## 2. SYNOPSIS

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

**Name of Finished Product:** Brodalumab

**Name of Active Ingredient:** Brodalumab

**Title of Study:** A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Brodalumab in Subjects With Inadequately Controlled Asthma and High Bronchodilator Reversibility

**Investigators and Study Centers:** This study was conducted at 157 centers in Asia, Australia, Canada, Europe, and the United States. Centers and principal investigators are listed in Section 16.1.4.

**Publications:** None

**Study Period:** 22 May 2013 (first subject enrolled) to 15 May 2015 (last subject completed follow-up)

**Development Phase:** 2

**Previous Reports for This Study:** None

**Objectives:**

**Primary Objective**

The primary objective was to evaluate the efficacy of brodalumab compared with placebo as measured by the change in asthma control (based on the asthma control questionnaire [ACQ]) from baseline at week 24 in subjects with inadequately controlled asthma and high reversibility despite standard of care.

**Key Secondary Objectives**

The key secondary objectives were as follows:

- to evaluate the effect of brodalumab compared with placebo at week 24 on asthma exacerbations (event rate defined as the number of events per subject-year)
- to evaluate the effect of brodalumab compared with placebo at week 24 on ACQ in inhaled corticosteroid (ICS) + long-acting β-agonist (LABA) strata
- to evaluate the effect of brodalumab compared with placebo at week 24 on asthma exacerbations (event rate) in ICS + LABA strata

Other secondary endpoints included additional efficacy endpoints, and the evaluation of safety and pharmacokinetics of brodalumab. A complete list of all objectives of the study is provided in the Protocol Section 1 (Section 16.1.1 of this report).

**Methodology:**

Subjects underwent 3 run-in visits over 4 weeks after completing all screening assessments and meeting all eligibility criteria. After the run-in visits, eligibility of ACQ, forced expiratory volume in 1 second ($FEV_1$), and reversibility were confirmed at baseline. Eligible subjects were randomized in a 1:1 ratio to receive brodalumab 210 mg or placebo every 2 weeks (Q2W), with an additional dose at week 1. Randomization was stratified based on the current use of LABAs and number of prior exacerbations (≤ 2 or > 2) in the past year before screening. Subjects received investigational product for up to 24 weeks in the double-blind placebo-controlled treatment period. Inhaled

corticosteroid and LABA dosing was kept stable from screening through the end of the study.

**Number of Subjects Planned:** 566 subjects (283 subjects per treatment arm)

**Diagnosis and Main Criteria for Eligibility:** This study enrolled adult subjects (≥ 18 to ≤ 75 years of age) with inadequately controlled asthma (ACQ ≥ 1.5 at both screening and baseline), an $FEV_1$ ≥ 40% and ≤ 80% (at screening and baseline), and ≥ 20% reversibility over prebronchodilator $FEV_1$ with short-acting β-agonist inhalation (up to 8 puffs) or nebulized equivalent (up to 2 treatments with 2.5 mg albuterol/salbutamol) at screening (and repeated with ≥ 15% reversibility at baseline). All subjects were required to be taking a stable dose of ICS (≥ 200 and ≤ 1000/μg/day fluticasone powder or equivalent) and were also required to be taking a stable dose of LABA, if applicable. Additionally, subjects were to have ≥ 1, but < 5 exacerbations in the year before screening.

**Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:** Brodalumab was supplied as a 140 mg/mL brodalumab, [redacted] mM L-glutamate, [redacted]% (w/v) L-proline, [redacted]% (w/v) polysorbate 20, pH [redacted] prefilled syringe (0.5 or 1.0 mL fill). The doses of brodalumab were administered by a subcutaneous (SC) injection to the abdomen, thigh, or upper arm. All subjects received 2 injections (one 1.0 mL and one 0.5 mL) at protocol-specified time intervals.

Placebo was supplied in identical containers, and was administered and stored/packaged in the same way as brodalumab during the study.

Manufacturing batch numbers are provided in Section 16.1.6.

**Duration of Treatment:** The estimated study duration for an individual subject was approximately 34 weeks, including a 2-week screening period; a 4-week run-in period; a 24-week randomized, double-blind, placebo-controlled treatment period; and a 4-week follow-up period.

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**Study Endpoints:**

The primary efficacy endpoint was change in the ACQ composite score from baseline at week 24.

The key secondary efficacy endpoints were as follows:

- number of asthma exacerbations (defined by use of oral corticosteroids) from baseline to week 24
- change in ACQ from baseline at week 24 in ICS + LABA strata
- number of asthma exacerbations from baseline to week 24 in ICS + LABA strata

The safety endpoints were adverse events, events of interest, presence of anti-brodalumab antibodies, clinical laboratory evaluations, and vital signs. Other secondary endpoints included additional efficacy endpoints and brodalumab pharmacokinetics.

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**Statistical Methods:**

The primary endpoint, change in the ACQ score from baseline at week 24, was tested for treatment effect (brodalumab versus placebo) using a mixed effects model with repeated measures at a significance level of 0.05 (2-sided). The model included the following fixed effects: treatment group, time, interaction of treatment group by time,

stratification variables, and baseline ACQ score with random intercept. For the primary endpoint, sensitivity analyses were to be performed using an analysis of covariance model that included treatment group, stratification variables, and baseline ACQ score.

The key secondary endpoints of event rate of asthma exacerbations from baseline to week 24 in the overall study population and in the ICS + LABA strata were assessed for treatment effect using a generalized linear model under a negative binomial distribution assumption adjusted for the stratification factors. The other key secondary endpoint of change in the ACQ score from baseline at week 24 in the ICS + LABA strata was analyzed using a mixed effects model.

The analyses of efficacy and safety endpoints included all randomized subjects who received ≥ 1 dose of investigational product.

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**Summary of Results:**

A planned interim analysis (per protocol amendment 3) was conducted in February 2015 (data snapshot date: 20 February 2015). Based on this interim analysis, the study was terminated early since brodalumab 210 mg Q2W did not provide evidence of efficacy benefit compared with placebo in subjects with inadequately controlled asthma and high bronchodilator reversibility. Efficacy data (including certain patient-reported outcomes) presented in this report are based on the tables/figures generated during the interim analysis (no efficacy-related tables/figures were generated during final analysis). For all other endpoints (besides efficacy), the final analysis data (tables/listings/figures) were used for writing this report.

**Subject Disposition:** A total of 421 subjects (211 brodalumab, 210 placebo) were randomized into the study. Of these, 415 subjects (98.6%) received at least 1 dose of investigational product. A total of 310 subjects (73.6%) completed study treatment and 320 subjects (76.0%) completed their end-of-study visit. Of the randomized subjects, 101 subjects (24.0%) discontinued the study and the reasons for discontinuation were decision by sponsor (11.9%), consent withdrawn (10.9%), lost to follow-up (1.0%), and death (0.2%).

**Baseline Demographics:**

**Sex:** 242 women (58.3%), 173 men (41.7%)

**Age:** mean (standard deviation [SD]) = 47.3 (13.6) years

**Ethnicity/Race:** 336 white (81.0%); 48 black (11.6%); 23 Asian (5.5%); 2 multiple (0.5%); 2 native Hawaiian/other Pacific Islander (0.5%); 1 American Indian/Alaska Native (0.2%); 3 other (0.7%).

**Efficacy Results:**

The mean (SD) change in ACQ composite scores from baseline at week 24 was -0.92 (0.82) in the brodalumab group and -0.80 (0.88) in the placebo group. The least squares (LS) mean difference from placebo was -0.05 (p = 0.52) for the brodalumab group. The mean (SD) change in ACQ composite scores from baseline at week 24 in ICS + LABA subjects was -0.90 (0.86) in the brodalumab group and -0.82 (0.85) in the placebo group. The LS mean difference from placebo was -0.04 (p = 0.66) for the brodalumab group.

From baseline to week 24, a total of 65 asthma exacerbations were reported in 49 subjects in the brodalumab group (rate per subject-year was 0.81) and 47 asthma exacerbations were reported in 41 subjects in the placebo group (rate per subject-year was 0.57). Brodalumab to placebo rate ratio was 1.41 (p = 0.10). From baseline to

week 24 in the ICS + LABA subjects, a total of 58 asthma exacerbations were reported in 43 subjects in the brodalumab group (rate per subject-year was 0.89). A total of 42 asthma exacerbations were reported in 37 subjects in the placebo group (rate per subject-year was 0.60). Brodalumab to placebo rate ratio was 1.45 (p = 0.10).

**Anti-brodalumab Antibody Data:**

Of the 414 subjects with on-study anti-brodalumab antibody results, 207 subjects received brodalumab. One subject out of 207 (0.5%) developed anti-brodalumab binding antibodies. No neutralizing anti-brodalumab antibodies were detected in the study.

**Pharmacokinetic Data:**

Individual pharmacokinetic concentrations and descriptive statistics are summarized in Section 16.1.13.1.

**Safety Results:**

A total of 415 subjects were included in the safety analysis set; adverse events were reported in 290 subjects (69.9%) (156 brodalumab [75.0%], 134 placebo [64.7%]). Commonly reported adverse events (≥ 5% subjects in either of the groups) were asthma, nasopharyngitis, upper respiratory tract infection, bronchitis, headache, and cough. Most of the events were mild or moderate in severity. In subjects ≥ 65 years of age (39 subjects; 21 brodalumab, 18 placebo), a higher subject incidence of adverse events was reported in the brodalumab group compared with the placebo group (81.0% versus 50.0%).

One subject in the placebo group died due to bile duct adenocarcinoma. None of the subjects discontinued the study due to adverse events. Twenty-two subjects (5.3%) (6.3% brodalumab, 4.3% placebo) discontinued investigational product due to adverse events. Lethargy, depression, asthma, and arthralgia were reported in 2 subjects each; all other events that led to discontinuation of investigational product were reported in 1 subject each. Fifteen subjects (3.6%) had serious adverse events (7 brodalumab [3.4%], 8 placebo [3.9%]). Appendicitis, pneumonia, and status asthmaticus were reported in 2 subjects each; all other serious events were reported in 1 subject each. None of the serious adverse events were considered treatment related in the brodalumab group.

Hypersensitivity was the most common event of interest category reported in 57 subjects (13.7%) (36 brodalumab [17.3%], 21 placebo [10.1%]), with asthma being the most common preferred term (24 brodalumab [11.5%], 16 placebo [7.7%]) in that category. In subjects who received 210 mg brodalumab, suicidal ideation was reported in 4 subjects (duration-adjusted subject incidence rate of 7.7 per 100 subject-years) with no prior [redacted] history; none of the subjects had any [redacted]. In the placebo group, suicidal ideation was reported in 6 subjects (duration-adjusted subject incidence rate of 11.9 per 100 subject-years); 1 subject had prior [redacted] history, while 5 subjects did not. In 1 subject, with no prior [redacted], suicidal behavior (subtype 7, aborted attempt) was reported.

**Conclusions:**

This study was terminated early due to lack of brodalumab efficacy based on the results from the interim analysis conducted in February 2015. The main conclusions from this study are as follows:

- For the primary efficacy endpoint of change in ACQ composite score from baseline at week 24, brodalumab was not significantly different when compared with placebo (LS mean difference of -0.05, p = 0.52).
- Similarly, other efficacy endpoints (mainly including the number of asthma exacerbations, change in the ACQ score in the ICS + LABA strata, and the number of asthma exacerbations in the ICS + LABA strata from baseline to week 24) did not show any statistically significant difference between the treatment groups.
- Commonly reported adverse events (≥ 5% subjects in either of the groups) were asthma, nasopharyngitis, upper respiratory tract infection, bronchitis, headache, and cough. Seven subjects (3.4%) in the brodalumab group and 8 subjects [3.9%] in the placebo group had serious adverse events. Appendicitis, pneumonia, and status asthmaticus were reported in 2 subjects each; all other serious adverse events were reported in 1 subject each. Thirteen subjects (6.3%) in the brodalumab group and 9 subjects (4.3%) in the placebo group had adverse events that led to the discontinuation of investigational product. One fatal adverse event (bile duct adenocarcinoma) was reported in the placebo group.