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, Multiple-dose Study with an Open Label Extension to Evaluate the Safety and Efficacy of AMG 827 in Subjects with Psoriatic Arthritis

Investigator(s) and Study Center(s): This study was conducted at 29 centers in the United States and Canada; centers and principal investigators are listed in Appendix 4.

Publication(s): None.

Study Period: 17 October 2011 (date first subject enrolled) to 14 September 2012 (data cutoff date)

Development Phase: Phase 2

Objectives:

The primary objective of the study was to evaluate the efficacy of AMG 827 in psoriatic arthritis as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 20% response at week 12.

The secondary objectives of the study were:

- To evaluate the effect of AMG 827 on the following:
  - ACR_{50} at week 12
  - ACR_{70} at week 12
  - components of ACR at week 12
  - clinical disease activity index (CDAI) at week 12
  - disease activity score with a 28 joint count (DAS 28) at week 12
  - dactylitis and enthesitis at week 12
- To characterize the pharmacokinetics of AMG 827 in subjects with psoriatic arthritis
- To evaluate the safety of AMG 827 in psoriatic arthritis with regard to the following:
  - adverse events
  - laboratory assessments
  - vital signs
  - antibodies to AMG 827

Exploratory objectives are listed in Protocol Section 1.4, Appendix 1.

Methodology:

This report summarizes the results of the primary analysis of efficacy for the double-blind phase of Study 20101227 (up to week 12). Adverse events and serious adverse events reported after week 12 and before the data cutoff (14 September 2012) for individual subjects are also included in the listings in Appendix 19. Narratives for all serious adverse events that occurred up to the data cutoff are presented in Appendix 11. At the time of the data cutoff 146 subjects were still ongoing and the longest time on study was 44 weeks.

This study began with a 12-week, randomized, double-blind, placebo-controlled phase. Subjects were randomized 1:1:1 to subcutaneous (SC) doses of AMG 827 (140 or 280 mg) or placebo every other week (Q2W) with 1 additional dose at week 1. Randomization was stratified by total body weight and by prior biologic use.

At the week 12 visit, subjects could enter an open-label extension period and receive 280 mg AMG 827 Q2W for the remainder of the study. Original treatment assignments remained blinded

until all subjects reached the week 12 visit. The entire study will be 264 weeks (approximately 5 years) in duration.

For 41 subjects, samples at additional timepoints were collected for pharmacokinetic analysis as a substudy, according to the schedule in Protocol Appendix A1, Appendix 1.

The primary endpoint was obtained at week 12. Safety of study participation was evaluated on an ongoing basis through regular review of safety data by an independent Data Review Team (DRT) during the blinded phase of the study.

Number of Subjects Planned: 156

Number of Subjects Enrolled: 168

Diagnosis and Main Criteria for Eligibility: The study enrolled men and women between 18 and 75 years of age with a diagnosis of psoriatic arthritis by the Classification of Psoriatic Arthritis criteria (CASPAR), with ≥ 3 tender and ≥ 3 swollen joints. For subjects using methotrexate or leflunomide, they must have been treated for ≥ 3months, with a stable dose (not to exceed 25 mg methotrexate per week or 20 mg leflunomide per day) for ≥ 4 weeks prior to initiation of investigational product and expected to remain stable for the next 24 weeks. For subjects using corticosteroids (not to exceed 10 mg per day) or nonsteroidal anti-inflammatory drugs (NSAIDs) they must have been on a stable dose for ≥ 4 weeks prior to initiation of investigational product and expected to remain stable for the next 24 weeks. All subjects must have had a negative tuberculosis test (or prophylaxis). Subjects who had prior anti-tumor necrosis factor (TNF) therapy within 2 months of investigational product initiation, anti-IL12/IL23 drug therapy within 3 months, or any prior use of rituximab or anti-IL-17 therapy including AMG 827 were excluded from participation.

For a full list of eligibility criteria, please refer to Protocol Section 4.1 and Section 4.2, Appendix 1.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects received AMG 827 at 140 or 280 mg by SC injection, at day 1, weeks 1, 2, 4, 6, 8, and 10. At week 12, both active treatment groups received AMG 827, 280 mg Q2W and will do so for the duration of the study. These subjects also received placebo injections at week 13 in order to maintain the blind to original treatment group. At weeks 12, 13, and 14, placebo subjects received AMG 827 280 mg and are receiving AMG 827 at 280 mg Q2W for the duration of the study. AMG 827 manufacturing batch numbers used were: [redacted], [redacted]

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Subjects in the control group received placebo at day 1, and weeks 1, 2, 4, 6, 8, and 10. The placebo manufacturing batch number used was: [redacted]

Duration of Treatment: Treatment duration for the double-blind phase was 10 weeks; efficacy was assessed at week 12. At the week 12 visit, all subjects entered an open-label extension and are receiving AMG 827, 280 mg Q2W for the remainder of the study (a total of 264 weeks or approximately 5 years).

Study Endpoints:

The primary efficacy endpoint was the ACR_{20} response at week 12.

The secondary efficacy endpoints were:

- ACR_{50} at week 12
- ACR_{70} at week 12
- components of ACR at week 12
- CDAI at week 12
- CDAI change from baseline at week 12
- DAS 28 at week 12
- DAS 28 change from baseline at week 12

- dactylitis change from baseline at week 12
- enthesitis change from baseline at week 12

Secondary pharmacokinetic endpoints included maximum observed drug concentration during a dosing interval (C_{max}), time to C_{max} (T_{max}), and area under the curve from time zero to time of last quantifiable concentration within the dosing interval (AUC_{0-t}) for data collected between weeks 10 and 12.

The safety endpoints were adverse events, events of interest, clinical laboratory assessments, vital signs, and anti-AMG 827 antibodies.

Other endpoints are listed in Protocol Section 10.1.5, Appendix 1.

Statistical Methods: The primary analysis was done at week 12, and an interim analysis will occur after all subjects complete week 24. The primary endpoint, ACR_{20} response at week 12, was tested using a stratified Cochran Mantel Haenszel (CMH) test between the high-dose treatment group and placebo group (stratified by baseline total body weight [≤ 100 kg, > 100 kg]; and prior biologic use [yes/no]). Hypothesis testing followed a hierarchical approach. Since the high-dose comparison was significant; the low dose was compared with placebo; since this comparison was significant, the high-dose treatment group was compared with the low-dose group. This sequential testing procedure preserved the family-wise 2-sided type one error rate at 0.05.

For secondary and exploratory endpoints, analysis of covariance (ANCOVA) model with stratification variables and baseline value as covariates was used for the continuous endpoints, and the Quade test was used for continuous endpoints that were not normally distributed. The stratified CMH test was used to analyze categorical endpoints.

Missing data for the primary and secondary dichotomous endpoints was analyzed with a non-responder imputation (NRI) method. Missing data for continuous measurements was imputed using the last observation carried forward (LOCF) approach.

All summary statistics of continuous variables included: n, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence interval (except for safety laboratory assessment). For categorical variables, summaries presenting frequencies and incidences included n, %, and N, where N was the number of subjects randomized to the corresponding arm.

No formal testing was performed on the safety data.

Summary of Results:

Subject Disposition: A total of 199 subjects were screened and 168 subjects were enrolled, 113 to AMG 827 and 55 to placebo. One subject in the AMG 827, 140 mg Q2W group was randomized in error and did not receive any investigational product. Therefore 167 subjects received at least 1 dose of investigational product (112 AMG 827 and 55 placebo); 159 subjects (106 [93.8%] AMG 827 and 53 [96.4%] placebo) completed the double-blind phase of the study.

Baseline Demographics:

Sex: 61 (36.3%) men, 107 (63.7%) women

Age: mean (SD): 52.2 (11.6) years; range 22 to 74 years

Ethnicity/Race: white: 157 (93.5%); American Indian/Alaska Native: 3 (1.8%); Asian: 3 (1.8%); black 2 (1.2%); Native Hawaiian/Other/Pacific Islander: 2 (1.2%); other: 1 (0.6%)

Efficacy Results: AMG 827 was shown to be more efficacious than placebo for the primary endpoint, as demonstrated by the ACR_{20} response at week 12 using NRI. ACR_{20} responses at week 12 were analyzed using a sequential testing procedure to preserve the family-wise type 1 error at 0.05 for all comparisons. The ACR_{20} response rate using NRI at week 12 (full analysis set) in the 280 mg group was 22 of 56 (39.3%) compared with 10 of 55 (18.2%) for placebo, a difference of 21.1% (adjusted p = 0.0156). The ACR_{20} response rate in the 140 mg group was 21 of 57 (36.8%) compared with 10 of 55 (18.2%) for placebo, a difference of 18.7% (adjusted

p = 0.0314). The difference in response rates between 280 mg and 140 mg was 2.4% (adjusted p = 0.8017).

The assessment of efficacy of AMG 827 over time (ACR_{20}) showed nominal p-values starting at week 4 (p = 0.0251) in the 140 mg group and (p = 0.0219) in the 280 mg group that persisted at p < 0.05 through week 12 in both the 140 mg (p = 0 0266) and the 280 mg (p = 0.0090) groups, compared with placebo.

All p-values in the non-primary analyses were nominal without adjustment for multiplicity.

More subjects achieved ACR_{50} response at week 12 in both the 140 mg (14.0%) (p = 0.0506) and the 280 mg (14.3%) (p = 0.0469) groups compared with the placebo (3.6%) group. The number of subjects who achieved ACR_{70} response was small and p-values for ACR_{70} response were > 0.05 in both AMG 827 treatment groups compared with placebo.

Individual ACR components tender/painful joint counts, swollen joint counts, subject global assessment of disease activity, and physician global assessment of disease activity, showed improvement at week 12; all p-values for percent change from baseline at week 12 were < 0.05 in both the 140 and 280 mg groups compared with placebo. Other ACR components: subject global assessment of joint pain, health assessment questionnaire – disability index (HAQ-DI), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) showed numerical trends toward improvement at week 12; however, p-values were all > 0.05 for both AMG 827groups compared with placebo with the exception of CRP in the 280 mg (p = 0.0204) group.

Other secondary endpoints, CDAI and DAS28 showed improvement at week 12; p-values for CDAI and DAS28 score change from baseline were all < 0.05 for both AMG 827 groups compared with placebo. Although there were numerical trends consistent with efficacy, p-values for score change from baseline at week 12 were > 0.05 for dactylitis and enthesitis in both AMG 827 treatment groups compared with placebo.

Although the study was not adequately powered to formally differentiate between the 2 tested doses of AMG 827, numerical-trends favoring the 280 mg group for a number of endpoints were observed.

Pharmacokinetics Results:

AMG 827 exposure, as assessed by pharmacokinetic concentration-time profiles, indicated nonlinear pharmacokinetics over the AMG 827 dose levels of 140 and 280 mg. For the 2-fold increase between the 140 and 280 mg doses, serum AMG 827 exposure increased greater than dose proportionally, with C_{max} and AUC_{0-t} increasing approximately 2.5- and 3-fold, respectively For both dose levels, average predose mean concentration values were similar after the second AMG 827 dose following the switch from a once weekly to an every-other-week regimen (week 6) indicative of the attainment of steady state. There was a significant relationship between total body weight and the pharmacokinetics of AMG 827, which was well-described by the population pharmacokinetic model.

The semi-mechanistic model predicted that administration of 140 mg would provide near maximal week 12 ACR_{20} response, whereas 210 mg doses would be on the response plateau. Graphical analysis showed that weight, did not significantly impact the pharmacodynamics.

Patient-reported Outcomes Results: Bath ankylosing spondylitis disease activity index (BASDAI) was summarized for the full analysis set and for a subset of subjects with baseline BASDAI score ≥ 4; BASDAI scores for both the full analysis set and the subset of subjects (baseline BASDAI score ≥ 4) showed similar improvement at week 12 in the 280 mg AMG 827 treatment group. Improvements were seen in Psoriasis Symptoms Inventory total weekly scores for the full analysis set and for the subset of subjects with baseline body surface area (BSA) involvement ≥ 3% (p < 0.01) beginning at week 2 and continuing through week 12 for both AMG 827 treatment groups compared with placebo. Improvements were also seen for all 8 individual items in the Psoriasis Symptoms Inventory (p < 0.05) beginning at week 4 and continuing through week 12 for both AMG 827 groups compared with placebo. Medical outcomes short form–36 (SF-36) scores for physical components showed improvement at week 12 in the 280 mg group (p = 0.0370).

Safety Results: This report summarizes safety data for the double-blind phase of the study (up to week 12). Adverse events reported after week 12 and up to the data cutoff (14 September 2012) for individual subjects are also included in the listings in Appendix 19. Narratives for all serious adverse events that occurred up to the data cutoff date are presented in Appendix 11. Exposure adjusted adverse events are summarized to the data cutoff.

During the double-blind phase of the study, 88 (78.6%) AMG 827 subjects and 43 (78.2%) placebo subjects received all 7 doses of investigational product and the mean (SD) duration of exposure to AMG 827 was 81.3 (13.2) days.

During the double-blind phase of the study, serious adverse events were reported by 4 subjects (3 AMG 827, 1 placebo):

- Placebo: cellulitis (left knee), grade 3, (No. [redacted])
- 140 mg: abdominal pain, grade 2, (No. [redacted])
- 280 mg: cholecystitis, grade 3, (No. [redacted]), and
  cellulitis (left upper chest), grade 3, (considered related) (No. [redacted])

An additional 4 subjects experienced 6 serious adverse events after entering into the open-label extension for this study, but before the data cutoff for this report. A 5th subject experienced a serious adverse event during the open-label extension of the study but after the cutoff date and is included in this report for completeness:

- coronary artery disease (worsening), grade 3 (No. [redacted] [140 mg, double-blind phase])
- 3 serious adverse events, 1 subject (No. [redacted] [140 mg, double-blind phase]):
  - acute myocardial infarction, grade 2
  - coronary artery disease, grade 3
  - thrombosis in device, grade 3
- pyelonephritis, grade 4 (considered related) (No. [redacted] [280 mg, double-blind phase])
- aortic stenosis, grade 3 (No. [redacted] [280 mg double-blind phase])
- lower gastrointestinal hemorrhage (after the data cutoff) (No. [redacted] (140 mg, double-blind phase])

Subject incidences of all treatment-emergent adverse events through week 12 were similar for both AMG 827 (67.0%) and placebo (65.5%) subjects. Subject incidences of all treatment-related adverse events were higher for AMG 827 subjects (29.5%) than for placebo subjects (18.2%).

Overall exposure-adjusted treatment-emergent adverse event rates were lower for AMG 827 subjects (797.9 per 100 subject-years) than for placebo (903.7 per 100 subject-years) through data cutoff. Overall exposure-adjusted treatment-related adverse event rates were lower for AMG 827 subjects (212.8 per 100 subject-years) than for placebo (228.4 per 100 subject-years) through data cutoff.

No fatal events were reported as of the data cutoff.

Neutropenia is an identified risk for AMG 827. No adverse events of neutropenia were reported during the double-blind phase of this study and no clinical laboratory CTCAE shifts ≥ 2 grades from baseline were observed.

Incidences of treatment-emergent infectious adverse events were similar for both AMG 827 (26.8%) and placebo (32.7%). Hypersensitivity reactions occurred more frequently in the AMG 827 groups compared with placebo. Injection site reactions occurred more frequently in the placebo group. Two subjects tested positive for anti-AMG 827 antibodies: 1 subject at baseline (negative for neutralizing antibodies) and 1 subject from the double-blind placebo group tested positive for anti-AMG 827 antibodies at weeks 16 and 24 (negative for neutralizing antibodies) after entering the open-label phase of the study at week 12 (this subject will be retested at week 52).

Clinically meaningful abnormalities in clinical laboratory values in the AMG 827 groups compared with the placebo group were not apparent.

Conclusions: The study showed the tested doses of AMG 827 to be more efficacious than placebo in subjects with psoriatic arthritis. AMG 827 exhibited an acceptable safety profile. The data support continued treatment of subjects with AMG 827 in the open-label extension phase of the study and further development as a therapeutic agent in this indication.