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, Open-Label Study in Healthy Subjects Evaluating the Tolerability, Safety, Acceptability and Performance of Two Auto-Injector Devices Used to Subcutaneously Administer AMG 827

Investigator(s) and Study Center(s): [redacted], MD, [redacted]

Publication(s): No publications

Study Period: 08 November 2011 to 11 January 2012

Development Phase: 1

Objectives:

The primary objectives were to:

- compare subject reported pain post subcutaneous (SC) injection of the positive control buffer with subject reported pain post injection of the negative control buffer;
- compare subject reported pain post SC injection of the newly formulated AMG 827 using the 2 auto-injectors being tested (3.1 kilogram-force [kgf] vs 4.2 kgf) with subject reported pain post injection of the positive and negative control buffers;
- evaluate the safety and tolerability of newly formulated AMG 827 (140 mg/mL) in healthy volunteers following administration of two 140 mg SC doses using 2 different auto-injectors;
- determine injection site tolerability of the newly formulated AMG 827 administered SC using the 2 auto-injectors being tested (3.1 kgf vs 4.2 kgf).

The secondary objectives were to:

- evaluate subject-reported ranking of pain associated with each of the 4 SC injections
- characterize the pharmacokinetics of AMG 827 after injection of the newly formulated AMG 827 in a subset of study subjects

The exploratory objectives were to:

[redacted]

Methodology: This was a single-center phase 1, randomized, open-label, crossover study in which 80 healthy men and/or women were randomized (1:1:1:1) to receive 4 different SC injections in 1 of 4 unique sequences. The 2 control buffers and the 2 auto-injectors were double blinded in the study.

Each subject was administered each of the 4 SC injections from the same staff member who was experienced in administering SC injections and trained in the use of the auto-injectors used in the study. Injections were administered approximately 1 hour apart in the deltoid area in alternating order of left to right and then left to right with a minimum 4-cm distance between each injection.

Immediately (less than approximately 30 seconds) after each of the 4 injections, subjects assessed their level of injection pain using a visual analog scale (VAS). Upon completion of the final injection, subjects ranked the order of pain associated with each injection from the least to the most painful.

In a subset of 16 study subjects equally randomized across the 4 injection randomization sequences, pharmacokinetic samples were collected over the duration of the study.

Assessments related to the mechanical performance of the auto-injectors were completed by study site staff for each injection by an auto-injector. Acceptability assessments of the auto-injector were completed by subjects as well as study site staff. Injection preference (auto-injectors vs a needle-syringe) was completed by the study site staff after completion of all injections for all the subjects.

Number of Subjects Planned: 80

Number of Subjects Enrolled: 80

Sex: Men: 58 (73%), women: 22 (28%)

Age: Mean (SD): 36.5 (6.8) years; range: 19 to 45 years

Ethnicity (Race): White: 70 (88%); black: 10 (13%)

Diagnosis and Main Criteria for Eligibility: This study enrolled healthy men and women between 18 to 45 years of age at the time of screening. Subjects had to sign an Institutional Review Board (IRB) approved informed consent form before any study specific procedures were conducted.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Subjects received 2 SC injections each containing 1.0 mL of 140 mg AMG 827. Injections were done using a single use pre-filled auto-injector with a 3.1 kgf spring or 4.2 kgf spring. AMG 827 manufacturing batch numbers used were: [redacted] and [redacted]

Duration of Treatment: 1 day, 4 doses, each 1 hour apart

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: Subjects received 2 SC injections each containing 1.0 mL positive sting control buffer or negative control buffer using a needle and syringe. Control manufacturing batch numbers used were: [redacted] and [redacted]

Study Endpoints

The primary endpoints included the subjects' perception of injection site pain using a VAS; adverse events related to injection site tolerability; other treatment emergent adverse events; clinically significant changes in safety laboratory tests, physical examination findings, vital signs, or electrocardiogram (ECGs); and anti-AMG 827 antibodies.

The secondary endpoints included the subject's ranking of injection site pain associated with each injection; and pharmacokinetic parameters (AUC_{last}, maximum observed plasma

concentration after dosing [C_{max}], time to reach C_{max} [t_{max}]) for AMG 827 after 2 separate 140 mg injections within a 3-hour period of time in a subset of healthy subjects.

Statistical Methods: Descriptive statistics are provided for selected demographic data, baseline characteristics, safety data, and pharmacokinetic parameters. Data for all endpoints are presented for all subjects and by the actual initial treatment they received. In addition, summaries are provided through descriptive statistics for the pain VAS scores and the ranking of injection site pain associated with each injection methods, the endpoints related to the acceptability of the auto-injectors, method of injection preference and time for injection. Descriptive statistics included means, medians, standard deviations (SD), 25th and 75th percentiles; ranges for continuous variables; and frequency counts and percentages for categorical variables. In addition, pain VAS scores were analyzed using repeated measures analysis of variance (ANOVA). [redacted]

[redacted] The estimate of sample size was based on 1-sided t-test. No adjustment was made for multiple comparisons.

Summary of Results:

Subject Disposition: Eighty subjects were enrolled; 78 (98%) completed the study and 2 (3%) subjects withdrew consent.

Efficacy Results: Efficacy was not assessed in this study.

Pharmacologic Results: Both 3.1 and 4.2 kpf auto-injectors had similar mean pain response profiles, which were also similar to the negative control pain buffer mean pain response. The subjects' pain rankings corroborated the VAS pain ratings. A post hoc analysis of injection site pain vs body weight or BMI did not show a relationship. A post hoc analysis of the relationship between VAS response (the primary measure of injection site pain) and sex showed that woman had higher mean VAS pain scores than men.

Device Performance Results: Visual inspection of the auto-injector after each injection confirmed that the full dose of AMG 827 was expelled for both auto-injectors for all injections administered. The mean (SD) time for injection was 7.1 (1.3) seconds for the 3.1 kgf auto-injector and 5.5 (0.9) seconds for the 4.2 kgf auto-injector. The injection time range for injections using auto-injectors was 3 to 12 seconds. A post hoc analysis showed that injection time was not related to body weight or BMI.

[redacted]

Pharmacokinetic Results: For the subjects in the pharmacokinetic sub-study, AMG 827 serum concentration-time profiles after administration of 280 mg (2 x 140 mg auto-injector administrations) AMG 827 exhibited nonlinear elimination. The mean (SD) C_{max} and AUC_{last} were 14.3 (5.42) µg/mL and 159 (82.4) µg•day /mL, respectively. Median t_{max} was 2.2 days (range: 1.1 to 4.2 days).

Safety Results: All 80 subjects enrolled in the study received 2 injections of AMG 827, 140 mg. No subjects died, withdrew from the study due to an adverse event, or experienced a serious adverse event. Two nonrelated grade 1 adverse events (ligament sprain and back pain) occurred during the study. No clinically significant findings were noted for laboratory evaluations, vital signs, ECGs, or physical examinations.

The low and similar injection site pain VAS scores reported post AMG 827 administration for both SureClick auto-injectors and for the manually administered negative pain control buffer suggest that administration of AMG 827 with either SureClick device is well tolerated. The safety profile for AMG 827 in this study is comparable to what has been observed in other larger AMG 827 studies.

Conclusions: Both auto-injectors had similar VAS pain profiles that were also similar to the VAS pain profile for the negative pain control. Subject's pain rankings corroborated the VAS pain scores. [redacted] and the safety profile, including injection site tolerability, for AMG 827 administered using the auto-injectors in this study was comparable to what has been observed in other larger AMG 827 studies. Based on these factors further development of an AMG 827 SureClick device for commercial purposes is warranted.