2. SYNOPSIS

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

Name of Finished Product: Brodalumab

Name of Active Ingredient: Brodalumab

Title of Study: An Open-label Study to Evaluate the Effect of Brodalumab on the Pharmacokinetics of Midazolam and Assess Single-dose Brodalumab Pharmacokinetics in Subjects with Moderate to Severe Plaque Psoriasis

Investigators and Study Centers: This study was conducted at 10 centers in Australia, New Zealand, and North America (see Section 16.1.4).

Publications: None

Study Period: 17 September 2013 (date first subject enrolled) to 26 July 2014 (date last subject completed follow-up)

Development Phase: 1

Previous Reports for This Study: None

Objectives:

Primary Objective: To characterize the effect of brodalumab on the pharmacokinetics (PK) of midazolam in subjects with moderate to severe plaque psoriasis based on area under the drug concentration-time curve (AUC) and maximum observed drug concentration (C_{max}).

Secondary Objectives:

- To assess brodalumab PK after single 140 mg and 210 mg dose subcutaneous (SC) administration in subjects with moderate to severe plaque psoriasis.
- To assess additional PK parameters of midazolam.
- To evaluate the safety, tolerability, and immunogenicity profile of brodalumab.

[redacted]

Methodology: Subjects were enrolled into 2 separate cohorts, as presented below.

Cohort 1 (n = 20 planned)	Cohort 2 (n = 10 planned)
Midazolam 2 mg oral (day 1 and day 9)[a] Brodalumab 210 mg SC (day 2)[b]	Brodalumab 140 mg SC (day 1)[c]

SC = subcutaneous
[a] Pharmacokinetic (PK) samples were collected predose to 24 hours postdose.
[b] PK samples were collected predose to 30 days postdose.
[c] PK samples were collected predose to 22 days postdose.

Number of Subjects Planned: 30 subjects (20 in cohort 1, 10 in cohort 2)

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men and women ≥ 18 to ≤ 75 years of age at the time of screening with stable, moderate to severe plaque psoriasis diagnosed at least 6 months before the first dose of investigational product, with involved body surface area (BSA) ≥ 10%, psoriasis area and severity index (PASI) ≥ 12, and static physician global assessment (sPGA) ≥ 3 at screening and at baseline.

Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number: Subjects in cohorts 1 and 2 were administered a 210 mg or 140 mg SC dose of brodalumab, respectively, via SC injection using single-use, prefilled syringes (PFS) containing a 140 mg/mL concentration of brodalumab. Manufacturing batch numbers for brodalumab are provided in Section 16.1.6.

Subjects in cohort 1 only were administered 2 mg of midazolam orally as a non-Amgen investigational product on day 1 and day 9. The package insert provides the manufacturer's information for midazolam.

Duration of Treatment*:* Total duration of treatment was approximately 30 and 22 days for cohorts 1 and 2, respectively.

Study Endpoints:

The primary endpoints were midazolam PK parameters (AUC from time zero to the time of the last quantifiable concentration [AUC_{last}], AUC from time zero to infinity [AUC_{inf}], and C_{max}).

The secondary endpoints were additional midazolam PK parameters (eg, time to reach C_{max} [t_{max}], half-life [$t_{1/2}$]), brodalumab PK parameters (AUC_{inf}, AUC_{last}, C_{max}, and t_{max}), treatment-emergent adverse events, vital signs, electrocardiograms (ECGs), physical examinations, laboratory safety parameters, and anti-brodalumab antibodies.

[redacted]

Statistical Methods:

Summary statistics were generated for each PK endpoint parameter. Primary and secondary PK parameters were estimated by noncompartmental analysis and calculated using dose and sample times.

The primary endpoints evaluating the effect of brodalumab on the PK of midazolam were assessed by comparing the AUC and C_{max} of midazolam on day 9 compared to day 1. No evidence of drug-drug interaction would be suggested if the 90% confidence intervals (CIs) for the ratios of geometric means for midazolam AUC and C_{max} (with versus without brodalumab) were within the range of 0.80 to 1.25.

Summary of Results:

Subject Disposition: Of the 31 subjects enrolled in the study, 21 were enrolled in cohort 1 and 10 subjects were enrolled in cohort 2. All subjects completed the study with the exception of 1 subject in cohort 1 who discontinued the study because of the sponsor's decision.

Baseline Demographics:

Sex: 24 men (77.4%) and 7 women (22.6%)

Age, mean (standard deviation [SD]): 43.0 (12.6) years

Race: 24 white (77.4%), 3 Asian (9.7%), 2 mixed race (6.5%), 1 black (3.2%), 1 native Hawaiian or other Pacific islander (3.2%)

Ethnicity: 3 Hispanic/Latino (9.7%) and 28 not Hispanic/Latino (90.3%)

Pharmacokinetics Results:

The AUC_{last} of midazolam was increased 1 week after brodalumab administration by approximately 23%, the AUC_{inf} was increased by approximately 24%, and the C_{max} of midazolam was increased by approximately 16%.

The 90% CIs for the ratios of geometric means of midazolam for day 9 versus day 1 were (1.12, 1.37) for AUC_{last}, (1.12, 1.38) for AUC_{inf}, and (1.00, 1.36) for C_{max}. Since the upper limit of these 90% CIs go beyond the upper limit of the pre-specified interval (0.80, 1.25), the presence of drug-drug interaction between brodalumab and midazolam is plausible but unlikely to be of clinical significance.

At single doses of either 140 mg and 210 mg in subjects with psoriasis, brodalumab exhibited mixed linear and non-linear elimination that was typical for a monoclonal antibody exhibiting target-mediated elimination. After a single 140 mg dose of brodalumab, the mean AUC_{inf}, AUC_{last}, C_{max}, and median t_{max} were 40.5 μg•day/mL, 27.8 μg•day/mL, 4.79 μg/mL, and 3 days respectively. After a single 210 mg dose of brodalumab, the mean AUC_{inf}, AUC_{last}, C_{max}, and median t_{max} were 119 μg•day/mL, 111 μg•day/mL, 13.4 μg/mL, and 3 days, respectively.

Safety Results: Treatment-emergent adverse events were reported for 13 subjects (61.9%) in cohort 1 (5 subjects [23.8%] after the initial oral dose of midazolam 2 mg on day 1 and prior to the administration of brodalumab on day 2, 4 subjects [19.0%] after the administration of brodalumab 210 mg SC dose on day 2 and prior to the administration of the second dose of midazolam on day 9, and 7 subjects [35.0%] after the administration of the second oral dose of midazolam 2 mg on day 9 and before the end-of-study). Subjects could have had adverse events in more than 1 period. In cohort 2, 5 subjects (50.0%) had treatment-emergent adverse events. The only treatment-emergent adverse event reported in more than 1 subject was somnolence, in 2 subjects (9.5%) from cohort 1. For both subjects, the somnolence occurred just after midazolam dosing (for 1 subject on day 1 and the other on day 9), resolved on the same day, and was considered by the investigator to be related to midazolam. Treatment-emergent adverse events were collected until the end of the study or 30 days after the last dose of investigational product (whichever occurred later).

No serious adverse events, deaths, or discontinuations due to treatment-emergent adverse events were reported in this study.

Three subjects (14.3%) in cohort 1 and 2 subjects (20.0%) in cohort 2 had adverse events of interest. In cohort 1, one subject had pruritis (2 days after receiving brodalumab 210 mg), 1 subject had infected bites (1 day after the second midazolam administration), and 1 subject had upper respiratory tract infection (12 days after the second midazolam administration). In cohort 2, one subject had upper abdominal pain (17 days after the brodalumab 140 mg dose) and 1 subject had vessel puncture site pain (2 days after the brodalumab 140 mg dose). All events of interest had a common terminology criteria for adverse events (CTCAE) severity grade of 1 or 2.

No clinically significant changes were noted in any vital signs or ECGs. No clinically significant changes in laboratory values were observed, except for a transient grade 3 decrease in hemoglobin level for 1 subject in cohort 2 that returned to normal by the end-of-study with no associated adverse events.

Blood specimens from 30 subjects were tested in the anti-brodalumab immunoassay for the presence of binding and neutralizing anti-brodalumab antibodies. No subject tested positive for the presence of binding or neutralizing anti-brodalumab antibodies at baseline or anytime during the study.

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Conclusions:

The AUC_{last} of midazolam was increased 1 week after brodalumab 210 mg administration by approximately 23%, the AUC_{inf} was increased by approximately 24%, and the C_{max} of midazolam was increased by approximately 16%. The 90% CIs for the ratios of geometric means of midazolam for day 9 versus day 1 were (1.12, 1.37) for AUC_{last}, (1.12, 1.38) for AUC_{inf}, and (1.00, 1.36) for C_{max}.

Based on the degree of midazolam PK exposure change after co-administration of brodalumab, the presence of a drug-drug interaction in patients with moderate to severe psoriasis is plausible but unlikely to be of clinical significance.

At single doses of either 140 mg or 210 mg in subjects with psoriasis, brodalumab exhibited mixed linear and non-linear elimination that was typical for a monoclonal antibody exhibiting target-mediated elimination.

The safety profile of 140 mg and 210 mg brodalumab after single dose SC administration was acceptable in subjects with moderate to severe plaque psoriasis. No subjects tested positive for anti-brodalumab antibodies.