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 Multiple-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 827 in Subjects With Rheumatoid Arthritis

Investigator(s) and Study Center(s): This study was conducted at 11 sites; 7 in the United States (US), 2 in Canada, and 2 in Mexico. A list of investigators is provided in Appendix 4.

Publication(s): None

Study Period: The first subject was enrolled on 27 October 2008 and the last subject completed the study on 25 May 2010.

Development Phase: 1b/2a

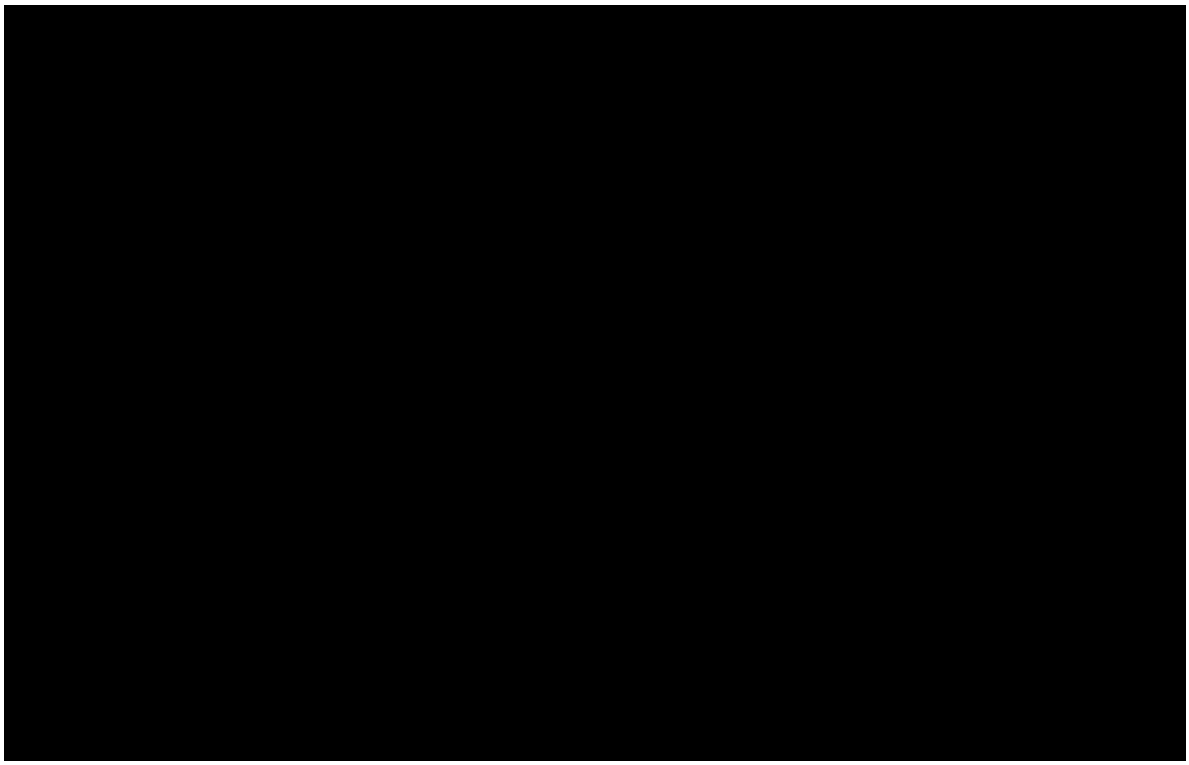
Introduction and Objectives: Interleukin-17A is an innate inflammatory cytokine linked to the pathogenesis of diverse autoimmune and inflammatory diseases, including rheumatoid arthritis (RA). The IL-17A receptor (IL-17R) is expressed ubiquitously, and hence most cells can potentially respond to this cytokine. AMG 827 is a fully human, immunoglobulin G_2 (IgG_2) monoclonal antibody that binds with high affinity (K_d = 239 pM) to human IL-17RA and blocks the biological activity of IL-17A, IL-17F, IL-17A/F heterodimers, and IL-25. Increased levels of IL-17A have been detected in the synovial fluid of patients with RA and furthermore, blockade of IL-17A signaling can inhibit osteoclast formation induced by culture media of RA synovial tissues. Children with juvenile inflammatory arthritis (JIA) have elevated numbers of IL-17A-positive T-cells in the inflamed joints. Interleukin-17A can directly stimulate synoviocyte production of inflammatory mediators including IL-6, granulocyte macrophage colony stimulating factor (GM-CSF) and prostaglandin E2 (PGE2). 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 [CTX-1]). Finally, results from early phase studies in RA have demonstrated clinical benefit of IL-17A blockade in RA subjects (Genovese et al, 2010; Hueber et al, 2010).

This was to have been a 2-part study. Part A (cohorts 1 to 3 and 5 to 6) was a phase 1b, multiple-dose, dose-escalation study and Part B (cohort 4) was to have been a phase 2 multiple-dose study with the dose and route of administration being determined from the results of Part A. An administrative decision was made to not conduct Part B of the study and instead a separate phase 2 multiple-dose study was conducted to evaluate the efficacy of AMG 827 in subjects with RA (Study 20090061). Information regarding the intended design of Part B is provided in the protocol in Appendix 1 and Part B information will not be presented in this study report.

The primary objective of Part A was to evaluate the safety and tolerability of AMG 827 following multiple dose subcutaneous (SC) and intravenous (IV) administration in subjects with RA.

The secondary objective of Part A was to characterize the pharmacokinetic profile of AMG 827 following multiple dose SC and IV administration in subjects with RA.

The exploratory objectives were as follows:



Methodology: This study was a multi-center, randomized, double-blind, placebo-controlled, multiple ascending dose study in subjects with RA. Subjects participated in only 1 part of the study. In Part A, subjects were randomized 6:2 to receive AMG 827 or placebo at 50, 140, or 210 mg SC every 2 weeks for a total of 6 doses (cohorts 1 to 3 , respectively) or AMG 827 or placebo at 420 or 700 mg IV every 4 weeks for a total of 2 doses (cohorts 5 and 6, respectively). For Cohorts 1 to 3 and 5, dose escalation occurred after the final subject in each cohort completed Day 15/Week 3 visit and, in addition, a minimum of 6 subjects in a cohort had been administered at least 3 doses of study drug. For Cohort 6 in Part A, dose escalation occurred after the final subject in Cohort 5 completed Day 15/ Week 3 visit and, in addition, a minimum of 6 subjects in Cohort 5 had been administered at least 2 IV infusions of study drug. The decision to dose escalate was based on the blinded review at the dose level review meeting (DLRM).

Number of Subjects Planned: 110

Number of Subjects Enrolled: 40 (30 AMG 827 and 10 placebo)

Sex: 6 men (15%); 34 women (85%)

Mean (SD) Age: 51.4 (9.7) years

Ethnicity (Race): White/Caucasian 18 subjects (45%); Black/African American 2 subjects (5%); Hispanic or Latino 19 subjects (48%); and Asian 1 subject (3%).

Diagnosis and Main Criteria for Eligibility: Men or women between the ages of 18 and 70 at the time of screening who had been diagnosed with RA according to American College of Rheumatology (ACR) criteria were eligible for participation in the study. Additionally, subjects had to have active RA defined as ≥ 6 swollen joints and ≥ 8 tender/ painful joints, at least 1 of the following: ESR ≥ 28 mm; CRP > 15 mg/L; or morning stiffness > 45 minutes; and duration of RA for at least 6 months. Subjects who were taking methotrexate (MTX) consecutively for ≥ 12 weeks and were on a stable dose of oral or SC MTX at 15 to 25 mg weekly for ≥ 4 weeks at day -1 were also eligible.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects in cohorts 1 to 3 received 6 SC injections of AMG 827 at 50, 140, or 210 mg. Subjects in cohorts 5 and 6 received 2 IV infusions of AMG 827 at 420 or 700 mg. Lot numbers used were [redacted]

Duration of Treatment: 10 weeks for cohorts 1 to 3 (6 SC doses every 2 weeks); 4 weeks for cohorts 5 and 6 (2 IV doses 4 weeks apart)

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

Subjects randomized to placebo in cohorts 1 to 3 received 6 SC injections and subjects randomized to placebo in cohorts 5 and 6 received 2 IV infusions. Lot numbers used were [redacted]

Study Endpoints

The primary endpoints of this study were subject incidence of treatment-emergent adverse event(s); 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.

The secondary endpoints were the pharmacokinetic parameters ($AUC_{0\text{-}t}$, C_{max}, and $T_{max)}$ for AMG 827 after multiple SC or IV dose administration. Other pharmacokinetic parameters (ie, accumulation ratio) were derived based on the pharmacokinetic data obtained.

[redacted]

Statistical Methods: Descriptive statistics are provided for selected demographic, safety, pharmacokinetic, pharmacodynamic, and biomarker data by dose cohort. Descriptive statistics on continuous data include means, medians, standard deviations, and ranges, while categorical data are summarized using frequency counts and percentages. Graphical summaries of the data are also presented.

Summary statistics for bdACR Hybrid, ACR20/50/70, change in DAS28, and ACR individual components are provided. No statistical inferences were made.

All treatment-emergent adverse events were tabulated by system organ class and preferred term. Tables and narratives of serious and significant treatment-emergent adverse events, including early withdrawals due to adverse events, are provided.

Summary of Results:

Subject Disposition: Of the 40 subjects who were enrolled in the study, all subjects (100%) received at least 1 dose of investigational product and were analyzed for safety; 39 subjects (98%) completed the study (1 subject [redacted] who received IV placebo discontinued from the study on day 85 due to an adverse event [disease activity that warranted systemic intervention]).

Efficacy Results: [redacted]

The following parameters showed improvement from baseline for both AMG 827 and placebo: ACR20, ACR50, change in DAS28, and ACR individual components. At any time point during the study, an ACR20 was achieved by 53.3% of AMG 827 subjects and 60.0% of placebo subjects, an ACR50 was achieved by 13.3% of AMG 827 subjects and 20% of placebo subjects, and an ACR70 level was achieved by 10.0% of placebo subjects; no subject who received AMG 827 achieved ACR 70. On day 85 (week 13) ACR20 was achieved by 11 (36.7%) of 30 subjects receiving AMG 827 and 2 (22.0%) of 9 subjects receiving placebo. Mean DAS28 scores decreased from 5.58 at baseline to 4.76 at day 85 (week 13) for AMG 827 subjects and decreased from 5.54 at baseline to 4.39 at day 85 for placebo subjects. For all post-baseline visits, mean changes from baseline in DAS28 reflected these modest decreases with the minimum of -0.81 at day 85 (week 13) for AMG 827 subjects and -1.34 at day 57 for placebo subjects. Mean bdACR hybrid score was 11.66 at day 15, and further increased to 23.77 at day 85 (week 13) for AMG 827 subjects. For placebo subjects the mean bdACR hybrid score was 17.50 at day 15 but decreased to 13.76 at day 85. For both AMG 827 and placebo groups, bdACR hybrid showed improvement from baseline in terms of a composite score encompassing all 7 ACR core set components. Mean AUC bdACR hybrid was higher for placebo than AMG 827 over time, with 1811.98 for placebo and 1270.93 for AMG 827 on day 85. Conclusions about efficacy cannot be reached given the study design, although limited clinical responses and no clear dose-response relationship was observed in RA subjects receiving AMG 827.

Pharmacokinetic Results: AMG 827 exhibited nonlinear pharmacokinetics in subjects with RA. Serum AMG 827 exposure, as measured by C_{max} and $AUC_{0\text{-}t}$, increased greater than dose proportionally across the dose range of 50 to 210 mg after a single or multiple SC doses of AMG 827. Accumulation (as measured by $AUC_{0\text{-}t,\ last\ dose}/AUC_{0\text{-}t,\ first\ dose}$) was less than 2-fold following multiple-dose SC administration of 140 or 210 mg AMG 827 and IV administration of 420 and 700 mg AMG 827. After SC administration, the median time to C_{max} (t_{max}) was approximately 2 to 4 days following either a single SC dose or 6 SC doses of AMG 827 at 50, 140, or 210 mg AMG 827.

Pharmacodynamic Results: Treatment with AMG 827 resulted in IL-17 receptor occupancy by AMG 827 on circulating granulocytes, lymphocytes, and monocytes. There was a dose-dependent trend in increased magnitude of mean receptor occupancy and clear evidence of dose-dependent prolongation of the duration of high receptor occupancy by AMG 827. Evidence for dose dependent directional changes in the percent of granulocytes, lymphocytes, monocytes, T cells, B cells, and NK cells was not observed.

Safety Results: Forty subjects were included in the safety analysis set (10 placebo and 30 AMG 827). Treatment-emergent adverse events were reported by 7 (70.0%) of 10 placebo subjects and 22 (77.0%) of 30 AMG 827 subjects. Headaches were the most common adverse event and were observed in 40% of placebo subjects and 27% of AMG 827 subjects.

Treatment-related adverse events were reported by 3 (30.0%) of 10 placebo subjects and 7 (23.0%) of 30 AMG 827 subjects. The most common treatment-related adverse event was headache (20%) for placebo subjects and leukocytosis (7%) for AMG 827 subjects.

Three serious adverse events (complicated migraine [placebo]; gastroesophageal reflux disease and non-cardiac chest pain [AMG 827, 420 mg IV]) occurred in 2 subjects during the study; none were considered by the investigator related to investigational product.

One subject received only 1 of 2 doses of AMG 827 (700 mg IV) due to an adverse event of oropharyngeal candidiasis that was considered by the investigator not to be drug-related. One placebo subject discontinued the study early because of an RA flare. There were 3 reports of treatment-related infections; 1 cellulitis (placebo), 1 herpes zoster (AMG 827, 420 mg IV) and 1 upper respiratory tract infection (AMG 827, 140 mg SC). No deaths occurred during the study.

Antibody Results: Serum samples collected from 40 subjects (30 AMG 827, 10 placebo) were tested in the anti-AMG 827 immunoassay for the presence of anti-AMG 827 binding antibodies. Two (6.7%) of the AMG 827-treated subjects tested positive for anti-AMG 827 binding antibodies, with both positives observed only on day 127. Both binding antibody samples 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.

Conclusions:

In conclusion, this small ascending dose phase 1b study demonstrates that multiple SC and IV doses of AMG 827 were tolerated in this study population with active RA.