2. SYNOPSIS

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

Name of Finished Product: Brodalumab (AMG 827)

Name of Active Ingredient: Brodalumab

Title of Study: A Long-term Assessment of the Safety and Efficacy of Brodalumab Subcutaneous Treatment in Subjects With Psoriasis

Investigators and Study Centers: This study is ongoing at 23 centers in Australia, Canada, Denmark, France, and the United States. A list of investigators and study centers is provided in Section 16.1.4.

Publications:

Papp K, Leonardi C, Menter A, et al. Results after 48 weeks of brodalumab (AMG 827) in subjects with moderate to severe plaque psoriasis in an open-label extension study. [abstract]. *Eur Acad Dermatol Venerol*. September 27-30, 2012.

Papp K, Leonardi C, Menter A, et al. Improvement of psoriasis in subjects with moderate to severe plaque psoriasis after 48 weeks of brodalumab (AMG 827) treatment in an open-label extension study. [abstract]. American Academy of Dermatology Fall Clinical Dermatology Meeting. October 4-7, 2012.

Papp K, Leonardi C, Menter A, et al. Improvement of psoriasis in subjects with and without prior brodalumab (AMG 827) treatment in an open-label extension study. [abstract]. *Am Acad Dermatol.* March 1-5, 2013.

Papp K, Leonardi C, Menter A, et al. Improvement of psoriasis in patients with and without prior brodalumab (AMG 827) treatment in an open-label extension study. [abstract]. *Canadian Dermatol Assoc*. June 27-30, 2013.

Papp K, Leonardi C, Menter A, et al. Maintenance of clinical response with long-term brodalumab (AMG 827) therapy for psoriasis: week 96 results from an open-label extension study. [abstract]. *Eur Acad Dermatol Venerol*. October 3-6, 2013.

Papp K, Leonardi C, Menter A, et al. Safety and efficacy of brodalumab for psoriasis after 120 weeks of treatment. *J Am Acad Dermatol.* 2014 October 10. pii: S0190-9622(14)01888-X. doi: 10.1016/j.jaad.2014.08.039. [Epub ahead of print]

Study Period: 13 April 2010 (date first subject enrolled) to 16 June 2014 (data cut-off date for this report)

Development Phase: 2

Objectives:

Safety Objective: To evaluate the safety of long-term exposure with brodalumab in subjects with moderate to severe plaque psoriasis

Efficacy Objectives:

To evaluate the efficacy of brodalumab as measured by the following:

- the proportion of subjects with a static Physician's Global Assessment (sPGA) of clear (0) or clear/almost clear (0/1)
- percent improvement in Psoriasis Area and Severity Index (PASI)
- the proportion of subjects with 50%, 75%, 90%, and 100% improvement in PASI (PASI 50, PASI 75, PASI 90, and PASI 100, respectively)
- body surface area (BSA) involvement

[redacted]

The remaining objectives are provided in Section 1.3 of the Protocol (Section 16.1.1).

Methodology: This study (20090403) is an open-label extension of the double-blind Study 20090062 in subjects with moderate to severe plaque psoriasis. Subjects who completed Study 20090062 ≥ 4 weeks previously underwent a screening visit prior to the baseline visit of Study 20090403.

At the baseline visit, subjects either restarted brodalumab after a hiatus of ≥ 6 weeks (subjects from 1 of the brodalumab-treated groups in Study 20090062) or started treatment with brodalumab for the first time (subjects from the placebo group). Study visits were at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, and every 24 weeks thereafter.

Subjects received brodalumab subcutaneously (SC) at baseline, at weeks 1 and 2, and then every 2 weeks (Q2W) thereafter.

The clinical study report (CSR) is in synopsis format to report results of the second interim analysis and includes data from study initiation to 16 June 2014.

Number of Subjects Planned: 155

Diagnosis and Main Criteria for Eligibility: Subjects are men or women who were ≥ 18 and ≤ 70 years of age at the time of screening for Study 20090062 and who had moderate to severe plaque psoriasis. Eligible subjects had to have completed the week 16 visit of Study 20090062 and could not have had any serious adverse events that were reported to be related to investigational product. A detailed list of the inclusion and exclusion criteria are provided in Sections 4.1 and 4.2 of the Protocol (Section 16.1.1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Initially, all subjects received brodalumab 210 mg. After Protocol Amendment 2, the dose of brodalumab was reduced to 140 mg in subjects who weighed ≤ 100 kg. After Protocol Amendment 3, subjects who had an inadequate response (defined as sPGA of 2 for ≥ 4 weeks or a single sPGA ≥ 3) during treatment with brodalumab 140 mg could increase the dose to 210 mg. Subjects who did not have their dose reduced as part of Protocol Amendment 2 continued to receive brodalumab 210 mg.

Brodalumab was initially provided as the "process 1" formulation: 70 mg/mL brodalumab formulated in [redacted] mM acetate, [redacted] % sucrose, [redacted] % w/v polysorbate 20 at pH [redacted] supplied as a frozen liquid in glass vials, each containing 1 mL deliverable volume, intended for single-use only. There was a planned change in March 2012 to the "process 2" formulation: 140 mg/mL brodalumab, [redacted] mM L-glutamate, [redacted] % (w/v) L-proline, [redacted] % (w/v) polysorbate 20, pH [redacted] in a prefilled syringe.

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was administered during this open-label study.

Duration of Treatment: Subjects will participate in the study for approximately 360 weeks or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or an administrative decision to close the study.

Study Endpoints:

Safety Endpoints:

- adverse events and serious adverse events
- changes in laboratory parameters (hematology, chemistry, and urinalysis)

Efficacy Endpoints

- sPGA 0 and sPGA 0/1 at all measured time points
- percent improvement in PASI at all measured time points
- PASI 50, 75, 90, and 100 at all measured time points
- BSA involvement at all measured time points

[redacted]

The remaining endpoints are provided in Section 10.1.1 of the Protocol (Section 16.1.1).

Statistical Methods:

All subjects who received ≥ 1 dose of brodalumab (the Full Analysis Set) were included in the data summaries and analysis of efficacy and safety until the data cut-off date of 16 June 2014.

Descriptive summary statistics were provided for study endpoints. Categorical variables were summarized by number and percentage of subjects and 2-sided 95% confidence interval (CI) for the percentage. Continuous variables were summarized by number of observations, mean, standard deviation (SD), standard error, 95% CI for the mean, median, minimum, and maximum. No formal statistical tests were performed. Missing values for safety endpoints were not imputed. Efficacy endpoints and patient-reported outcome data were analyzed as observed.

Summary tables were provided for treatment-emergent adverse events, including fatal adverse events, serious adverse events, treatment-related adverse events, and treatment-related serious adverse events. Adverse events of special interest, including neutropenia, infections, injection site reactions, nervous system disorders, psychiatric disorders, and hypersensitivity were also summarized.

Laboratory results were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The number and percentage of subjects who developed anti-brodalumab antibodies were tabulated.

Further details are provided in the Statistical Analysis Plan (Section 16.1.9).

Summary of Results:

Subject Disposition: One hundred eighty-one subjects (148 who received brodalumab in Study 20090062 and 33 who received placebo) entered Study 20090403 and received

≥ 1 dose of brodalumab. Of those 181 subjects, 141 subjects completed week 168 (Table 14a-4.1). A total of 135 subjects (74.6%) were continuing the study by the time of the data cut-off (16 June 2014). A total of 46 subjects (25.4%) discontinued the study; 14 subjects (7.7%) discontinued because of adverse events, 13 subjects (7.2%) withdrew consent, 11 subjects (6.1%) discontinued due to other reasons, 3 subjects (1.7%) were lost to follow-up, 2 subjects each (1.1%) were discontinued due to administrative reasons, and pregnancy, and 1 subject (0.6%) died (Table 14a-1.1).

Per Amendment 2, 118 subjects (65.2%) had a dose reduction from 210 mg to 140 mg brodalumab because their body weight was ≤ 100 kg. Per Amendment 3, 30 subjects (16.6%) had a dose increase to 210 mg because of an inadequate response (Table14a-5.2).

Baseline Demographics:

Sex: 117 men (64.6%), 64 women (35.4%)

Age: mean (SD) 43.1 (12.2) years, range, 22 to 70 years

Ethnicity/Race: 162 white (89.5%); 6 Hispanic or Latino (3.3%); 5 Asian (2.8%); 4 black (2.2%); 3 American Indian or Alaska Native (1.7%); 1 "other" (Table 14a-2.1)

The mean (SD) weight at Study 20090062 baseline was 90.77 (22.23) kg with a range of 45.0 to 147.7 kg and the mean (SD) body mass index was 30.47 (6.89) kg/m^2. The subjects were categorized into various subgroups based on their weights at baseline (Table 14a-2.2).

A total of 45 subjects (24.9%) had psoriatic arthritis at the Study 20090062 baseline and the mean (SD) duration of psoriasis was 18.9 (11.2) years with a range of 1 to 52 years. Eight subjects (4.4%) had a sPGA score of 5 (severe) at the Study 20090062 baseline (Table 14a-2.3).

Efficacy Results: The description of efficacy in this report will focus on results through week 168 since all continuing subjects completed this visit.

Results for all efficacy endpoints followed a similar time course, with improvement at week 12 compared with week 2. The results were generally stable from weeks 12 through 168. For each endpoint, efficacy was consistent through week 168 and included responses ≥ 90% for PASI 75, ≥ 80% for PASI 90 and ≥ 50% for PASI 100 at week 168, as shown in Table 1 (all subjects who received ≥ 1 dose of brodalumab, regardless of dose level). The slight decrease in efficacy observed during weeks 96 and 120 may reflect the decrease in dosing for subjects <100 kg due to Amendment 2.

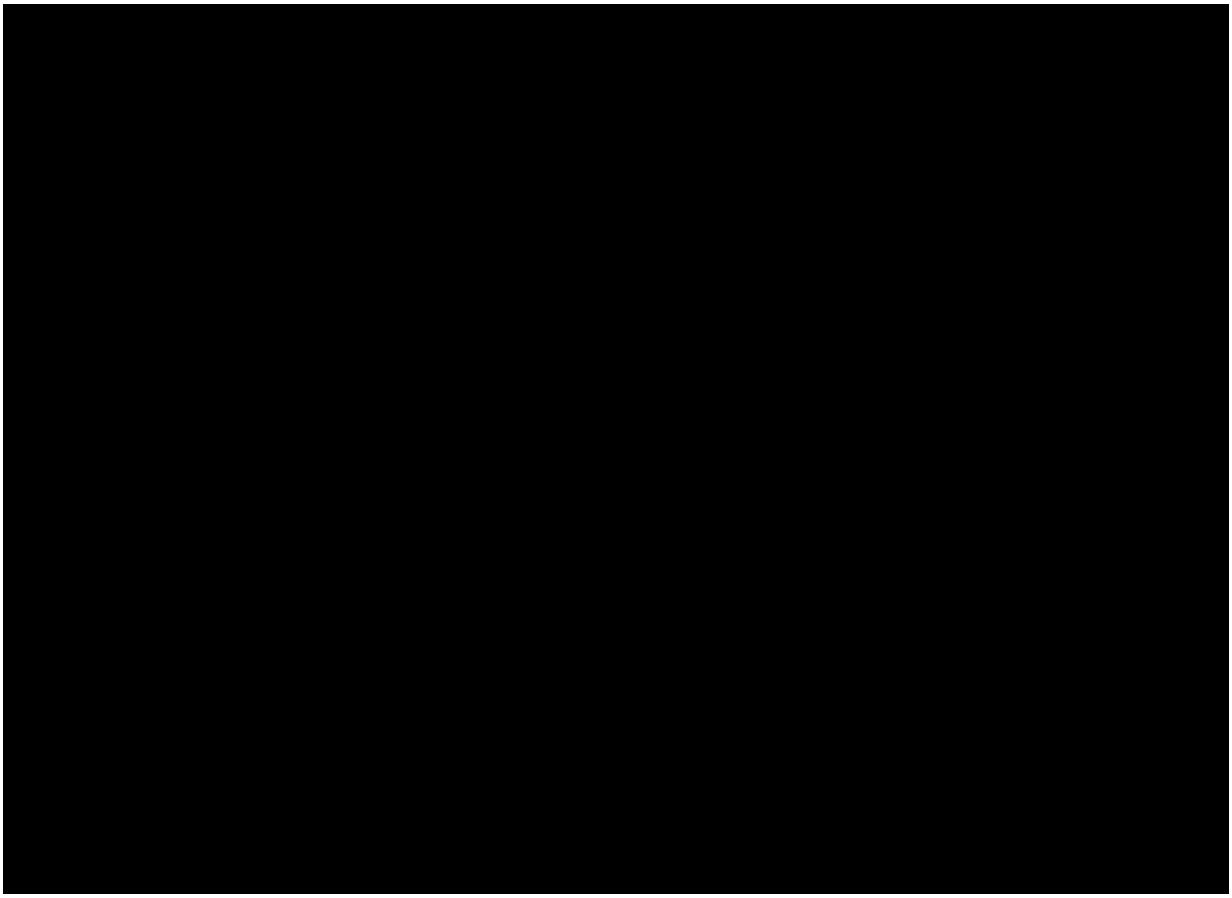
Table 1. Efficacy Results by Visit (Full Analysis Set)

	Week 2 N1 = 173	Week 12 N1 = 175	Week 24 N1 = 168	Week 48 N1 = 165	Week 96 N1 = 153	Week 120 N1 = 148	Week 168 N1 = 141	Week 192 N1 = 132
sPGA 0/1 (Responder n [%])	109 (63.0)	158 (90.3)	149 (88.7)	140 (84.8)	116 (75.8)	107 (72.3)	113 (80.1)	110 (83.3)
sPGA 0 (Responder n [%])	38 (22.0)	110 (62.9)	111 (66.1)	103 (62.4)	80 (52.3)	75 (50.7)	85 (60.3)	88 (66.7)
PASI 50 (Responder n [%])	151 (87.3)	173 (98.9)	166 (98.8)	163 (98.8)	147 (96.1)	144 (97.3)	136 (96.5)	128 (97.0)
PASI 75 (Responder n [%])	118 (68.2)	167 (95.4)	159 (94.6)	154 (93.3)	137 (89.5)	127 (85.8)	131 (92.9)	123 (93.2)
PASI 90 (Responder n [%])	66 (38.2)	149 (85.1)	146 (86.9)	137 (83.0)	120 (78.4)	104 (70.3)	113 (80.1)	112 (84.8)
PASI 100 (Responder n [%])	37 (21.4)	110 (62.9)	110 (65.5)	102 (61.8)	81 (52.9)	75 (50.7)	84 (59.6)	86 (65.2)
Mean PASI % improvement	78.7	95.4	95.7	94.6	91.7	90.4	93.7	94.0
Mean BSA % improvement	69.8	94.5	95.4	95.5	92.4	91.7	93.4	93.7

N1 = Number of subjects who were enrolled and had a valid measurement value at the specified week; % = n/N1* 100; sPGA = static Physician's Global Assessment; sPGA 0 = clear; sPGA 0/1 = clear/almost clear; PASI 75/90/100 = proportion of subjects with a 75%/90%/100% improvement in Psoriasis Area and Severity Index (PASI); BSA % improvement = percent improvement in body surface area involvement.
Sources: Table 14a-4.1, Table 14a-4.7, Table 14a-4.13, Table 14a-4.20, and Table 14a-4.27

Efficacy results (combined for all doses) were more favorable for subjects with body weight ≤ 100 kg than for those with body weight > 100 kg (Table 14a-4.5 and Table 14a-4.6).

[redacted]



Pharmacokinetic Results:

The pharmacokinetic results are presented in Section 16.1.13.3.

[redacted]

Safety Results:

Brodalumab Exposure Data

All 181 subjects who were enrolled in Study 20090403 received ≥ 1 dose of brodalumab and were included in the safety analysis set. As of the data cut-off date, the mean (SD) duration of exposure to brodalumab (combined exposure in Studies 20090062 and 20090403) for all subjects in Study 20090403 was 1285.7 (427.4) days, with a range of 107 to 1604 days (Table 14a-5.1).

Over the course of the study, subjects contributed 637.1 patient-years of exposure to brodalumab and had 1887 adverse events (event rate 296.2 per patient-year) (Table 14a-6.22.3).

All Adverse Events

Most subjects in Study 20090403 had treatment-emergent adverse events (175 subjects; 96.7%). Grade ≥ 3 treatment-emergent adverse events occurred in 35 subjects (19.3%). Adverse events leading to brodalumab discontinuation were reported in 19 subjects (10.5%) and the adverse events leading to study termination were reported in 15 subjects (8.3%) (Table 14a-6.1). No particular trend was reported.

Treatment-emergent adverse events by individual preferred term occurring in ≥ 10% of subjects included nasopharyngitis (49 subjects; 27.1%), upper respiratory tract infection (41 subjects; 22.7%), arthralgia (34 subjects;18.8%), influenza (23 subjects; 12.7%), gastroenteritis (21 subjects; 11.6%), back pain (20 subjects; 11.0%), and sinusitis (20 subjects; 11.0%) (Table 14a-6.2.1). The subject incidence of treatment-emergent adverse events for various subgroups are presented in Table 14a-6.17.1 to Table 14a-6.21.3.

Serious Adverse Events

Twenty-three subjects (12.7%) had at least 1 serious adverse event (Table 14a-6.1); the only adverse event reported by more than 1 subject was myocardial infarction (3 subjects; 1.7%) (Table 14a-6.4).

Six subjects (3.3%) had a total of 7 serious adverse events that were considered related to brodalumab, as presented in Table 4 and Table 14a-6.5.

Fatal Adverse Event

One death was reported in Study 20090403 (Table 14a-6.1). [redacted] The event was not considered by the investigator to be related to brodalumab.

Adverse Events of Interest

Treatment-emergent adverse events of interest (based on either Amgen-defined queries or standard medical queries) occurring in ≥ 10% of subjects by events of interest category (Table 14a-6.25) included:

- nervous system-related adverse events reported in 38 subjects (21.0%)
- psychiatric disorder adverse events reported in 30 subjects (16.6%)
- oropharyngeal candidiasis adverse events reported in 25 subjects (13.8%)
- Adverse events potentially associatied with Crohn's disease reported in 21 subjects (11.6%)

A total of 11 subjects had 13 serious adverse events of interest as shown Table 4. Six subjects (3.3%) had a total of 7 serious adverse events of interest that were considered related to brodalumab. None of the adverse events of interest were fatal.

Table 4. Serious Adverse Events (Safety Analysis Set)

Preferred Term	N = 181 n (%)
Number of subjects reporting serious adverse events	23 (12.7)
Myocardial infarction[a, b]	3 (1.7)
Angina pectoris[b, c]	1 (0.6)
Atrial fibrillation	1 (0.6)
Cardiac failure congestive	1 (0.6)
Supraventricular tachycardia	1 (0.6)
Abscess [b]	1 (0.6)
Hepatitis C [b]	1 (0.6)
Meningitis viral[b, c]	1 (0.6)
Necrotising fasciitis streptococcal [b]	1 (0.6)
Pyelonephritis[b, c]	1 (0.6)
Pyelonephritis acute[b, c]	1 (0.6)
Septic shock[b, c]	1 (0.6)
Urosepsis [b]	1 (0.6)
Duodenal ulcer	1 (0.6)
Gastroenteritis eosinophilic	1 (0.6)
Intestinal obstruction[b, c]	1 (0.6)
Oesophageal adenocarcinoma	1 (0.6)
Parathyroid tumour benign	1 (0.6)
Prostate cancer	1 (0.6)
Bile duct stone	1 (0.6)
Cholecystitis	1 (0.6)
Cholecystitis acute	1 (0.6)
Intervertebral disc protrusion	1 (0.6)
Osteoarthritis	1 (0.6)
Lower limb fracture	1 (0.6)
Nephrolithiasis	1 (0.6)
Toxic skin eruption	1 (0.6)
Breast prosthesis implantation	1 (0.6)
Aortic aneurysm rupture	1 (0.6)

[a]one event of myocardial infarction was treatment-related; [b]adverse event of interest; [c]treatment-related; N = Number of subjects who were enrolled and received at least one dose of investigational product; n = Number of subjects reporting at least one occurrence of an adverse event; % = n/N*100

Sources: Table 14a-6.4, Table 14a-6.5, and Table 14a-6.25

Laboratory Data

Five subjects had a grade 2 decrease in their absolute neutrophil counts (Listing 16a-2.8.6); neutropenia was reported in 1 subject (0.6%) (Table 14a-6.2.1).

Increased grade 3 shifts in glucose levels from Study 20090403 baseline were reported in 8 subjects (4%), 2 subjects (1%) had increased grade 3 shifts in sodium level, 1 subject (1%) had decreased grade 3 shift in sodium level, and 4 subjects (2%) had decreased grade 3 shifts in phosphorus level (Table 14a-7.1 to Table 14a-7.40).

Hematuria and proteinuria were reported as adverse events in 2 subjects and bilirubinuria was reported in 1 subject (Table 14a-6.2.1). The summaries of subjects with urine protein, urine leukocyte esterase, and urine blood are presented in Table 14a-7.76 to Table 14a-7.78. High uric acid levels were reported in 47 subjects (26%) (Table 14a-7.40).

Increased grade 3 shifts in aspartate aminotransferase (AST) level from Study 20090403 baseline were reported for 2 subjects (1%) (Table 14a-7.37) and increased grade 3 shift in alanine aminotransferase (ALT) level was reported for 1 subject (1%) (Table 14a-7.38). Incidence of ≥ grade 2 liver enzyme elevations was low (n = 11) (Listing 16a-2.8.6). An ALT or AST > 3 x upper limit of normal (ULN) was identified in 1 subject at the Study 20090403 baseline and in 7 subjects during the study; 2 subjects during the study had total bilirubin ≥ 2 x ULN. No subject met Hy's law laboratory criteria. (Table 14a-7.75).

Conclusions:

- In this open-label extension study, brodalumab administered SC Q2W (210 mg, later reduced to 140 mg in subjects weighing ≤ 100 kg, and subsequently increased to 210 mg in subjects with an inadequate response) had an acceptable safety profile in long-term treatment of moderate to severe plaque psoriasis.
- The most frequently reported adverse events included nasopharyngitis, upper respiratory tract infection, arthralgia, influenza, gastroenteritis, back pain, and sinusitis.
- The efficacy of brodalumab was exhibited for all endpoints and was stable through week 168, including responses ≥ 90% for PASI 75, ≥ 80% for PASI 90, and ≥ 50% for PASI 100 at week 168.

[redacted]