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 Phase 2 Study to Determine the Safety and Efficacy of AMG 827 in Subjects With Inadequately Controlled Asthma

Investigator(s) and Study Center(s): This study was conducted at 47 centers in Austria, Belgium, Canada, Finland, Hungary, Netherlands, Poland, Russia, South Korea, and United States. Centers and principal investigators are listed in Appendix 4.

Publication(s): None

Study Period: 04 October 2010 to 21 December 2011

Development Phase: 2

Objectives: The primary objective was to determine if AMG 827 is effective compared to placebo as measured by change in Asthma Control Questionnaire (ACQ) composite scores from baseline to week 12.

The secondary objectives were to evaluate the efficacy of AMG 827 as measured by: pre and postbronchodilator forced expiratory volume in 1 second (FEV_1); morning and evening peak expiratory flow rate (PEFR); use of rescue short-acting β-agonist (SABA); daily symptoms (aggregate/night and individual symptoms; and symptom free days); and asthma quality of life questionnaire (AQLQ), as well as to evaluate the pharmacokinetics of AMG 827.

Methodology: This was a randomized, placebo-controlled, double blind, dose-ranging study in subjects with inadequately controlled asthma. The study was designed to evaluate the safety, tolerability and clinical effect of AMG 827 with every other week (Q2W) dosing for 12 weeks of treatment. Subjects were randomized in a 1:1:1:1 ratio to receive 140, 210, or 280 mg SC AMG 827 Q2W plus an additional dose at week 1 or placebo. Randomization was stratified based on atopy status and inhaled corticosteroid (ICS) dose (< 500 μg and ≥ 500 μg fluticasone powder or equivalent) at baseline. Subjects were considered atopic if they were positive to a skin prick (wheal diameter ≥ 3 mm and documented negative control) or RadioAllergoSorbent Test™ (RAST) to any allergen during the screening period or within the last 12 months before screening.

Subjects underwent screening, followed by a 4-week run-in period. Subjects who required a washout of certain specified asthma medications went through a wash-out, after the informed consent had been obtained and all screening procedures had been performed, but before the run-in period. Subjects who washed out from a LABA remained on the equivalent dose of ICS that was contained in the combination product. The run-in period ensured stable baseline values and accustomed subjects to the assessments before study start. The primary endpoint was obtained at week 12. Durability of effect and safety were monitored during a 4-week follow-up period after treatment cessation.

Number of Subjects Planned: 300

Number of Subjects Enrolled: 315

Diagnosis and Main Criteria for Eligibility: This study enrolled men and women between 18 and 65 years of age, with inadequately controlled asthma determined by a combination of the percent predicted FEV_1 (≥ 50% and ≤ 80%) and ACQ composite scores (≥ 1.5) at screening and baseline. All subjects had to demonstrate ≥ 12% reversibility over prebronchodilator FEV_1 with SABA inhalation, demonstrated in the office during the screening period. All subjects had to be receiving a total daily ICS dose ≥ 200 and ≤ 1000 μg/day of fluticasone powder or equivalent for ≥ 3 months before screening and had to be on a stable dose for ≥ 30 days before screening. Subjects were not allowed to use long acting beta agonists (LABAs) from 1 week before the run-in period through the remainder of the study.

Subjects were excluded if they had had an acute asthma exacerbation requiring emergency room treatment or hospitalization within 2 months of screening or a history of endotracheal intubation for asthma-related exacerbation within 3 years of screening. The following conditions were also exclusionary: history of chronic obstructive pulmonary disease or other chronic pulmonary condition other than asthma, current diagnosis of sleep apnea with ongoing symptoms or requiring continuous positive airway pressure, or history of aspirin-sensitive asthma.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects received AMG 827 at 140, 210, or 280 mg at day 1, week 1, 2, 4, 6, 8, and 10. Investigational product was administered as 4 subcutaneous (SC) injections for each dose. AMG 827 manufacturing batch numbers used were: [redacted].

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Subjects received placebo at day 1, week 1, 2, 4, 6, 8, and 10. Investigational product was administered as 4 subcutaneous (SC) injections for each dose. Placebo manufacturing batch numbers used were: [redacted].

Duration of Treatment: Treatment was 12 weeks, efficacy was assessed at week 12, end of study was at week 16.

Study Endpoints:

The primary endpoint was the change in ACQ composite scores from baseline to week 12. The secondary endpoints were: change in FEV_1 pre and postbronchodilator treatment from baseline to week 12; change in morning and evening PEFR from baseline to week 12; change in frequency of rescue SABA use from baseline to week 12; change in daily asthma symptoms (aggregate/night and individual) from baseline to week 12; change in AQLQ score from baseline to week 12; proportion of symptom-free days from baseline to week 12; and pharmacokinetic measures.

Statistical Methods:

The primary endpoint, change from baseline in ACQ at week 12, was tested for the linear trend of treatment effect (placebo, 140, 210, and 280 mg Q2W dose) using linear contrast with contrast coefficients of (-3, -1, 1, 3) in ANCOVA adjusting for the baseline value of ACQ, and stratification factors (atopy status, baseline ICS dose category).

The following covariates were assessed for any impact on key endpoints: disease duration, atopy status, baseline inhaled corticosteroid dose, baseline FEV_1 (or percent predicted FEV_1), body mass index, baseline ACQ, baseline reversibility, baseline blood eosinophil level, region, and previous LABA use.

For subgroup analyses of efficacy and safety, the following parameters were used to segregate the overall study population: sex, race, atopy, baseline ICS (total daily dose < 500 μg and ≥ 500 μg fluticasone or equivalent), baseline blood eosinophil level (≥ 6% vs < 6%), baseline reversibility (< 20% vs ≥ 20%), FeNo (< median vs ≥ median), baseline weight (< 100 kg vs ≥ 100 kg) and ACQ composite score tertile

For continuous endpoints, descriptive statistics including mean, standard deviation, median, minimum, maximum, and number of subjects were summarized. Similar ANCOVA analyses were performed for atopic status, ICS dose category at baseline. For any continuous endpoints that were not normally distributed, the non-parametric Quade test was used.

All categorical endpoints were summarized using the number and percent of subjects. The generalized linear regression model was used for the treatment comparisons of binary efficacy endpoints and Van Elteran's test or Quade test were used for ordinal efficacy endpoints.

All efficacy endpoints (except AQLQ, sleep-MOS, patient global assessment, and PGRC) were analyzed using the last observation carried forward (LOCF) imputation method for missing data. Results using observed data are also presented.

Safety endpoints were summarized descriptively.

Summary of Results:

Subject Disposition:

A total of 607 subjects were screened and 315 subjects were enrolled; 228 to AMG 827 and 77 to placebo. Ten subjects from site 12002 were excluded from all analyses due to major issues of GCP compliance including refusal of source document verification (Section 7.3.1).
Three subjects were randomized in error and did not receive investigational product. Therefore, 302 subjects received investigational product (226 AMG 827 and 76 placebo) and 272 subjects (204 [89.5%] AMG 827; 68 [88.3%] placebo) completed the study.

Baseline Demographics:

Sex: 123 (40.7%) men, 179 (59.3%) women

Age: mean (SD): 45.7 (11.4) years; range 20 to 66 years

Ethnicity/Race: white: 254 (84.1%); black: 31 (10.3%); Asian: 10 (3.3%); American Indian/Alaska Native: 2 (0.7); multiple: 4 (1.3%); other: 1 (0.3%)

Efficacy Results: Across endpoints for the overall study population, no consistent clinically or statistically significant findings were observed. There was evidence of a treatment effect and dose response across multiple endpoints in pre-specified analyses for the subpopulation with bronchodilator reversibility in $FEV_1 \geq 20\%$. This subpopulation included 112 (37%) of 302 subjects in the final analysis set. Results for the high reversibility subpopulation showed a greater magnitude of response for the primary endpoint of ACQ, which is a validated composite measure of asthma control. There were also consistent effects noted for secondary endpoints, some of which reached levels of clinical, though not statistical, significance.

Pharmacokinetic Results: For the subjects in the pharmacokinetic substudy, AMG 827 serum concentration-time profiles exhibited nonlinear pharmacokinetics. A population pharmacokinetic model described the pharmacokinetics of AMG 827 in adult subjects with asthma. There was a significant relationship between body weight and the pharmacokinetics of AMG 827. The covariate effect of eosinophil count on AMG 827 pharmacokinetics was not statistically significant.

Safety Results: No subjects died. Seven subjects reported 8 serious adverse events; 2 events (herpes zoster and viral meningitis) occurred in 1 subject; were considered by the investigator to be possibly related; and led to withdrawal of the subject from the study. A higher percentage of subjects discontinued from the 280 mg group; adverse events represented the highest number of study discontinuations for this group. Treatment-emergent and treatment-related adverse events occurred with greater frequency in the AMG 827 treatment arms compared with the placebo arm; however, the difference was minimal for most events. For the events of interest (neutropenia, infectious episodes, injection site reactions, and hypersensitivity), rates were similar across AMG 827 and placebo groups. However, there was an imbalance between placebo and the AMG 827 treatment group in the incidence of oral candidiasis (0% vs 3.5%, respectively).

Eight (3.5%) subjects tested positive for anti-AMG 827 binding antibodies post-baseline; none tested positive for neutralizing antibodies.

Conclusions: In conclusion, no consistent clinically or statistically significant findings were observed across endpoints for the overall study population. Results for the subpopulation with bronchodilator reversibility in $FEV_1 \geq 20\%$ suggested that these subjects responded favorably to treatment with AMG 827. Treatment effects achieved levels of clinical meaningfulness across daily and weekly composite measures of asthma control and daily symptom scores. Within the subpopulation of subjects with bronchodilator reversibility in $FEV_1 < 20\%$, the placebo group had a larger improvement with respect to symptom-based endpoints, and therefore efficacy relative to placebo was not demonstrated in this subpopulation. The current benefit:risk assessment supports further clinical studies in the high reversibility subpopulation of responders.