2. SYNOPSIS

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

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 Rheumatoid Arthritis and an Inadequate Response to Methotrexate

Investigator(s) and Study Center(s): This study was conducted at 64 sites in the United States (US), Bulgaria, Canada, Czech Republic, Latvia, Hungary, Mexico, Poland, and the United Kingdom. Investigators and the centers where the subjects were treated during the study are listed in Appendix 2.

Publication(s): None as of the date of this report

Study Period: 30 December 2009 (first subject enrolled) to 11 February 2011 (last subject completed follow-up)

Development 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-17A pathway. It binds with high affinity to human IL-17R and blocks the biological activity of IL-17A and IL-17F. Recent studies have revealed that AMG 827 also blocks IL-25 (or IL-17E) in a dose-dependent manner (R20080129).

A potential role for IL-17A signaling in rheumatoid arthritis (RA) has been supported by data from several studies. Interleukin-17A can directly stimulate synoviocyte production of inflammatory mediators including IL-6, granulocyte macrophage colony stimulating factor, and prostaglandin E2 (Fossiez et al, 1996). Increased levels of IL-17A have been detected in the synovial fluid of patients with RA (Kotake et al, 1999; Ziolkowska et al, 2002; Raza et al, 2005) and, furthermore, blockade of IL-17A signaling can inhibit osteoclast formation induced by culture media of RA synovial tissues. In an ex vivo model using explanted synovial tissue from human RA patients, blockade of IL-17A can reduce the spontaneous production of IL-6 and collagen breakdown products (C-telopeptide of type I collagen) (Chabaud and Miossec, 2001). Finally, in a prospective study synovial membrane mRNA levels of IL-17A were predictive of damage progression, and the effects of IL-17A were shown to be synergistic with TNF (Kirkham et al, 2006).

The primary objective of this study was to evaluate the efficacy of AMG 827 compared with placebo as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 50 response at week 12.

The secondary objectives of the study were:

- To evaluate the efficacy of AMG 827 as measured by the following:
  - The proportion of subjects with an ACR 20 and 70 at week 12
  - Disease Activity Score 28 joint (DAS28) at week 12
- To evaluate the short term safety profile of AMG 827 in subjects with RA
- To characterize the pharmacokinetics of AMG 827 in subjects with RA
- Exploratory objectives of the study are presented in Section 1.3 of the protocol in Appendix 1.

Methodology: The protocol and complete text of the amendment are provided in Appendix **1**.

This was a randomized, double-blind, placebo-controlled study in subjects with RA who had an inadequate response to methotrexate (ie, continuing symptoms of RA as defined in the inclusion/exclusion criteria). This study evaluated the efficacy of AMG 827 compared with placebo as measured by the proportion of subjects achieving an ACR 50 at week 12. All subjects were required to maintain a stable dose of methotrexate during the study and were to be biologic-naïve, meaning they could not have ever received a commercial or experimental biologic disease-modifying anti-rheumatic drug (DMARD). After signing the informed consent form and then completing all screening assessments and meeting all eligibility criteria, approximately 240 subjects were planned to be randomized in a 1:1:1:1 ratio to receive AMG 827 (doses of 70, 140, or 210 mg) or placebo administered subcutaneously (SC) at day 1 and weeks 1, 2, 4, 6, 8, and 10. Subjects randomized to active drug received additional placebo injections as necessary to maintain the blind. Additionally, randomization was stratified by sex, with enrollment of women limited to 200 subjects to ensure that a maximum of 150 women would receive active therapy.

For the subjects (approximately 240 subjects) in the main study, pharmacokinetic assessments with sparse sampling were performed. For a small subset of subjects (n = 40), additional samples at additional timepoints for pharmacokinetic analysis were collected as a substudy. In order to assure treatment balance in the pharmacokinetic substudy, treatment group randomization was stratified by participation in the pharmacokinetic substudy.

Clinical assessments were performed and patient reported outcomes (PRO) were collected at predefined times. Safety assessments, blood collection timepoints for laboratory safety tests, pharmacokinetic and pharmacodynamic analyses are described in the schedule of assessments in Appendix A of the protocol provided in Appendix **1**. An independent data review team (DRT) reviewed all safety data throughout the study. The members of the DRT were internal to Amgen, but not directly involved in the conduct of the study.

An administrative interim analysis (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) was performed by an independent statistician when 67 subjects had completed the first 4 weeks in the study. This interim analysis was added to facilitate administrative decisions. No decisions regarding study conduct were to be made on the basis of this analysis.

Number of Subjects Planned: Approximately 240

Number of Subjects Enrolled: 252

Sex: Placebo: 51 (81%) women; 12 (19.0%) men
AMG 827: 149 (78.8%) women; 40 (21.2%) men

Age: Placebo: mean (SD) 50.6 (11.5) years (range: 22 to 70)
AMG 827: mean (SD) 53.3 (10.3) years (range: 19 to 70)

Ethnicity (Race): Placebo: white: 48 (76.2%); black: 1 (1.6%); Hispanic/Latino: 14 (22.2%)
AMG 827: white: 159 (84.1%); black: 2 (1.1%); Hispanic/Latino: 26 (13.8%); Asian: 2 (1.1%)

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women ≥ 18 and ≤ 70 years of age who had active RA for at least 6 months as diagnosed by meeting 1987 ACR classification criteria. Active RA was defined as ≥ 6 swollen joints (out of 66 joints examined) and ≥ 8 tender/painful joints (out of 68 joints examined) at screening and baseline (swollen and tender/painful joint count could not include distal interphalangeal joints) and at least 1 of the following at screening: erythrocyte sedimentation rate ≥ 28 mm or C-reactive protein > 15 mg/L. In addition, a subject had to have at least 1 of the following at screening: rheumatoid factor positive and/or anti-cyclic citrullinated peptide antibody positive. Subjects were to be taking methotrexate consecutively for ≥ 12 weeks and on a stable dose of methotrexate at 15 to 25 mg weekly for ≥ 4 weeks at day -1. A lower dose of methotrexate was acceptable (but no lower than 10 mg per week) if that was the highest tolerated dose. All subjects were required to take folic acid (at least 5 mg per week) to minimize toxicity of methotrexate.

Subjects taking stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids for at least 4 weeks prior to screening were permitted to continue stable treatment. Corticosteroid doses were not to exceed the equivalent of 10 mg of prednisone per day.

Exclusion criteria included: active Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher infection within 30 days prior to screening, or during screening period; a serious infection requiring hospitalization or intravenous (IV) antibiotics within 8 weeks before screening; or recurrent or chronic infections.

Non-permitted drugs prior to investigational product initiation are listed in Section 6.5 of the protocol in Appendix 1.

Full inclusion and exclusion criteria are provided in Sections 4.1 and 4.2 of the protocol in Appendix 1.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: AMG 827 was administered SC at a dose of 70, 140, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10. The manufacturing batch numbers of AMG 827 administered in this study 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 12 weeks, with an end-of-study visit 4 weeks after the week 12 visit. The total duration of study for an individual subject was therefore up to 20 weeks.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: Subjects randomized to placebo received SC injections at day 1 and weeks 1, 2, 4, 6, 8, and 10. The manufacturing batch numbers for placebo were [redacted], and [redacted].

Study Endpoints

The primary efficacy endpoint was the ACR 50 response at week 12.

Secondary efficacy endpoints included:

- ACR 20 and 70 at week 12
- DAS28 score at week 12

The secondary pharmacokinetic endpoints for AMG 827 pharmacokinetic parameters included: maximum observed concentration (C_{max}) time to C_{max} (T_{max}) AUC_{tau} for weeks 8 to 10.

Safety endpoints included:

- 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

Exploratory endpoints are presented in Section 10.2.5 of the protocol (Appendix 1).

Analysis of the clinical disease activity index (CDAI) assessment at week 12 was added post hoc.

Statistical Methods: The goal of the primary statistical analysis was to evaluate the efficacy of AMG 827 compared with placebo as measured by the proportion of subjects achieving an ACR 50 response at week 12.

The primary endpoint, ACR 50 at week 12, and the key secondary endpoints, ACR 20 and 70 at week 12, were analyzed using a Cochran-Mantel-Haenszel test adjusting for sex. The

comparisons of distribution location parameters (for continuous variables) between treatments arms were compared based on the analysis of variance (ANOVA) or covariance (ANCOVA) models adjusting for sex.

ACR 50 at week 12 was compared between placebo and AMG 827 210 mg. All the primary and secondary efficacy endpoints, except for DAS28, were tested sequentially in a pre-specified order to control the overall family-wise type 1 error rate at 0.05 (2-sided). DAS28 was tested using a closed testing procedure with type 1 error rate of 0.025 (1-sided). To help establish a dose-response profile, a secondary analysis of between-dose comparisons was to be performed using DAS28 at week 12 within the step-down multiple testing framework.

Summary statistics of continuous variables included: n, mean, median, standard deviation, minimum, maximum, and 95% confidence interval (except for safety laboratory assessments). All summaries presenting frequencies and incidences included n, % and N, where N is the total number of subjects with recorded values in the corresponding arm.

For the subjects in the pharmacokinetic substudy, the AMG 827 pharmacokinetic parameters (such as C_{max}, T_{max}, and AUC_{tau}) were estimated using non-compartmental methods for data collected between weeks 8 and 10. Actual dosing and sampling times were used for all calculations. Descriptive statistics were provided by dose for each pharmacokinetic parameter. Graphs of serum AMG 827 concentration-time profiles for individual subjects, and the mean profiles for each dose were provided using the nominal time. For all other sparse pharmacokinetic samples, AMG 827 concentrations at each time point were summarized graphically by dose using the nominal time.

Subject incidence rates of all treatment-emergent adverse events were tabulated by system organ class, high-level term, and severity.

The efficacy and safety analyses were performed in 2 stages. At the first stage, after all subjects had either completed their week 12 visit or had completed the end-of-study (EOS) visit (week 16 or early termination), the study was unblinded and the analysis was performed based on all available data. At the second stage, final database lock took place after all subjects had completed their EOS visit. The analysis was updated and finalized at this stage.

Summary of Results:

Subject Disposition: 252 subjects were enrolled; 189 to AMG 827 and 63 to placebo. All 252 subjects randomized received investigational product. Two hundred forty-two subjects (183 [96.8%] AMG 827; 59 [93.7%] placebo) completed the study, which was defined as completing 16 weeks of study evaluations.

Efficacy Results: AMG 827 was not shown to be more efficacious than placebo, as demonstrated by the ACR 50 at week 12, with response rates of 15.9%, 15.9%, and 9.5% for AMG 827, 70, 140, and 210 mg Q2WK treatment groups, respectively, compared with 12.7% for placebo (p-values for comparison to placebo group were 0.598, 0.635, and 0.572, respectively). Adjusted p-values for ACR 20, 50, and 70 comparing all AMG 827 treatment groups with placebo were non-significant ($p > 0.05$) for any treatment group. The adjusted p-values for secondary endpoints (DAS28) comparing DAS28 in AMG 827 treatment groups with placebo at week 12 were all non-significant ($p > 0.025$).

Other Evaluations:

Pharmacodynamics:

[redacted]

Pharmacokinetics: After doses of 70 mg to 210 mg AMG 827, exposure increased with C_{max} and AUC_{tau} for the subjects in the pharmacokinetic substudy ranging from 3.02 to 17.9 µg/mL and 18.1 to 199 µg•day /mL, respectively. AMG 827 serum concentration-time profiles exhibited nonlinear pharmacokinetics. Exposure, as measured by C_{max} and AUC_{tau}, increased greater than dose proportionally across the dose range of 70 to 210 mg after multiple SC doses of AMG 827.

Patient-reported Outcome: PRO outcomes did not detect improvement. Medical Outcomes Short-Form-36 Questionnaire (SF-36) scores for both mental component and physical component showed no improvements from week 4 through week 12 for AMG 827 treatment groups and no differences between AMG 827 treatment groups and placebo. MOS Optimal Sleep scores in AMG 827 treatment groups showed some small improvements over time that were variable. The Patient Global Rating of Change showed improvement for all treatment groups including placebo, however, p-values comparing Patient Global Rating of Change for AMG 827 treatment groups with placebo were generally non-significant ($p > 0.05$) at all study timepoints.

Safety Results: Subject incidences of all adverse events, regardless of causality, ranged from 50.8% (placebo) to 63.5% (140 mg). Subject incidence of all treatment-related adverse events ranged from 12.7% (70 mg) to 22.2% (140 mg). Subject incidences of treatment-emergent grade 3 and above adverse events ranged from 3.2% (140 mg) to 6.3% (210 mg and placebo). These events were similar across treatment groups. The most common treatment-emergent adverse events (incidence rates) in all AMG 827 treatment groups combined and the placebo group were upper respiratory tract infection (6.3% AMG 827, 1.6% placebo), nasopharyngitis (5.8% AMG 827, 3.2% placebo), urinary tract infection (5.8% AMG 827, 1.6% placebo), and RA (5.8% AMG 827, 9.5% placebo).

Seven serious adverse events occurred during the study. One subject (70 mg) reported blepharitis. Three subjects in the 210 mg group reported 1 serious adverse event each: lumbar vertebral fracture, thrombosis, and a suicide attempt. One subject (140 mg) died of cardiopulmonary failure (not related to investigational product) approximately 1 week after her last dose of AMG 827. Two placebo subjects reported 1 serious adverse event each: tibia fracture and RA. None of the serious adverse events reported for AMG 827 or placebo subjects were assessed by the investigators as related to investigational product.

Five subjects (1 placebo and 4 AMG 827) had adverse events leading to withdrawal from investigational product administration. One placebo subject reported RA, and 4 subjects in the AMG 827 treatment groups reported 1 adverse event each: osteomyelitis (70 mg), upper respiratory tract infection (140 mg), pleurisy (210 mg), and laryngitis (210 mg). Three adverse events leading to discontinuation of investigational product were considered by the investigator to be related to investigational product: osteomyelitis, pleurisy, and laryngitis.

Events of interest for this study were neutropenia, infectious episodes, injection site reactions, and immunogenicity. One subject in the 70 mg group had a grade 2 shift (decrease) in both absolute and total neutrophil counts; neither laboratory result was reported as an adverse event. The subject was asymptomatic and the laboratory values returned to normal without intervention (they occurred at day 56 and normalized by day 64); AMG 827 treatment continued without interruption. An infectious adverse event was reported in 24.9% of AMG 827 subjects and 17.5% of placebo subjects. The most commonly reported infectious events were upper respiratory tract infection (12 [6.3%] AMG 827, 1 [1.6%] placebo), nasopharyngitis (11 [5.8%] AMG 827, 2 [3.2%] placebo) and urinary tract infection (11 [5.8%] AMG 827, 1 [1.6%] placebo). Grade 3 infectious adverse events were noted in 2 subjects: bronchitis (placebo), and osteomyelitis (70 mg). In addition, a grade 3 event of influenza-like illness was described in the system organ class of General Disorders and Administration Site Conditions (140 mg). Injection-site reactions were reported by 7 (3.7%) AMG 827 subjects and 6 (9.5%) placebo subjects; all injection site reactions were grade 1.

Of the 189 subjects treated with AMG 827, 4 (2.1%) tested positive for anti-AMG 827 binding antibodies, and all tested negative for the presence of neutralizing anti-AMG 827 antibodies. None of the placebo subjects tested positive for the presence of anti-AMG 827 binding antibodies. Of these 4 AMG 827 subjects, 3 did not experience any adverse events during the study; 1 of these subjects, (a 31-year old Hispanic female), reported several adverse events in various system organ classes (SOCs); the adverse event profile in this subject was broad and non-specific, as evidenced by the spread of adverse events across various SOCs. The broad distribution of adverse events across various SOCs did not allow for a meaningful analysis of any potential association between the antibody data and safety profile.

Conclusions: In summary, the study showed that short-term treatment with AMG 827 was well tolerated across a dose range of 70 to 210 mg in subjects with RA who had an inadequate response to methotrexate; however, AMG 827 was not effective for the treatment of RA compared with placebo in any AMG 827 treatment group evaluated and based on these data, further evaluation of AMG 827 as a treatment for RA does not appear to be warranted.