2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 827

Name of Active Ingredient: Brodalumab

Title of Study: A Study to Evaluate the Intra-subject Variability of Brodalumab Pharmacokinetic Parameters in Healthy Subjects

Investigator and Study Center: This study was conducted at [redacted]. The principal investigator was [redacted], MD.

Publications: None

Study Period: 14 March 2013 (first subject enrolled) to 10 May 2013 (last subject end of study visit)

Development Phase: 1

Objectives:
Primary Objective: To evaluate the intra-subject variability in the pharmacokinetics of brodalumab after subcutaneous (SC) administration of 140 mg doses in healthy men and women

Secondary Objectives: Following repeat 140 mg SC administrations of brodalumab:

- to characterize the pharmacokinetic (PK) profile
- safety, tolerability, and immunogenicity profile of brodalumab

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Methodology: In this phase 1 study, approximately 26 healthy adults were planned for enrollment to receive two 140 mg SC doses of brodalumab. In period 1, subjects received the first dose on day 1 with a 21-day PK collection period. In period 2, subjects received the second dose of brodalumab on day 22 with a 21-day PK collection period.

Number of Subjects Planned: 26 subjects

Diagnosis and Main Criteria for Eligibility: Healthy women of non-reproductive potential and men aged 18 to 55 years were included in the study. Subjects were excluded if they had a known history or diagnosis of Crohn's disease, a positive test for tuberculosis, or a screening neutrophil count at or below the age-based lower limit. Further details regarding the eligibility criteria are provided in Section 4 of the protocol (Appendix 16.1.1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Brodalumab was administered using 1.0 mL pre-filled syringe (PFS) containing 140 mg/mL brodalumab (140 mg/dose).

The manufacturing batch number was [redacted]

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was used.

Duration of Treatment: Subjects received brodalumab on day 1 and day 22, each followed by 21-day PK collection periods. The estimated study duration for subjects was approximately 64 days including a 21-day screening period followed by an on-study period of approximately 43 days (excluding telephonic follow-up on day 52). The end of study visit occurred on day 43 and the follow-up call occurred on day 52 to report the incidence of any adverse events between end of study visit and day 52.

Study Endpoints:

Primary Endpoint: Serum PK parameters (area under the drug concentration-time curve from time zero to tau [$AUC_{0-\tau}$] and maximum observed drug concentration after dosing [C_{max}])

Secondary Endpoints:

- serum PK parameters (eg, area under the drug concentration-time curve from time zero to infinity [AUC_{inf}]) after first and second dose
- treatment-emergent adverse events
- vital signs, electrocardiograms (ECGs), physical exams, and laboratory safety tests
- anti-brodalumab antibodies

Statistical Methods: Descriptive statistics were provided for selected demographics, safety, and PK data. Descriptive statistics for continuous measurements included means, medians, standard deviations (SD), and ranges while categorical data were summarized using frequency counts and percentages.

The intra-subject variability of the natural log-transformed PK parameters ($AUC_{0-\tau}$ and C_{max}) was estimated using a mixed-effect analysis of variance model with period as a fixed effect and subject as a random effect.

Summary of Results:

Subject Disposition: A total of 27 subjects were enrolled in the study, of whom 26 subjects (96.3%) received brodalumab in period 1. Of the 26 subjects (96.3%) who completed period 1, 25 subjects (92.6%) received brodalumab in period 2, and 23 subjects (85.2%) completed period 2.

Baseline Demographics:

Sex: [redacted] men ([redacted]), [redacted] women ([redacted])

Age: Mean (SD) 37.5 (10.1) years

Ethnicity/Race: [redacted] white ([redacted]), [redacted] black ([redacted])

Pharmacokinetic Results: After a washout period of 21 days, only 1 of 26 subjects had a quantifiable predose concentration in period 2. Mean C_{max} and AUC values were similar in both the periods. Median time to reach C_{max} (t_{max}) values (3.0 days) was the same for both the periods. The inter-subject and intra-subject variability (% coefficient of variation [CV] [90% CI]) for C_{max} was 87.8% (65.0% to 143.4%) and 46.6% (36.9 to 64.8%), respectively, after brodalumab administration. The $AUC_{0-\tau}$ intersubject and intrasubject variability (%CV [90% CI]) was 108.9% (78.6% to 191.4%) and 56.3% (44.0 to 80.3%), respectively.

Anti-brodalumab Antibody Assays: None of the 26 subjects had samples that tested positive for binding anti-brodalumab antibodies.

Safety Results: Treatment-emergent adverse events were reported for 9 subjects (34.6%); treatment-related adverse events were reported for 3 subjects (11.5%). One subject did not receive the second dose in period 2 due to the preferred term of abnormal liver function test (ie, increased aminotransferases) on day 22, which was considered to be treatment-related. No serious adverse events or deaths were reported in this study.

No clinically significant changes were noted in any vital signs. No subject had a QT or QTc interval > 500 msec or a change from baseline of > 60 msec.

All changes in laboratory values were mild to moderate, with the exception of the grade 3 increases in AST and ALT for 1 subject. Grade 2 decreases were reported for neutrophil count in 2 subjects. No infectious adverse events were reported for these subjects.

Conclusions: The intra-subject variability (% CV [90% CI]) of C_{max} and $AUC_{0-\tau}$ after 2 separate 140 mg SC administrations was 46.6% (36.9% to 64.8%) and 56.3% (44.0% to 80.3%) respectively. The safety profile of 140 mg brodalumab after two SC administrations 21 days apart was acceptable in healthy subjects. No anti-brodalumab antibodies were detected.