2. SYNOPSIS

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

Name of Finished Product: Brodalumab

Name of Active Ingredient: AMG 827

Title of Study: A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1

Investigators and Study Centers: This study was conducted at 73 centers in Europe, Canada, and the United States (US). Study centers and principal investigators are listed in Section 16.1.4.

Publications: None.

Study Period: 29 August 2012 (first subject enrolled) to 12 March 2014 (data cutoff date for primary analysis)

Development Phase: 3

Objectives: The key objectives of this study are listed below.

Primary Objectives (compared with placebo):

- to evaluate the efficacy of brodalumab (210 mg every 2 weeks [Q2W]; and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving 75% improvement in Psoriasis Area and Severity Index (PASI; PASI 75) at week 12.
- to evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving success (clear [0] or almost clear [1]) on the static physician's global assessment (sPGA) at week 12.

Key Secondary Objectives (compared with placebo):

- to evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in clearing psoriasis, as measured by the proportion of subjects achieving PASI 100 at week 12.
- to evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in clearing psoriasis, as measured by the proportion of subjects achieving sPGA of 0 at week 12.
- to evaluate maintenance of effect with continued brodalumab treatment (210 mg Q2W and 140 mg Q2W), as measured by the proportion of subjects achieving sPGA success at week 52.
- to evaluate the effect of brodalumab (210 mg Q2W and 140 mg Q2W) on patient-reported symptoms of psoriasis, as measured by the proportion of subjects who meet the responder definition for the Psoriasis Symptom Inventory (PSI) (total score ≤ 8, with no item scores > 1) at week 12.

Safety Objective

- to evaluate the short- (12 week) and long-term (5 year) safety profile of brodalumab in subjects with moderate to severe plaque psoriasis.

Other objectives during the induction phase included evaluations of psoriasis severity, scalp and nail disease, and patient-reported outcome measures. Evaluations during the randomized withdrawal phase included maintenance of effect with continued brodalumab treatment, effect of retreatment, patient-reported outcome measures, and pharmacokinetics.

All study objectives are provided in Protocol Section 1 (Section 16.1.1 of this report).

Methodology: After the screening period (up to 30 days), subjects entered a randomized, double blind, placebo-controlled induction phase where they were randomized in a 1:1:1 ratio to receive brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, or placebo, stratified by baseline total body weight (≤ 100 kg; > 100 kg), by prior biologic use (subjects with prior biologic use were capped at 50% of the study population), and by geographic region (defined by country for non-US countries and by geographic region in the US [US-West, US-Midwest, US-Northeast, US-South]).

At the week-12 visit:

- Subjects originally randomized to either of the brodalumab treatment arms who had sPGA success at week 12 were rerandomized in a 1:1 ratio to receive either placebo or continued brodalumab at their induction dose, stratified by week 12 total body weight (≤ 100 kg; > 100 kg) and week-12 response (sPGA 0; sPGA 1).
- All subjects originally randomized to placebo and any subjects not qualifying for rerandomization received brodalumab 210 mg Q2W.

Subjects who did not attend their week-12 visit did not receive any additional investigational product.

Subjects continued at their week-12 rerandomized treatment unless they had return of disease (sPGA ≥ 3) at or after week 16 through week 52. If a subject had return of disease, he or she began retreatment (retreatment phase) with his or her induction dose as described in Protocol Section 6.1.1 (Section 16.1.1 of this report). Subjects could qualify for rescue treatment (rescue phase) with brodalumab 210 mg Q2W according to the rules in Protocol Section 6.1.1 (Section 16.1.1 of this report). Original and rerandomized treatment assignments remained blinded until all subjects reached week 52 or discontinued from the study, whichever occurred first. This study report presents data through week 52 of the study.

Number of Subjects Planned: Approximately 600 subjects.

Diagnosis and Main Criteria for Eligibility: men and women ≥ 18 and ≤ 75 years of age with stable moderate to severe plaque psoriasis diagnosed at least 6 months before first dose of investigational product (eg, no morphology changes or significant flares of disease activity in the opinion of the investigator). Subjects needed to have involved body surface area (BSA) ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline. A complete list of eligibility criteria is provided in Protocol Section 4.1 (Section 16.1.1 of this report).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Brodalumab is presented as a clear to slightly opalescent, colorless to slightly yellow liquid and is supplied in pre-filled syringes. After week 24, brodalumab was self-administered by subjects as a subcutaneous injection 210 mg Q2W or 140 mg Q2W to the abdomen, thigh, or upper arm. Subsequent injections could be administered to the same body region. During the induction phase, subjects randomized to 210 mg Q2W received 2 injections of brodalumab (1.0 mL and 0.5 mL) and subjects randomized to 140 mg Q2W received 2 injections (1.0 mL of brodalumab and 0.5 mL of placebo); subjects randomized to placebo received 2 injections (1.0 mL of placebo and 0.5 mL of placebo). These doses were administered at day 1 and weeks 1, 2, 4, 6, 8, and 10. Retreatment and rescue treatment are described above and details are provided in Protocol Section 6.1.1 (Section 16.1.1 of this report). Manufacturing batch numbers for brodalumab are provided in Listing 16-1.6.1.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Brodalumab placebo is identical in appearance to brodalumab and contains the same deliverable volume and excipients without the active ingredient. The subcutaneous administration schedule for placebo was identical to that for brodalumab specified above. Manufacturing batch numbers for placebo are provided in Listing 16-1.6.1.

Duration of Treatment: The total duration of treatment was planned to be 266 weeks (including the induction, withdrawal and retreatment phase, and long-term extension phase). The entire study was planned to be up to 271 weeks (approximately 5 years) in duration.

Study Endpoints:

Co-primary Endpoints:

- PASI 75 at week 12
- sPGA success at week 12

Key Secondary Endpoints:

- PASI 100 at week 12
- sPGA of 0 at week 12
- sPGA success at week 52 (in rerandomized subjects)
- PSI responder definition (total score ≤ 8, with no item score > 1) at week 12

Safety Endpoints:

- adverse events
- events of interest
- anti-brodalumab antibodies

Other endpoints included sPGA success, time to sPGA success, PASI 75, PASI 90, and PASI 100, time to PASI response, percentage improvement in PASI, patient-reported outcome measures, and pharmacokinetics. Complete descriptions of other secondary endpoints and exploratory endpoints are provided in Protocol Section 10.1.1 (Section 16.1.1 of this report).

This report presents the results of the week-12 and week-52 efficacy endpoints; safety data are presented through 52 weeks.

Statistical Methods: The primary analysis occurred after all subjects completed their week 52 visit (or terminated from the study). This analysis included induction-phase co-primary endpoints for data through week 12, as well as endpoints for data through week 52.

To maintain the 2-sided family-wise type-1 error rate at 5%, a sequential testing procedure was followed. The co-primary endpoints, sPGA success and PASI 75 at week 12, for the comparisons between the 210 mg Q2W treatment group and placebo were tested simultaneously each at alpha = 0.05 level. If the null hypothesis for both of the co-primary endpoints for the 210 mg Q2W comparison were rejected, the hypotheses for the co-primary endpoints for the comparisons between the 140 mg Q2W treatment group and placebo were tested simultaneously. If either hypothesis was not rejected, all subsequent hypotheses for key secondary endpoints were not tested. If the hypotheses for co-primary endpoints were rejected, the hypotheses corresponding to the key secondary endpoints were tested sequentially in the order listed in Protocol Section 10.1.1 (Section 16.1.1 of this report). The p-values for primary and key secondary comparisons were adjusted for multiplicity, whereas the p-values for the analyses of other secondary and exploratory endpoints were reported without adjusting for multiplicity.

At week 12, dichotomous variables, including the proportion of subjects achieving success on sPGA, the proportions of subjects achieving PASI 75 and PASI 100, and the proportion of subjects meeting the responder definition for the PSI, were compared between the brodalumab treatment groups and placebo group using a Cochran-Mantel-Haenszel (CMH) test adjusting for baseline total body weight (≤ 100 kg; > 100 kg), prior biologic use, geographic region (US, Canada and outside North America), and baseline measurement value group (≤ median; > median; for sPGA-related endpoints, baseline sPGA = 3, 4, or 5 were adjusted).

At week 52, dichotomous variables including the proportion of subjects achieving success on sPGA were compared between the treatment arms using a CMH test adjusting for week 12 total body weight (≤ 100 kg; > 100 kg) and sPGA response at week 12 (sPGA of 0; sPGA ≥ 1).

Continuous variables were compared between the treatment arms using a stratified analysis of covariance model adjusted for the relevant baseline or week 12 covariates.

For the analysis of the key secondary endpoint of sPGA success at week 52, subjects who had a return of disease and required subsequent retreatment during the withdrawal phase, were imputed as non-responders for dichotomized variables for visits after qualifying for retreatment up to week 52.

Baseline demographics and disease characteristics were summarized descriptively. The subject incidence and exposure-adjusted event rates of adverse events were tabulated by system organ class and preferred term. Subject incidence and exposure-adjusted event rates of adverse events of interest were also summarized according to their categories. Exposure-adjusted event rates were provided through week 52 based on groups defined by the planned treatment group based on randomization, rerandomization, retreatment and/or rescue, as appropriate, as constant 210 mg Q2W, constant 140 mg Q2W, combination of 140 mg Q2W/210 mg Q2W and mixed dosing.

A detailed description of the statistical methods is provided in
Statistical Analysis Plan, Section 10 (Section 16.1.9 of this report).

Summary of Results:

Subject Disposition: A total of 661 subjects were randomized into the study: 222 were allocated to receive 210 mg Q2W, 219 were allocated to receive 140 mg Q2W, and 220 subjects were allocated to receive placebo during the induction phase. A total of 33 subjects discontinued from the study during the induction phase: 10 subjects (4.5%) in the 210 mg Q2W group, 11 subjects (5.0%) in the 140 mg Q2W group, and 12 subjects (5.5%) in the placebo group. A total of 628 subjects entered the withdrawal phase; 283 subjects were rerandomized and 345 were not rerandomized. A total of 55 non-rerandomized subjects (15.9%) and 7 rerandomized (2.5%) subjects discontinued the study during the withdrawal phase. An additional 6 subjects discontinued the study during the retreatment phase and 2 discontinued during the rescue phase. A total of 558 subjects (84.4%) continued in the study after week 52.

Baseline Demographics:

Sex: 484 men (73.2%); 177 women (26.8%)

Age: mean (min, max): 46.3 (19, 86) years

Ethnicity/Race: 601 white (90.9%); 28 Asian (4.2%); 17 black or African American (2.6%); 8 other (1.2%); 5 native Hawaiian/other Pacific Islander (0.8%); 2 American Indian or Alaska native (0.3%)

Efficacy Results:

Co-primary Endpoints:

Analysis results of the co-primary endpoints are presented below.

	Brodalumab		Placebo		
Comparison	n/N (%)	95% CI of %	n/N (%)	95% CI of %	Adjusted p-value
PASI 75[a]					
210 mg vs placebo	185/222 (83.3)	(77.8, 88.0)	6/220 (2.7)	(1.0, 5.8)	<.001
140 mg vs placebo	132/219 (60.3)	(53.5, 66.8)	6/220 (2.7)	(1.0, 5.8)	<.001
sPGA success[a]					
210 mg vs placebo	168/222 (75.7)	(69.5, 81.2)	3/220 (1.4)	(0.3, 3.9)	<.001
140 mg vs placebo	118/219 (53.9)	(47.0, 60.6)	3/220 (1.4)	(0.3, 3.9)	<.001

CI = confidence interval; N = Number of subjects who were randomized and had a valid measurement value at the specified week, after imputation; % = n/N * 100; PASI = Psoriasis Area and Severity Index; sPGA = static physician's global assessment.
[a] At week 12
P-values for week 12 endpoints are based on Cochran-Mantel-Haenszel (CMH) tests adjusting for baseline body weight (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline value of the endpoint
Adjusted p-values are obtained by applying a sequential testing procedure for multiplicity adjustment, so that the statistical significance of a test can be obtained by comparing the adjusted p-value with a nominal significance level 0.05 (see Section 8.8.5.2).
Non-responder imputation (NRI) is used to impute missing data
Source: Table 14-4.34

Key Secondary Endpoints:

Analysis results of the key secondary endpoints are presented below.

	Brodalumab		Placebo		
Comparison	n/N (%)	95% CI of %	n/N (%)	95% CI of %	Adjusted p-value
PASI 100[a]					
210 mg vs placebo	93/222 (41.9)	(35.3, 48.7)	1/220 (0.5)	(0.0, 2.5)	<.001
140 mg vs placebo	51/219 (23.3)	(17.9, 29.5)	1/220 (0.5)	(0.0, 2.5)	<.001
sPGA of 0[a]					
210 mg vs placebo	93/222 (41.9)	(35.3, 48.7)	1/220 (0.5)	(0.0, 2.5)	<.001
140 mg vs placebo	51/219 (23.3)	(17.9, 29.5)	1/220 (0.5)	(0.0, 2.5)	<.001
sPGA success[b]					
210 mg vs placebo	69/83 (83.1)	(73.3, 90.5)	0/84 (0.0)	(0.0, 4.3)	<.001
140 mg vs placebo	40/57 (70.2)	(56.6, 81.6)	3/59 (5.1)	(1.1, 14.1)	<.001
PSI responder[a]					
210 mg vs placebo	135/222 (60.8)	(54.1, 67.3)	9/220 (4.1)	(1.9, 7.6)	<.001
140 mg vs placebo	116/219 (53.0)	(46.1, 59.7)	9/220 (4.1)	(1.9, 7.6)	<.001

CI = confidence interval; N = Number of subjects who were randomized and had a valid measurement value at the specified week, after imputation; % = n/N * 100; PASI = Psoriasis Area and Severity Index; PSI = Psoriasis Symptom Inventory; sPGA = static physician's global assessment.
[a] At week 12
[b] At week 52
P-values for week 12 endpoints are based on Cochran-Mantel-Haenszel (CMH) tests adjusting for baseline body weight (≤100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline value of the endpoint
Nominal p-values for sPGA success at week 52 is based on CMH test adjusting for week 12 total body weight (≤ 100 kg, > 100 kg) and week 12 sPGA (0, ≥ 1)
Adjusted p-values are obtained by applying a sequential testing procedure for multiplicity adjustment, so that the statistical significance of a test can be obtained by comparing the adjusted p-value with a nominal significance level 0.05
Non-responder imputation (NRI) is used to impute missing data
For sPGA success at week 52, subjects who experience return of disease through week 52 are imputed as non-responders at the time of qualification for retreatment
Source: Table 14-4.34

Pharmacokinetic Results:

Pharmacokinetic trough and intensive (week 10 and 16 substudy) samples were collected in this study. At week 10, after multiple subcutaneous injections of brodalumab, C_{max} and AUC_{tau} increased approximately greater than dose proportionally from the 140 mg Q2W to 210 mg Q2W dose. C_{max} increased 2.5-fold and AUC_{tau} increased 3.2-fold for a 1.5-fold increase in dose. The mean C_{max} and AUC_{tau} values from the 140 mg Q2W/140 mg Q2W group at week 16 remained similar to those of the 140 mg Q2W group at week 10. Mean C_{max} and AUC_{tau} values were similar at week 16 in the 140 mg Q2W/210 mg Q2W open-label group when compared to week 10 in the 210 mg Q2W group. The mean C_{max} and AUC_{tau} values from the 210 mg Q2W/210 mg Q2W group at week 16 remained similar to that of the 210 mg Q2W group at week 10. The mean C_{max} and AUC_{tau} values were similar in the placebo/210 mg Q2W group at week 16 when compared to the 210 mg Q2W group at week 10. The median t_{max} value remained around 3 days across all the different treatment arms at week 10 and week 16.

Safety Results: During the induction phase, the percentage of subjects reporting adverse events was 59.0% in the 210 mg Q2W group, 57.5% in the 140 mg Q2W group, and 50.9% in the placebo group. The most commonly reported (≥ 5%) adverse events in all treatment groups were nasopharyngitis (9.3% in subjects exposed to brodalumab, 10% in subjects exposed to placebo), upper respiratory tract infection (8.2% in subjects exposed to brodalumab, 6.4% in subjects exposed to placebo), and headache (5.2% in subjects exposed to brodalumab, 3.2% in subjects exposed to placebo). Through week 52, the exposure-adjusted event rate of treatment-emergent adverse events during the withdrawal phase was 368.8 events per 100 subject-years for all subjects who received at least 1 dose of brodalumab. The most frequently reported treatment-emergent adverse events (per 100 subject-years) were nasopharyngitis (24.7), upper respiratory tract infection (22.0), headache (14.9), and arthralgia (11.6).

During the induction phase, 6 subjects (1.4%) exposed to brodalumab and 3 subjects (1.4%) exposed to placebo had adverse events that led to withdrawal of investigational product. Through 52 weeks, the exposure-adjusted event rate of adverse events leading to discontinuation of investigational product was 3.1 events per 100 subject-years for all subjects exposed to brodalumab. Adverse events leading to withdrawal that occurred in more than 1 subject were psoriasis (3 subjects) and myocardial infarction (3 subjects).

Serious adverse events were reported for 2.3% of subjects exposed to brodalumab and 1.4% of subjects exposed to placebo. The most commonly reported serious adverse event was cellulitis in subjects exposed to brodalumab (0.5%) and psoriasis in subjects exposed to placebo (0.9%). The exposure-adjusted event rate of serious adverse events for subjects exposed to brodalumab was 9.5 events per 100 subject-years.

A total of 4 subjects died through week 52; all deaths were reported by investigators as unrelated to investigational product. No deaths occurred during the induction phase. One subject ([redacted]) died (cerebrovascular accident) during retreatment with 210 mg Q2W. During the withdrawal phase, 2 subjects who were not rerandomized (ie, received 210 Q2W) died: sudden death was reported for 1 subject ([redacted]); 1 ([redacted]) subject died of an intentional overdose. Esophageal varices hemorrhage resulted in death for 1 subject ([redacted]) in the 210 mg Q2W group.

There were no clinically notable trends in vital sign or clinical laboratory results.

Five subjects (< 1%) who tested positive for anti-brodalumab antibodies during the study were negative for anti-brodalumab antibodies at the last time point tested within the study period. Neutralizing anti-brodalumab antibodies were not detected in any subjects in the study.

Conclusions:

Efficacy

- The results of this study show that brodalumab at both doses improves response rates for all co-primary and secondary endpoints. Statistically significant response rates were observed based on the adjusted p-values ($p < 0.001$) for the brodalumab treatment groups compared with placebo for the co-primary (PASI 75 at week 12; sPGA success at week 12) and key secondary endpoints (PASI 100 at week 12; sPGA of 0 at week 12; sPGA success at week 52; PSI responder).
- Across the co-primary and key secondary endpoints, a higher proportion of subjects responded to treatment with 210 Q2W than with 140 mg Q2W, with both doses statistically superior to placebo.

Pharmacokinetics

- C_{max} and AUC_{tau} increased approximately greater than dose proportionally from the 140 mg Q2W to 210 mg Q2W dose at week 10. Mean C_{max} and AUC_{tau} values were generally similar at week 16 compared to week 10 for each respective brodalumab dosing regimen.

Safety

- The most commonly reported adverse events occurring in ≥ 5% in any treatment group during the induction period were nasopharyngitis, upper respiratory tract infection, and headache. These events were also the most commonly reported through week 52 indicating that the adverse event profile remained similar with longer exposure. There was no evidence of a dose effect on the adverse event rates through 52 weeks of treatment.
- The incidence of serious adverse events was similar across the treatment groups. The most commonly reported serious adverse event was cellulitis in subjects exposed to brodalumab (0.5%) and psoriasis in subjects exposed to placebo (0.9%). The exposure-adjusted event rate of serious adverse events for subjects exposed to brodalumab was 9.5 events per 100 subject-years.
- A total of 4 subjects died through 52 weeks. All deaths were considered by investigators to be unrelated to investigational product.
- Five subjects (< 1%) who tested positive for anti-brodalumab antibodies during the study were negative for anti-brodalumab antibodies at the last time point tested within the study period. Neutralizing anti-brodalumab antibodies were not detected in any subjects in the study.