (IP), the treatment period for an individual subject was approximately 10 weeks, with additional follow-up visits at weeks 12, 16, and 22. If subjects were eligible and choose to participate in the open-label extension study (20090403), subjects could complete this study at week 16 and were not required to complete the week 22 visit.

Number of Subjects Planned: 175

Number of Subjects Enrolled: 198

Diagnosis and Main Criteria for Eligibility: Eligible subjects were healthy men and women between 18 and 70 years of age (inclusive) who had moderate to severe plaque psoriasis (BSA ≥ 10% and PASI ≥ 12) at screening and baseline. Subjects were to have had stable disease for ≥ 6 months and to have either received ≥ 1 photo/systemic therapy or been a candidate to receive phototherapy or systemic psoriasis therapy in the opinion of the investigator.

Subjects excluded from participation were those with evidence of skin conditions at the time of the screening visit that would interfere with evaluations of the effect of IP on psoriasis and subjects diagnosed with serious infection, had recurrent or chronic infections, or had a significant concurrent medical condition, or any condition that, in the opinion of the investigator, might cause this study to be detrimental to the subject were excluded from the study.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: All subjects received 4 single subcutaneous (SC) injections at day 1 and weeks 4 and 8 and 3 single SC injections at weeks 1, 2, 6, and 10. AMG 827 manufacturing batch numbers used were: [redacted], and [redacted].

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Matching placebo was administered as 4 single SC injections at day 1 and weeks 4 and 8 and 3 single SC injections at weeks 1, 2, 6, and 10. Placebo manufacturing batch numbers used were: [redacted], and [redacted].

Duration of Treatment: Subjects entered a screening period of up to 30 days. Starting with the first dose of investigational product, the treatment period for an individual subject was approximately 10 weeks, with additional follow-up visits at weeks 12, 16, and 22. If there was an available open-label extension study and subjects are eligible and choose to participate, subjects could complete this study at week 16 and were not required to complete the week 22 visit. The maximum duration of study participation for an individual subject was approximately 26 weeks.

Study Endpoints:

Primary:

- Percent improvement from baseline in PASI at week 12

Secondary Endpoints:

- PASI 75 at week 12
- PASI 50, 90, and 100 at week 12
- sPGA of clear or almost clear at week 12
- sPGA of clear at week 12
- BSA involvement at week 12

PK Endpoints:

- AMG 827 PK parameters such as C_{max}, T_{max}, AUC0-t for week 8 to 10

Safety Endpoints:

- Adverse events and infectious adverse events
- Serious adverse events and serious infectious events
- Severity of injection site reactions
- Significant changes in laboratory values, and vital signs

Statistical Methods: Descriptive statistics were provided for baseline demographics and disease characteristics. Summary descriptive statistics by each treatment group were provided. For categorical endpoints, the descriptive statistics contain the frequency and percentage. For continuous endpoints, the descriptive statistics include the number of observations, mean standard deviation, median, minimum and maximum. Missing data for continuous endpoints, including the primary endpoint % PASI improvement, were imputed as baseline values carried forward (BVCF). For dichotomous endpoints, missing data were analyzed with non-responder imputation method. Sensitivity analyses were performed based on data being imputed by the last observation carried forward. The primary endpoint was the percent improvement in the PASI at 12 weeks. Analysis of Covariate (ANCOVA) trend test, using baseline BMI and PASI as the covariates, under the order-restricted inference, with a multiple testing procedure was used as the primary analysis. All statistical tests were 1-sided with a significance level of 0.025.

The secondary and exploratory endpoints were summarized and p-values provided. P-values should be interpreted as descriptive statistic only, because all of α was spent on the primary analysis of the primary endpoint. Population pharmacokinetic analysis and pharmacokinetic/ pharmacodynamic analysis were performed as specified the separate pharmacokinetic/ pharmacodynamic analysis plan.

Safety endpoints were summarized descriptively.

Summary of Results:

Subject Disposition: 198 subjects were enrolled; 160 to AMG 827 and 38 to placebo. Of those randomized, 158 subjects received AMG 827 and 37 subjects received placebo. One hundred eighty-four subjects (152 [95.0%] AMG 827; 32 [84.2%] placebo) completed the study, which was defined as completing16 weeks of study evaluations if the subject enrolled into the extension study (20090403) prior to week 22, or completing 22 weeks of study evaluations if they did not continue into the extension study.

Disposition and baseline demographic data are presented as total AMG 827 (ie, pooled across all AMG 827 cohorts).

Baseline Demographics:

Sex: Placebo: 16 (42.1%) women; 22 (57.9%) men
AMG 827: 55 (34.4%) women; 105 (65.6%) men

Age: Placebo: mean (SD) 41.8 (14.4) years (range: 23 to 69)
AMG 827: mean (SD) 42.6 (11.7) years (range: 21 to 70)

Ethnicity/Race: Placebo: white: 32 (84.2%); black: 3 (7.9%); Hispanic/Latino: 2 (5.3%); Asian: 1 (2.6%)
AMG 827: white: 143 (89.4%); black: 3 (1.9%); Hispanic/Latino: 4 (2.5%); Asian: 6 (3.8%); American Indian/Alaska Native: 3 (1.9%); other: 1 (0.6%)

Efficacy Results:

AMG 827 was shown to be more efficacious than placebo, as demonstrated by the percent improvement from baseline in PASI score at week 12, with 16.0%, 45.0%, 85.9%, 86.3%, and 76.0% improvement in the placebo, 70, 140, and 210 mg Q2WK, and 280 mg Q4WK treatment groups, respectively (all p-values < 0.0001). The proportions of subjects achieving PASI 75, 90, and 100 were all higher than placebo at 76.9%, 71.8%, and 38.5%, respectively in the 140 mg Q2WK dose group; no placebo subjects achieved a PASI 75, 90, or 100.

Dose response increased monotonically within the studied dose range. Though the study was not adequately powered to formally differentiate among doses, especially the top 3 doses (from low to high: AMG 827, 280 mg Q4WK, 140 mg Q2WK, and 210 mg Q2WK), numerically increasing trends among the doses regarding response in primary and the key secondary endpoints were observed. Although the 70 mg Q2WK dose was submaximal, the 140 mg Q2WK dose gave near maximal response across the study population and provided support for the 140 mg Q2WK dose being chosen for phase 3 clinical studies.

The data also suggested that the mean response was lower in subjects who weighed > 100 kg. As noted in the pharmacokinetic analyses, there was a significant relationship between total body weight and the pharmacokinetics/pharmacodynamics of AMG 827. Results showed decreased trough concentrations in heavier subjects, which was consistent with the lower percentage of heavier subjects achieving PASI 75/90/100. These data would suggest that investigation of a higher dose (280 mg Q2WK) in subjects weighing > 100 kg is warranted.

Other Evaluations:

Pharmacodynamics:

[redacted]

Pharmacokinetics:

For the subjects in the pharmacokinetic sub-study, AMG 827 serum concentration-time profiles exhibited nonlinear pharmacokinetics.

Modeling and simulation was used to describe the population pharmacokinetics, dose-response, and exposure-response of AMG 827. There was a significant relationship between total body weight and the pharmacokinetics/pharmacodynamics of AMG 827. Modeling and simulation indicated that the 140 mg Q2WK dose provided near-maximal response. The effect of total body weight on AMG 827 exposure and efficacy was well characterized by modeling and simulation.

Patient-reported Outcomes:

Improvements in mean Psoriasis Symptoms Inventory scores were seen beginning at week 2 and continuing through week 12 for the 140 and 210 mg AMG 827 treatment groups for 24-hour and 7-day for all 8 items ($p < 0.01$). Improvements in mean 24-hour and 7-day total scores were also seen beginning at week 2 and continuing through week 12 for the 140 and 210 mg AMG 827 treatment groups ($p < 0.0001$).

At week 12, the SF-36 mental and physical component scores (BVCF) showed improvements for subjects in the 140 mg Q2WK groups ($p < 0.05$).

The DLQI total scores also showed improvements from week 4 through week 12 for all AMG 827 groups and through week 16 for the 140 and 210 mg Q2WK and 280 mg Q4WK groups ($p < 0.01$).

Safety Results:

Subject incidences of all adverse events ranged from 62.2% (placebo), to 82.5% (210 mg Q2WK). The most common treatment emergent adverse events (incidence rates) in the all AMG 827 treatment groups combined were nasopharyngitis (8.2%), upper respiratory tract infection (8.2%), injection site erythema (5.7%), and pharyngitis (5.7%). Subject incidence of all treatment-related adverse events ranged from 18.9% in the placebo group to 37.5% in the 210 mg Q2WK group.

Three serious adverse events occurred during the study. One subject (AMG 827, 210 mg Q2WK) reported asymptomatic and transient neutropenia that was considered related to investigational product. Another subject (AMG 827, 70 mg Q2WK) reported renal colic, which was assessed by the investigator as being unrelated to study drug. The third subject (placebo) reported an ectopic pregnancy, which was also assessed by the investigator as being unrelated to study drug.

Four subjects (3 in AMG 827 groups and 1 in placebo) had adverse events leading to withdrawal from investigational product administration. Two subjects in the AMG 827, 210 mg Q2WK group had asymptomatic and transient neutropenia. One event was reported by the investigator as a serious adverse event considered related to investigational product; the other event was reported as a non-serious adverse event considered related to investigational product. One subject (AMG 827, 280 mg Q4WK) experienced non-serious, treatment-related grade 1 urticaria that led to discontinuation of investigational product and from the study. A placebo subject experienced non-serious, treatment-related sinusitis that led to discontinuation of investigational product. No deaths or life-threatening serious adverse events occurred during the study.

Events of interest for this study were neutropenia, infectious episodes, and injection site reactions. Two subjects (AMG 827 210 mg Q2WK) had asymptomatic transient events of neutropenia. An infectious adverse event was reported in 38.0% of AMG 827 subjects and 35.1% of placebo subjects. The most commonly reported infectious events were nasopharyngitis (13 [8.2%] AMG 827, 3 [8.1%] placebo), upper respiratory tract infection (13 [8.2%] AMG 827, 2 [5.4%] placebo), and pharyngitis (9 [5.7%] AMG 827, 1 [2.7%] placebo). Injection site reactions were reported by 14 (8.9%) AMG 827 subjects and 2 (5.4%) placebo subjects; all were grade 1.

Of the 158 subjects treated with AMG 827, 12 (7.6%) tested positive for binding, non-neutralizing AMG 827 antibodies; no subject tested positive for neutralizing antibodies. None of the placebo subjects tested positive for the presence of anti-AMG 827 binding antibodies.

Conclusions: In summary, the study showed AMG 827 to be well-tolerated at all doses tested and significantly effective compared with placebo, particularly in the higher dose treatment arms. The risk-benefit profile of AMG 827 appears favorable.