2. SYNOPSIS

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

Name of Finished Product: Brodalumab

Name of Active Ingredient: AMG 827

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 827 in Subjects With Moderate to Severe Crohn's Disease

Investigator(s) and Study Center(s): This study was conducted at 39 centers in Australia, Belgium, Canada, Spain, France, Netherlands, Poland, and the United States (US); centers and principal investigators are listed in Appendix 2.

Publication(s): Targan S, Feagan B, Vermeire S, et al. A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 827 in Subjects With Moderate to Severe Crohn's Disease, Poster number Mo2083, presented at Digestive Disease Week® (DDW®), 2012; San Diego, CA.

Study Period: 09 November 2010 (first subject enrolled) to 15 October 2011 (last subject visit). The study was terminated early on 25 August 2011.

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).

In preclinical animal models of intestinal inflammation, the absence of IL-17A (Ito et al, 2008) or IL-17F (Yang et al, 2008) or IL-17R (Zhang et al, 2006) appeared to be protective in some murine models of chemically-induced colitis. Antibody blockade of IL-17A has also been demonstrated to abrogate inflammatory bowel disease (IBD) in the CD45RBhi T cell transfer model of intestinal inflammation (Yen et al, 2006; Leppkes et al, 2009). Collectively, these data suggest that blocking IL-17A and IL-17F may have therapeutic potential in IBD.

In other preclinical animal model studies, however, the data have been somewhat conflicting. For example, dextran sulphate sodium (DSS) studies by Yang et al (2008) report exacerbated disease in the absence of IL-17A, contrasting with the results from Ito et al, mentioned above. Exacerbation of disease has also been reported for IL-17A antibody blockade in DSS colitis by Ogawa et al (2004). Finally, the transfer of IL-17A-/- or IL-17R-/- T cells in the CD45RBhi T cell transfer model of colitis did not attenuate, and may even have accelerated, disease (Izcue et al, 2008; O'Connor et al, 2009).

The variable outcomes of these preclinical studies may have arisen as a result of (i) lack of neutralization of all 3 ligands for the IL-17R in the case of the antibody neutralization studies or (ii) dysregulation of the IL-17R ligands, IL-17A, IL-17F or IL-25, as a result of compensation for congenital cytokine/cytokine receptor deficiency in the gene knockout mouse studies.

Some studies in humans have indicated a role for IL-17A in Crohn's disease. For example, Fujino et al (2003) demonstrated an increase in mucosal IL-17A-expressing cells in active Crohn's disease. Ileal biopsy samples from subjects with active or inactive Crohn's disease have shown elevated IL-17A expression (mRNA) compared with samples from control subjects

(Holtta et al, 2008). Elevated IL-17A positive T-cells (CD8 positive and CD4 positive) have been seen in subjects with active Crohn's disease compared with controls (Holtta et al, 2008). More recently Rovedatti et al (2009) have shown an increase in spontaneous IL-17A production from cultured colonic biopsies from inflamed gut tissue compared with un-inflamed tissue. McGovern et al (2009) have also shown an association of the IL-17A and IL-17RA genes with Crohn's disease, and interactions with the IL-23R gene. Much less is known about the regulation of IL-17F and IL-25 in human IBD, including Crohn's disease.

Despite some conflicting preclinical IBD data, it is evident that IL-17A plays an important role in driving the biology of proinflammatory immune responses (Abraham and Cho, 2009; Andoh et al, 2008). There is also strong evidence that IL-17A is dysregulated in the gut tissues of patients with active intestinal inflammation. Therefore, a therapeutic agent with the ability to block the IL-17 pathway posed an attractive option for clinical research in Crohn's disease at the time this study was initiated.

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 Crohn's Disease Activity Index (CDAI) remission (≤ 150) at week 6.

The secondary objectives were to evaluate the efficacy of AMG 827 as measured by the proportion of subjects with a CDAI response (reduction from baseline of ≥ 100) at week 6; to evaluate improvement from baseline in CDAI at week 6; to evaluate the short term safety profile of AMG 827 in subjects with Crohn's disease; to characterize the pharmacokinetics of AMG 827 in subjects with Crohn's disease.

Methodology:

This was a randomized, double-blind, placebo-controlled study to evaluate the efficacy of AMG 827 (at intravenous [IV] doses of 210, 350, or 700 mg) compared with placebo as measured by the proportion of subjects in remission (CDAI ≤ 150) at week 6. After completing all screening assessments and meeting all eligibility criteria, subjects were randomized in a 1:1:1:1 ratio to receive AMG 827 or placebo at baseline (day 1) and week 4. Subjects were to be followed out to week 12 for assessments of safety and sustainability of response.

Approximately 15 subjects per treatment arm (approximately 60 subjects, total) were to be enrolled in a pharmacokinetic substudy where the subjects were to visit the clinic for additional pharmacokinetic sampling. Participation in the pharmacokinetic substudy was optional. In order to assure treatment balance in the pharmacokinetic substudy, randomization was to be stratified by participation in the pharmacokinetic substudy.

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

An independent data review team (DRT) reviewed all safety data throughout the study. The members of the data review team were internal to Amgen but not directly involved in the conduct of the study. This study was terminated early following the recommendation of the independent DRT and was based on the observation that there were a disproportionate number of cases of Crohn's disease worsening in the active treatment groups. The clinical study report is being written in an abbreviated study report format because the study was terminated early and AMG 827 will not be developed further in Crohn's disease.

Diagnosis and Main Criteria for Eligibility: Subjects must have had a diagnosis of Crohn's disease ≥ 6 months, with moderate to severe disease activity (based on a CDAI score ≥ 250 and ≤ 450) at time of enrollment and evidence of active inflammation (by at least one of the following: endoscopic evidence of inflammation, C-reactive protein (CRP) > upper limit of normal [ULN] by central laboratory, or fecal calprotectin assay indicative of active inflammation [> ULN by central laboratory]). Subjects were allowed to continue on stable doses of protocol-specified medications

to treat their Crohn's disease. Subjects had to complete appropriate washout periods for certain drugs, be free of infections and significant concurrent medical conditions at study entry as described in the protocol (Appendix 1), and meet regional recommendations for immunizations, eg, US Centers for Disease Control and Prevention (CDC) recommendations for subjects enrolled in the US.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Subjects received IV AMG 827 at 210, 350, or 700 mg, or a matching placebo, at day 1 and week 4 (Q4W). Investigational product was administered as an IV infusion over at least 30 minutes. AMG 827 manufacturing batch numbers used were: [redacted]

Duration of Treatment: 4 weeks

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: placebo was administered as a single IV infusion over at least 30 minutes on day 1 and week 4. Placebo manufacturing batch numbers used were: [redacted] and [redacted]

Study Endpoints

The primary efficacy endpoint was remission at week 6, as defined by a CDAI score of ≤ 150.

The secondary efficacy endpoints were: CDAI response at week 6, as defined by a reduction from baseline of ≥ 100, and change from baseline in CDAI at week 6.

The secondary safety endpoints were: adverse events and infectious adverse events; serious adverse events and serious infectious events; severity of infusion (site) reactions; and significant changes in laboratory values, and vital signs.

The secondary pharmacokinetic endpoints were: pharmacokinetic parameters including maximum observed drug concentration during a dosing interval (C_{max}), time to reach C_{max} (T_{max}), and area under the drug concentration-time curve from time zero to time) AUC_{0-t} for the time periods between day 1 and week 4 and between weeks 4 and 8.

Statistical Methods:

Summary statistics were provided for continuous endpoints including: n, mean, median, standard deviations, standard error, first and third quartiles, minimum and maximum, and 95% confidence intervals of the means (except safety laboratory analyses). For categorical endpoints, summaries of the number and percentage of subjects falling into each category were provided.

The comparisons of proportions (for dichotomous variables) between treatment arms were performed using Chi-square tests. The linear trend test, based on logistic regression model was used to detect trend across the treatment arms. For comparisons of distributions of location parameters (for continuous variables) between treatment arms, analyses of covariance (ANCOVA) model were performed.

Missing data for dichotomous endpoints were analyzed using the non-responder imputation method. Missing CDAI scores were imputed using baseline values. Sensitivity analyses were performed on the data as observed, and were also conducted by using the last observation carried forward (LOCF) approach.

Summary of Results:

Number of Subjects Planned: 216

Number of Subjects Enrolled: 130

Sex: Placebo: 17 (53.1%) women; 15 (46.9%) men
AMG 827: 61 (62.2%) women; 37 (37.8%) men

Age: Placebo: mean (SD) 36.8 (13.0) years (range: 19 to 58 years)
AMG 827: mean (SD) 35.5 (11.0) years (range: 18 to 63 years)

Ethnicity (Race): Placebo: white: 24 (75.0%); other: 1 (3.1%); unknown: 7 (21.9%)
AMG 827: white: 76 (77.6%); black: 1 (1.0%); Asian: 1 (1.0%); other: 3 (3.1%); unknown: 17 (17.3%)

Subject Disposition: 130 subjects were randomized; 98 to AMG 827 and 32 to placebo. Of those randomized, 96 received AMG 827 and 32 received placebo. Eighty-four subjects (56 [57.1%] AMG 827; 28 [87.5%] placebo) completed the study, which was defined as completing 12 weeks of study evaluations.

Efficacy Results: AMG 827 was not shown to be more efficacious than placebo, as demonstrated by the proportion of subjects achieving CDAI remission at week 6. The remission rate (using non-responder imputation [NRI]) at week 6 was 3.1%, 15.2%, and 9.1% for 210-, 350-, and 700-mg AMG 827 groups respectively, compared with 3.1% for placebo (p-values for comparison with placebo group were 0.8983, 0.1030, and 0.3718, respectively). The nominal p-values for secondary endpoints, CDAI response and change from baseline in CDAI at week 6 comparing AMG 827 treatment groups with placebo were all > 0.05.

Efficacy results for the subset of 33 subjects (30 AMG 827, 3 placebo) with worsening of Crohn's disease were generally similar to the efficacy results for the overall study population with the following exception: an increase in the mean (SD) CDAI change from baseline was observed at week 6 in the 210-, 350- and 700-mg groups (56.7 [96.2], 17.5 [95.1] and 74.8 [75.1], respectively) compared with placebo (-36.7 [43.1]) and at week 8 in the 350- and 700-mg groups (24.5 [59.7] and 31.3 [60.6], respectively) compared with placebo (-47.1 [19.4]) consistent with worsening of Crohn's disease.

Other Evaluations:

Pharmacodynamics: Based on the results of the study, a decision was made to defer the exploratory biomarker analysis at this time.

Pharmacokinetics: The pharmacokinetics of AMG 827 was characterized following IV infusion Q4W of AMG 827, 210, 350, and 700 mg in subjects with moderate to severe Crohn's disease. The mean exposure (AUC_{0-28}) of AMG 827 after IV administration on day 1 (weeks 1 to 4) was similar to the exposure observed in weeks 5 to end of study, suggesting minimal accumulation from the first to second dose of AMG 827 in subjects with Crohn's disease.

Patient-reported Outcome: Based on the lack of efficacy and the adverse safety results of the study, analyses of patient-reported outcomes (PRO) were not done.

Safety Results: Subject incidence of all treatment-emergent adverse events regardless of causality, was 81.3% AMG 827 and 78.1% placebo. The most common treatment-emergent adverse events in all AMG 827 groups combined and placebo were Crohn's disease (25.0% AMG 827, 6.3% placebo) and pyrexia (12.5% AMG 827, 12.5% placebo). Subject incidence of all treatment-related, treatment-emergent adverse events was 50.0% in AMG 827 and 31.3% in placebo groups. The most common treatment-related, treatment-emergent adverse events were Crohn's disease (10.4% AMG 827; 0% placebo), and pyrexia (5.2% AMG 827; 3.1% placebo). Subject incidence of treatment-emergent grade 3 and above adverse events was

23 (24%) AMG 827 subjects and 5 (15.6%) placebo subjects. The most common treatment-emergent grade 3 and above adverse events were Crohn's disease (17.7% AMG 827; 6.3% placebo).

Twenty-two subjects (20 [20.8%] AMG 827, 2 [6.3%] placebo) experienced 37 serious adverse events, and the higher rate in the AMG 827 groups was largely due to Crohn's disease. The system organ class of gastrointestinal disorders had the highest subject incidence of serious adverse events (19 [19.8%] AMG 827, 1 [3.1%] placebo). The most frequently reported serious adverse event (preferred term) was Crohn's disease (14 [14.6%] AMG 827, 1 [3.1%] placebo). Twelve (12.5%) AMG 827 subjects (0 placebo subjects) experienced 17 serious adverse events considered related to investigational product including 8 events of Crohn's disease, 2 events each of abdominal pain and diarrhea, 1 event each of anal abscess, pneumonia, fatigue, fistula, and chronic obstructive pulmonary disease. In addition, 3 subjects experienced 4 serious adverse events considered related to investigational product that were not included in the study summary tables or listings due to the date of onset being either before administration of AMG 827 (Crohn's disease, initially reported 3 days before AMG 827 administration), or after termination from the study (increased ALT, 9 days post-termination; large intestine perforation, 51 days post-termination; and systemic inflammatory response, 3 days post-termination).

Ten subjects (10 AMG 827, 0 placebo) experienced adverse events leading to withdrawal from the study; 4 subjects reported adverse events leading to discontinuation from study that were considered by the investigator to be related to investigational product. Ten subjects (9 AMG 827, 1 placebo) experienced 13 adverse events leading to withdrawal from investigational product administration: 5 subjects experienced adverse events leading to discontinuation of investigational product that were considered by the investigator to be related to investigational product.

Events of interest were neutropenia, infectious episodes, infusion reactions, and immunogenicity; worsening of Crohn's disease was identified as an event of interest based on the independent DRT findings. No adverse events of neutropenia were reported during the study. Infectious adverse events were reported for 34 (35.4%) AMG 827 subjects and 11 (34.4%) placebo subjects. Four (4.2%) AMG 827 subjects and 0 (0%) placebo subjects experienced an infusion reaction event; all infusion reactions were grade 1. Forty-one (42.7%) AMG 827 subjects and 8 (25.0%) placebo subjects experienced an adverse event associated with worsening of Crohn's disease. Hypersensitivity reactions were reported by 16 (16.7%) AMG 827 subjects and 7 (21.9%) placebo subjects.

In the subset of subjects with worsening of Crohn's disease (30 AMG 827 subjects, 3 placebo subjects), subject incidence of all treatment-emergent-adverse events was 29 (96.7%) in AMG 827 and 3 (100.0%) in placebo groups. The most common treatment-emergent adverse event (incidence rate) in all AMG 827 groups combined and placebo group was Crohn's disease (80.0% AMG 827, 66.7% placebo). Subject incidences of all treatment-related treatment-emergent adverse events were 17 (56.7%) AMG 827 subjects, 2 (66.7%) placebo subjects. Subject incidences of treatment-emergent grade 3 and above adverse events were 17 (56.7%) in AMG 827 and 2 (66.7%) in placebo groups. Sixteen subjects (15 AMG 827, 1 placebo) reported serious adverse events; 9 AMG 827 subjects reported serious adverse events considered related to investigational product.

In the same subset of subjects with worsening of Crohn's disease, 10 AMG 827 and no placebo subjects had adverse events leading to withdrawal from study; 9 AMG 827 and no placebo subjects had adverse events leading to withdrawal from investigational product administration. No adverse events of neutropenia or infusion reactions were reported. Infectious adverse events were reported in 10 (33.3%) AMG 827 subjects and 2 (66.7%) placebo subjects.

No subjects in the study tested positive for anti-AMG 827 binding antibodies.

Conclusions: In summary, AMG 827 was not shown to be effective for the treatment of Crohn's disease when compared with placebo. Treatment with AMG 827 showed an imbalance between the placebo and AMG 827-treated groups with regard to worsening of Crohn's disease in a moderate to severe active Crohn's disease population, with a disproportionate number of cases in the active treatment groups. No additional safety risks beyond worsening of Crohn's disease were identified and no new cases of neutropenia were reported. The benefit:risk assessment clearly showed a new identified risk of worsening Crohn's disease for subjects with moderate to severe Crohn's disease resulting in the termination of this clinical study and Amgen's clinical program in subjects with Crohn's disease.