2. SYNOPSIS

Name of Sponsor: Amgen, Inc

Name of Finished Product: Brodalumab

Name of Active Ingredient: Brodalumab

Title of Study: A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2

Investigators and Study Centers: This study was conducted at 142 centers in Australia, Austria, Canada, Czech Republic, France, Hungary, Netherlands, Poland, Portugal, Spain, and the United States (US; US-Midwest, US-Northeast, US-South, US-West). Centers and principal investigators are listed in Section 16.1.4.

Publications: None

Study Period: 22 August 2012 (first subject enrolled) to 22 September 2014 (primary analysis data cutoff date)

Development Phase: 3

Objectives:

Primary Placebo-family 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

Primary Ustekinumab-family Objectives (Compared With Ustekinumab)

- to evaluate the efficacy of brodalumab (210 mg Q2W; and 140 mg Q2W for subjects ≤ 100 kg with 210 mg dosage for subjects > 100 kg) in clearing psoriasis in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving PASI 100 at week 12

Key Secondary Placebo-family 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 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

Key Secondary Ustekinumab-family Objectives (Compared With Ustekinumab)

- to evaluate the efficacy of brodalumab (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 for subjects ≤ 100 kg with 210 mg dosage for subjects > 100 kg), as measured by the proportion of subjects achieving PASI 75 at week 12

Maintenance Objectives

- to compare the efficacy of brodalumab maintenance regimens, as measured by the proportion of subjects achieving success on the sPGA at week 52

Safety Objectives

- to evaluate the short- (12 week) and long-term (5 year) safety profile of brodalumab in subjects with moderate to severe plaque psoriasis
- To evaluate the safety profile of brodalumab manufactured at 2 different manufacturing sites (Amgen Thousand Oaks [ATO] and Amgen Rhode Island [ARI])

A complete list of all objectives of the study is provided in the Protocol Section 1 (Section 16.1.1 of this report).

Methodology: After the screening period, subjects entered a 12-week, double-blind, active comparator and placebo-controlled induction phase where they were randomized in a 2:2:1:1 ratio to 1 of the following treatment groups: brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, ustekinumab (45 mg if ≤ 100 kg at the baseline visit, 90 mg if > 100 kg at the baseline visit), or placebo. Randomization was stratified by baseline total body weight (≤ 100 kg; > 100 kg), by prior biologic use, and by geographic region. Subjects with prior biologic use were limited to 50% of the study population. Starting on day 1 and through week 10, all subjects received Amgen investigational product (brodalumab and/or placebo) Q2W with an additional dose at week 1 and non-Amgen investigational product (ustekinumab or placebo) at day 1 and week 4.

At the week-12 visit:

- Subjects originally randomized to either brodalumab groups were rerandomized (2:2:2:1) into the maintenance phase to receive brodalumab 210 mg Q2W, 140 mg Q2W, 140 mg every 4 weeks (Q4W), or 140 mg every 8 weeks (Q8W). Rerandomization was stratified by week 12 total body weight (≤ 100 kg; > 100 kg), original induction regimen, and week 12 response (sPGA 0 vs sPGA ≥ 1).
- Subjects originally randomized to ustekinumab continued to receive ustekinumab.
- Subjects originally randomized to receive placebo began receiving brodalumab 210 mg Q2W.
- Subjects who did not attend their week-12 visit did not receive any further investigational product.

Through week 52, all subjects received Amgen investigational product (brodalumab and/or placebo) Q2W with an additional dose at week 13 and non-Amgen investigational product (ustekinumab or placebo) at weeks 16, 28, and 40. In addition, to maintain the blind to rescue treatment, Amgen investigational product (brodalumab and/or placebo) was also administered at week 17.

Subjects may have qualified for rescue treatment at or after week 16 with an inadequate response (defined as a single sPGA of ≥ 3 or persistent sPGA values of 2 over ≥ a 4-week period). Through week 52, subjects could only qualify for rescue at scheduled study visits. At week 16, rescue treatment was with brodalumab 210 mg for

all subjects, including those on ustekinumab. After week 16 and through week 52, subjects on brodalumab rescued with brodalumab 210 mg Q2W and subjects on ustekinumab rescued with ustekinumab. Rescue treatment was blinded (ie, subjects continued to receive Amgen investigational product and non-Amgen investigational product according to the maintenance phase dosing schedule).

At week 52, subjects who were on brodalumab continued to receive brodalumab at their maintenance or rescue phase dose; subjects who were originally randomized to ustekinumab received brodalumab 210 mg Q2W.

Original and rerandomized treatment assignments, as well as assignments in the long-term extension phase, remained blinded until all subjects reached week 52 or terminated the study, whichever came first.

Additional details on dosage, administration, and treatment schedules are provided in the Protocol Section 6.3 (Section 16.1.1 of this report).

This clinical study report presents data through week 52 and through the data cutoff.

Number of Subjects Planned: 1800

Number of Subjects Enrolled: 1831

Diagnosis and Main Criteria for Eligibility:

Eligible subjects were men and women who were ≥ 18 and ≤ 75 years of age at the time of screening with stable, moderate to severe plaque psoriasis diagnosed ≥ 6 months before first dose of investigational product, involved body surface area (BSA) ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline.

The complete list of eligibility criteria is listed in Protocol Section 4 (Section 16.1.1 of this report).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Brodalumab (Amgen Investigational Product)

Brodalumab (process 2 ATO and process 2 ARI drug substances) was supplied as a 140 mg/mL injectable solution.

Amgen investigational product (brodalumab and/or matching placebo) was administered as 2 blinded subcutaneous (SC) injections (one 1.0-mL [140 mg] and one 0.5-mL [70 mg]) Q2W starting on day 1, with additional doses at week 1 and week 13. In addition, to maintain the blind to rescue treatment, Amgen investigational product (brodalumab and/or placebo) was also administered at week 17.

Amgen investigational product was administered as a SC injection to the abdomen, thigh, or upper arm.

Manufacturing batch numbers for brodalumab are provided in Section 16.1.6.

Ustekinumab (Non-Amgen Investigational Product)

Non-Amgen investigational product (ustekinumab or matching placebo) was administered as 1 or 2 blinded SC injections (0.5 mL [45 mg]) at day 1 and weeks 4, 16, 28, and 40, depending on subject weight at the baseline visit (1 injection if ≤ 100 kg and 2 injections if > 100 kg).

For subjects who received 2 injections of non-Amgen IP per dose, the 2 injections were to be administered in different body regions (upper arms, gluteal regions, thighs, or abdomen). Ustekinumab was sourced in the US.

Manufacturing batch numbers for ustekinumab are provided in Section 16.1.6.

Duration of Treatment: The total duration of treatment is planned to be 266 weeks (including the induction, maintenance, and long-term extension phases).

For the purpose of the primary analysis, the duration of treatment was 52 weeks.

Study Endpoints:

Co-primary (Brodalumab Arms vs Placebo):

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

Primary (Brodalumab vs Ustekinumab):

- PASI 100 at week 12
  - brodalumab 210 mg Q2W
  - brodalumab 140 mg Q2W for subjects ≤ 100 kg with 210 mg dosage for subjects > 100 kg

Key Secondary (Brodalumab Arms vs Placebo):

- PASI 100 at week 12
- sPGA of 0 at week 12
- PSI responder definition at week 12

Key Secondary (Brodalumab vs Ustekinumab):

- PASI 100 at week 12
  - 140 mg Q2W
- PASI 75 at week 12
  - 210 mg Q2W
  - 140 mg Q2W for subjects ≤ 100 kg with 210 mg dosage for subjects > 100 kg

Maintenance (After Rerandomization at Week 12): sPGA success at week 52

Safety: Adverse events, events of interest, presence of binding and/or neutralizing anti-brodalumab antibodies, and electrocardiograms.

Other endpoints included sPGA success (at other time points), time to sPGA success, PASI 75, PASI 90, and PASI 100 (at other time points), time to PASI response, percentage improvement in PASI, patient-reported outcome (PRO) 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). Summary tables include a weight-based subgroup, which groups data for subjects on brodalumab 140 mg Q2W who weighed ≤ 100 kg at baseline and subjects on brodalumab 210 mg Q2W who weighed > 100 kg at baseline.

This report presents the results of the week-12 and week-52 efficacy endpoints; safety data are presented through week 12, through week 52 and through the data cutoff (22 September 2014).

The safety, efficacy, and immunogenicity of brodalumab manufactured at 2 different sites (ATO and ARI) was evaluated in subjects enrolled at sites in the US and Canada who continued on the study after week 52. Subjects were switched from ATO product to ARI product at or after week 52. These data are presented through the data cutoff.

Statistical Methods: The primary analysis was performed after all subjects had completed their week-52 visit (or terminated from the study). This analysis included induction phase primary and co-primary endpoints that included data through week 12, as well as the maintenance endpoint that included data through week 52. The primary analysis consisted of 2 families of primary and key secondary endpoints (placebo and ustekinumab family). To maintain the 2 sided family-wise type-1 error rate at 5%, a combination of parallel and sequential testing was followed for the week 12 primary and key secondary endpoints in the placebo family at alpha = 0.01 (2-sided) and in the ustekinumab family at alpha = 0.04 (2-sided). If the null hypothesis for any of the primary endpoints within a family was not rejected, all the subsequent hypotheses for the key secondary endpoints at week 12 within that family were not tested. However, if the null hypotheses for the primary endpoints within a family were rejected, then the hypotheses corresponding to the key secondary endpoints at week 12 within that family were to be tested sequentially at alpha = 0.01 (2-sided level) for the placebo family and alpha = 0.04 (2-sided) for the ustekinumab family.

After rerandomization at week 12, the maintenance endpoints PGA success at week 52 was tested sequentially between the brodalumab maintenance regimens at full alpha = 0.05.

At week 12, the dichotomous efficacy and PRO endpoints between the treatment arms, including the proportion of subjects achieving sPGA success, the proportion of subjects achieving PASI 75 and PASI 100, and the proportion of subjects achieving the responder definition of PSI, were compared using the Cochran Mantel-Haenszel (CMH) test adjusted by baseline total body weight group (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and the baseline value of the outcome measure (≤ median, > median; for sPGA-related endpoints, baseline sPGA = 3, 4, or 5 were used for adjustment).

At week 52, dichotomous variables, including the proportion of subjects achieving success on sPGA, were compared between the treatment arms using the CMH test adjusting for week 12 total body weight group (≤ 100 kg, > 100 kg), randomized induction treatment regimen (brodalumab 210 mg Q2W, brodalumab 140 mg Q2W), and week 12 sPGA response (sPGA 0,sPGA ≥ 1). For testing the maintenance endpoint (sPGA success at week 52), subjects who had an inadequate response (sPGA ≥ 3 or persistent sPGA values of 2 over ≥ a 4-week period at or after week 16) at or before week 52 were imputed as non-responders.

Continuous variables were compared between the treatment arms using an analysis of covariance (ANCOVA) model adjusted for relevant baseline or week 12 covariates.

Descriptive statistics were produced to describe the exposure to investigational product by treatment group. The Medical Dictionary for Regulatory Activities (MedDRA, version 17.1) was used to code all adverse events to a system organ class and a preferred term. The percentages of subjects with laboratory toxicities by Common Terminology Criteria for Adverse Event (CTCAE, version 4.03) grade were summarized. Events of interest were predefined; search terms used for events of interest queries are provided in Section 16.1.13.1. Vital signs (ie, heart rate, body temperature, systolic and diastolic blood pressures) were summarized. The electrocardiogram measurements from this clinical study were performed per standard of care for routine safety monitoring rather than for purposes of assessment of potential corrected QT (QTc) effect. Since these evaluations may not have been performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, neither summaries nor statistical analyses were provided.

Pharmacokinetic parameters were estimated based on individual serum brodalumab concentration on weeks 10 and 20 for the maximum observed drug concentration (C_{max}) value after SC injection, time (t_{max}) to reach C_{max}, area under the serum concentration-time curve during the dosing interval (AUC_{tau}, with tau equal to 336 hours), and area under the serum concentration-time curve from time zero to 14 days postdose (AUC_{14d}). Details of these analyses are described in Section 16.1.13.2.

For a detailed description of statistical methods, see Statistical Analysis Plan (SAP) Section 10 (Section 16.1.9 of this report).

Summary of Results:

Subject Disposition:

A total of 1831 subjects were enrolled in the study. Subject disposition for the induction phase is summarized below.

			Brodalumab	
Number of Subjects	Placebo	Ustekinumab	140 mg Q2W	210 mg Q2W
Randomized	309	300	610	612
Received Amgen IP	309	300	607	612
Completed phase	300	291	588	597
Discontinued phase	9	9	22	15

IP = investigational product; Q2W = every 2 weeks

Subject disposition for the maintenance phase is summarized below

	Non-rerandomized at Week 12		Rerandomized at Week 12			
			Brodalumab			
Number of Subjects	Placebo/Brodalumab 210 mg Q2W	Ustekinumab	140 mg Q8W	140 mg Q4W	140 mg Q2W	210 mg Q2W
Rerandomized	-	-	168	335	337	334
Non-Rerandomized	297	289	-	-	-	-
Received Amgen IP	297	288	167	335	337	334
Completed phase	274	148	14	39	158	219
Discontinued phase	22	7	5	9	16	14
Entered rescue	0	133	149	287	163	101

IP = investigational product; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks

Baseline Demographics:

Sex: 1258 men (68.7%); 573 women (31.3%)

Mean age (range): 44.6 (18 to 76) years

Ethnicity/Race: 1652 White (90.2%); 68 Asian (3.7%); 53 Black (2.9%); 31 other (1.7%); 10 multiple (0.5%); 9 native Hawaiian/other Pacific Islander (0.5%); 8 American Indian or Alaska native (0.4%)

Efficacy Results:

Induction Endpoints at Week 12

Comparison With Placebo, Co-primary and Key Secondary Endpoints:

Comparisons with placebo yielded statistically significant results in favor of brodalumab 210 mg Q2W and 140 mg Q2W for both co-primary endpoints and the key secondary endpoints (adjusted p < 0.001). Analysis results are summarized below.

Comparison (Brodalumab vs Placebo)	Brodalumab n/N (%)	Brodalumab 95% CI of %	Placebo n/N (%)	Placebo 95% CI of %	Nominal p-value	Adjusted p-value
Co-primary efficacy endpoints at week 12						
PASI 75: 210 mg Q2W	528/612 (86.3)	(83.3, 88.9)	25/309 (8.1)	(5.3, 11.7)	< 0.001	< 0.001
sPGA success: 210 mg Q2W	481/612 (78.6)	(75.1, 81.8)	12/309 (3.9)	(2.0, 6.7)	< 0.001	< 0.001
PASI 75: 140 mg Q2W	406/610 (66.6)	(62.7, 70.3)	25/309 (8.1)	(5.3, 11.7)	< 0.001	< 0.001
sPGA success: 140 mg Q2W	354/610 (58.0)	(54.0, 62.0)	12/309 (3.9)	(2.0, 6.7)	< 0.001	< 0.001
Key secondary efficacy endpoints at week 12						
PASI 100: 210 mg Q2W	272/612 (44.4)	(40.5, 48.5)	2/309 (0.6)	(0.1, 2.3)	< 0.001	< 0.001
sPGA of 0: 210 mg Q2W	274/612 (44.8)	(40.8, 48.8)	2/309 (0.6)	(0.1, 2.3)	< 0.001	< 0.001
PASI 100: 140 mg Q2W	157/610 (25.7)	(22.3, 29.4)	2/309 (0.6)	(0.1, 2.3)	< 0.001	< 0.001
sPGA of 0: 140 mg Q2W	157/610 (25.7)	(22.3, 29.4)	2/309 (0.6)	(0.1, 2.3)	< 0.001	< 0.001
PSI responder: 210 mg Q2W	414/612 (67.6)	(63.8, 71.3)	21/309 (6.8)	(4.3, 10.2)	< 0.001	< 0.001
PSI responder: 140 mg Q2W	314/610 (51.5)	(47.4, 55.5)	21/309 (6.8)	(4.3, 10.2)	< 0.001	< 0.001

CI = confidence interval; N = Number of subjects who had a valid measurement value at the specified week, after imputation; n = Number of responders; % = n/N * 100; NRI = Non-responder Imputation;
PASI = Psoriasis Area and Severity Index; PSI = Psoriasis Symptom Inventory; sPGA = static Physician's Global Assessment; Q2W = every 2 weeks

Note: NRI was used to impute missing data. Treatment groups are defined as planned treatment for the induction phase.

Comparison With Ustekinumab, Primary and Key Secondary Endpoints:

Comparisons with ustekinumab yielded statistically significant results in favor of brodalumab 210 mg Q2W and the weight-based group for the primary endpoint. Results of the first key secondary endpoint, PASI 100 at week 12 (140 mg Q2W vs ustekinumab; p = 0.078), were not statistically significant, and therefore subsequent endpoints were not formally tested as a consequence of the sequential testing procedure. Therefore, statistical significance was not demonstrated for differences in PASI 75 at week 12 for the brodalumab 210 mg Q2W and brodalumab weight-based groups compared with ustekinumab, though the response rates for PASI 75 in the brodalumab 210 mg Q2W and brodalumab weight-based groups were both nominally significantly greater compared with ustekinumab.

Results of the co-primary and key secondary endpoints at week 12 are presented below:

Comparison (Brodalumab vs Ustekinumab)	Brodalumab		Ustekinumab		Nominal p-value	Adjusted p-value
	n/N (%)	95% CI of %	n/N (%)	95% CI of %		
Primary efficacy endpoints at week 12						
PASI 100: 210 mg Q2W	272/612 (44.4)	(40.5, 48.5)	65/300 (21.7)	(17.1, 26.8)	< 0.001	< 0.001
PASI 100: weight-based[a]	205/610 (33.6)	(29.9, 37.5)	65/300 (21.7)	(17.1, 26.8)	< 0.001	< 0.001
Key secondary endpoints at week 12						
PASI 100: 140 mg Q2W	157/610 (25.7)	(22.3, 29.4)	65/300 (21.7)	(17.1, 26.8)	0.078	0.078
PASI 75: 210 mg Q2W	528/612 (86.3)	(83.3, 88.9)	210/300 (70.0)	(64.5, 75.1)	< 0.001	0.078
PASI 75: weight-based[a]	470/610 (77.0)	(73.5, 80.3)	210/300 (70.0)	(64.5, 75.1)	0.026	0.078

NRI = Non-responder Imputation; N = Number of subjects who had a valid measurement value at the specified week, after imputation; n = Number of responders; % = n/N * 100; CI = confidence interval; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks
[a] Weight-based = Subjects ≤ 100 kg at baseline randomized to 140 mg Q2W or > 100 kg at baseline randomized to 210 mg Q2W.
Note: NRI was used to impute missing data. Treatment groups are defined as planned treatment for the induction phase.

Maintenance Endpoint at Week 52:

The percentage of subjects who achieved sPGA success at week 52 was 62.6% in subjects rerandomized to brodalumab 210 mg Q2W, 42.7% in subjects rerandomized to 140 mg Q2W, 9.0% in subjects rerandomized to 140 mg Q4W, and 4.8% in subjects rerandomized to 140 mg Q8W. All planned comparisons between the brodalumab groups yielded statistically significant results in favor of the higher dose/more frequent dosing regimen (adjusted p-values of < 0.001), with the 210 mg Q2W group achieving the highest rates of sPGA success at week 52.

Safety Results:

Safety Results During the Induction Phase:

During the induction phase, treatment with brodalumab demonstrated an acceptable safety profile. A summary of treatment-emergent adverse events observed through week 12 is provided below:

			Brodalumab	
Treatment-emergent adverse events	Placebo (N = 309) n (%)	Ustekinumab (N = 300) n (%)	140 mg Q2W (N = 607) n (%)	210 mg Q2W (N = 612) n (%)
All adverse events	165 (53.4)	177 (59.0)	365 (60.1)	354 (57.8)
Serious adverse events	8 (2.6)	4 (1.3)	13 (2.1)	6 (1.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Common adverse events (≥ 5% in any group)				
Nasopharyngitis	14 (4.5)	18 (6.0)	45 (7.4)	45 (7.4)
Upper respiratory tract infection	23 (7.4)	20 (6.7)	30 (4.9)	33 (5.4)
Headache	9 (2.9)	12 (4.0)	35 (5.8)	31 (5.1)
Arthralgia	12 (3.9)	9 (3.0)	33 (5.4)	28 (4.6)

N = Number of subjects who were randomized and received ≥ 1 dose of investigational product; n = Number of subjects reporting ≥ 1 occurrence of an adverse event; % = n/N * 100;Q2W = every 2 weeks.

Serious adverse events reported by > 1 subject were appendicitis (1 brodalumab 210 mg Q2W, 1 brodalumab 140 mg Q2W), cellulitis (1 brodalumab 210 mg Q2W, 1 brodalumab 140 mg Q2W), and pancreatitis acute (1 brodalumab 140 mg Q2W, 1 placebo). One subject (brodalumab 210 mg Q2W) died due to a cerebral infarction.

Safety Results Through Week 52:

Through week 52, treatment with brodalumab demonstrated a safety profile similar to that during the induction phase. Exposure-emergent adverse events through week 52 were analyzed according to a collapsed treatment group defined by their planned sequence of treatments:

- brodalumab constant dose 210 mg Q2W (ie, subjects randomized to brodalumab 210 mg Q2W during induction and rerandomized to 210 mg Q2W at week 12 or subjects randomized to placebo during induction and who began receiving brodalumab 210 mg Q2W at week 12)
- brodalumab constant dose 140 mg Q2W (ie, subjects randomized to brodalumab 140 mg Q2W during induction and rerandomized to 140 mg Q2W at week 12)
- brodalumab variable dose 140 mg Q2W/210 mg Q2W (ie, subjects originally randomized to 140 mg Q2W who were rerandomized to 210 mg Q2W and vice versa or subjects randomized to 140 mg Q2W who were rerandomized to 140 mg Q2W and then rescued with 210 mg Q2W)
- brodalumab variable mixed dosing group (subjects originally randomized to either 140 mg Q2W or 210 mg Q2W who were rerandomized to either 140 mg Q4W or 140 mg Q8W)
- brodalumab 210 mg Q2W after rescue from ustekinumab (ie, subjects randomized to ustekinumab during induction who rescued with brodalumab at week 16)
- constant ustekinumab (ie, subjects randomized to ustekinumab during induction and who continued receiving ustekinumab during maintenance)

Note that the above groups were assigned retrospectively based on the subject's treatment sequence and not based soley on randomized groups.

A summary of treatment-emergent exposure-emergent adverse events observed through week 52 is provided below:

		Brodalumab				
		Variable Dose			Constant Dose	
Treatment-emergent adverse events	Ustekinumab (N = 300) n (r)	210 mg Q2W after ustekinumab (N = 51) n (r)	Mixed dosing (N = 503) n (r)	140 mg Q2W / 210 mg Q2W (N = 423) n (r)	140 mg Q2W (N = 104) n (r)	210 mg Q2W (N = 486) n (r)
Subject years[a]	246.1	31.3	478.5	400.7	76.6	379.7
All adverse events	1017 (413.3)	102 (325.9)	2015 (421.1)	1629 (406.5)	316 (412.8)	1531 (403.2)
Serious adverse events	32 (13.0)	1 (3.2)	36 (7.5)	31 (7.7)	8 (10.4)	38 (10.0)
Fatal adverse events	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)
Common adverse events (≥ 10 events per 100 subject years)						
Nasopharyngitis	54 (21.9)	11 (35.1)	114 (23.8)	123 (30.7)	22 (28.7)	84 (22.1)
Upper respiratory tract infection	62 (25.2)	7 (22.4)	107 (22.4)	79 (19.7)	6 (7.8)	79 (20.8)
Headache	29 (11.8)	1 (3.2)	77 (16.1)	42 (10.5)	13 (17.0)	47 (12.4)
Arthralgia	30 (12.2)	6 (19.2)	63 (13.2)	60 (15.0)	16 (20.9)	39 (10.3)

IP = investigational product; N = number of subjects who were randomized and received ≥ 1 dose of active investigational product; n = number of adverse events; r = exposure adjusted event rate per 100 subject years (n/Subj-yr*100); Q2W = every 2 weeks

[a] Subject years = total subject years of exposure through week 52

A total of 7 deaths were reported through the data cutoff, including 1 during the induction phase, and 1 which was a grade 5 event of [redacted] reported for a subject's partner that did not result in death of a study subject. All fatal adverse events are summarized below.

Treatment (Induction/Maintenance/Rescue)	Preferred Term of Fatal Adverse Event	Related to IP
Through week 52 (on-study treatment)		
Placebo/brodalumab 210 mg Q2W/NA	death[a]	no
Brodalumab 140 mg Q2W/ 210 mg Q2W/NA	[redacted]	no
Ustekinumab/ustekinumab/NA	death[a]	no
Ustekinumab/ustekinumab/NA	pancreatic carcinoma	yes
Through week 52 (after exposure end date[b])		
Brodalumab 210 mg Q2W/NA/NA	cerebral infarction	no
Placebo/brodalumab 210 mg Q2W/NA	completed suicide	no
Through data cutoff (after exposure end date)		
Brodalumab 210 mg Q2W/140 mg Q4W/210 mg Q2W	traumatic lung injury	no

IP = investigational product; NA = not applicable; Q2W = every 2 weeks
[a] Event was adjudicated by the Cardiovascular Events Committee as a sudden death.
[b] Exposure end date was defined as 14 days after last dose of brodalumab 210 mg Q2W

Events of interest categories with preferred terms occurring at an exposure-adjusted event rate > 1 per 100 subject years in all brodalumab subjects included nervous system disorder adverse events, hypersensitivity adverse events, oropharyngeal candidiasis adverse events, depression events, and psychiatric disorder adverse events. Headache was the most common preferred term mapping to an event of interest category. The exposure-adjusted event rate for headache was 13.2 per 100 subject years for the all-brodalumab group and 11.8 per 100 subject years for the ustekinumab group.

Through week 52, the exposure-adjusted rate (per 100 subject-years) for the oropharyngeal candidiasis AMQ was 9.7 in the all-brodalumab group and 4.1 in the ustekinumab group. No serious oropharyngeal candidiasis events were identified by AMQ.

Through the data cutoff, 13 events mapping to the suicide-self-injury SMQ occurred in 9 subjects in the all-brodalumab group (rate of 0.6 events per 100 subject years). Additionally, after the exposure end date, 1 subject (placebo/brodalumab 210 mg Q2W) completed suicide. One ustekinumab subject attempted suicide through week 52.

One subject in the placebo treatment group met laboratory criteria for potential Hy's law (ALT/AST > 3x ULN, total bilirubin > 2x ULN, and ALP ≤ 2X ULN at same visit) during the induction phase and 1 subject (brodalumab 140 mg Q2W/140 mg Q4W/210 mg Q2W) met the criteria after week 52 during the open-label extension phase. Both subjects had alternative etiologies for the elevations, and therefore are not considered cases of Hy's law. Absolute neutrophil count (ANC) decreases of grade 3 or 4 were reported for 9 brodalumab subjects and 1 ustekinumab subject through week 52. Clinically notable trends in changes in vital sign or other clinical laboratory results during the induction phase or through week 52 were not noted.

For the all-brodalumab group, exposure-adjusted rates of treatment-emergent adverse events through the data cutoff were consistent with the rates observed through week 52 in the all-brodalumab group. The overall exposure-adjusted event rate (per 100 subject-years) from first dose of brodalumab through the data cutoff was 360.6 for all brodalumab subjects.

The profile of treatment-emergent adverse events was similar for subjects who switched to ARI product at or after week 52 and those who remained on ATO product. Exposure-adjusted event rates (per 100 subject-years) of treatment-emergent adverse events were similar across subjects who remained on the ATO product through the data cutoff date (369.3) and for those who switched to the ARI product, before the switch (349.3) and through the data cutoff (325.9).

Pharmacokinetic Results:

PK trough and intensive (week 10 and 20 substudy) samples were collected in this study. On weeks 10 to 12, after multiple SC injections of brodalumab, C_{max} and AUC_{tau} increased greater than dose proportionally from the 140 mg Q2W to brodalumab 210 mg Q2W dose. The mean C_{max} increased 2.9-fold and mean AUC_{tau} increased 2.8-fold for a 1.5-fold increase in dose. The median t_{max} values were observed at approximately 3 days across all the different treatment groups on weeks 10 to 12 and weeks 20 to 22.

Anti-brodalumab Antibody Assay Results:

Samples from 1787 subjects who received at least one dose of brodalumab were tested for anti-brodalumab antibodies through the data cutoff. Samples from 34 subjects (2.0%) had positive binding anti-brodalumab antibodies after brodalumab administration through the data cutoff. Of these, samples from 18 subjects (1.0%) were negative for anti-brodalumab antibodies at the last time point tested prior to the data cutoff date. Neutralizing anti brodalumab antibodies were not detected in samples from any subjects. No impact of anti-brodalumab antibodies on subject safety was observed.

Conclusions:

Efficacy Results

- Statistically significant response rates were observed based on adjusted p-values ($p < 0.001$) for the brodalumab 210 mg Q2W and 140 mg Q2W 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; PSI responder at week 12). In addition, while both 210 mg Q2W and 140 mg Q2W were statistically superior to placebo, a higher proportion of subjects responded to treatment with 210 mg Q2W compared with 140 mg Q2W at week 12.
- Statistically significant response rates were observed based on adjusted p-values ($p < 0.001$) for the brodalumab 210 mg Q2W treatment group and weight based subgroup compared with ustekinumab for the primary endpoint (PASI 100 at week 12). The first key secondary endpoint (PASI 100 at week 12 in subjects randomized to 140 mg Q2W) did not reach statistical significance ($p = 0.078$). Based on the sequential testing scheme, all subsequent endpoints were not rejected regardless of their nominal significance level. Therefore, the 2 hypotheses for the PASI 75 endpoint testing the brodalumab 210 mg Q2W and weight-based treatment groups against placebo were also not statistically significant based on the adjusted p-values (0.078). The nominal p-values were < 0.001 and 0.026 for the brodalumab 210 mg Q2W and weight-based treatment group against ustekinumab, respectively.
- All protocol-specified comparisons for the maintenance endpoint sPGA success at week 52 were statistically significant based on adjusted p-values ($p < 0.001$), with the brodalumab 210 mg Q2W regimen achieving the highest rates of sPGA success at week 52.

Safety Results

- Adverse events occurring in ≥ 5% in any treatment group during the induction phase were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. The most commonly reported adverse event in the brodalumab treatment groups was nasopharyngitis (7.4% in both brodalumab groups). Headache and arthralgia occurred at higher frequencies in the brodalumab groups (range of 4.6% to 5.8%) compared with the ustekinumab and placebo (range of 2.9% to 4.0%).
- Through week 52, the exposure-adjusted event rate of treatment-emergent adverse events was 409.2 per 100 subject-years for all brodalumab subjects and 413.3 per 100 subject-years for ustekinumab subjects. The profile of treatment-emergent adverse events observed through week 52 was similar to that observed during the induction phase.
- Most serious adverse events occurred in ≤ 1 subject during the induction phase. Serious adverse events reported by > 1 subject during the induction phase were appendicitis (1 brodalumab 210 mg Q2W, 1 brodalumab 140 mg Q2W), cellulitis (1 brodalumab 210 mg Q2W, 1 brodalumab 140 mg Q2W), and pancreatitis acute (1 brodalumab 140 mg Q2W, 1 placebo). Through week 52, the exposure-adjusted event rate of serious adverse events was 8.3 events per 100 subject years in all brodalumab subjects and 13.0 events per 100 subject years in ustekinumab subjects.
- A total of 7 deaths were reported through the data cutoff, however, 1 of these events was not a true fatal adverse event as it did not result in a fatal outcome in a study participant. This event, which was a grade 5 event, was reported as a [redacted] and occurred in the subject's partner. Treatment-emergent fatal adverse events occurred in 1 placebo/brodalumab 210 mg Q2W subject (death [adjudicated as sudden cardiac death]) and 2 ustekinumab subjects (1 pancreatic carcinoma and 1 death [adjudicated as sudden cardiac death]). After the exposure end date and through the data cutoff, 3 additional fatal adverse events occurred in subjects who received brodalumab 210 mg Q2W (1 cerebral infarction, 1 completed suicide, and 1 traumatic lung injury).
- Events of interest categories with preferred terms occurring at an exposure-adjusted event rate > 1 per 100 subject years in all brodalumab subjects included nervous system disorder adverse events, hypersensitivity adverse events, oropharyngeal candidiasis adverse events, depression events, and psychiatric disorder adverse events.
- Through week 52, the exposure-adjusted rate (per 100 subject-years) for the oropharyngeal candidiasis AMQ was 9.7 in the all-brodalumab group and 4.1 in the ustekinumab group. No serious oropharyngeal candidiasis events were identified by AMQ.
- Through the data cutoff, 13 events mapping to the suicide-self-injury SMQ occurred in 9 subjects in the all-brodalumab group (rate of 0.6 events per 100 subject years). Additionally, after the exposure end date, 1 subject (placebo/constant 210 mg Q2W) completed suicide. One ustekinumab subject attempted suicide through week 52.
- Notable trends in changes from baseline in vital signs were not observed during the induction phase or through week 52.
- ANC decreases of grade 3 or 4 were reported for 9 brodalumab subjects and 1 ustekinumab subject through week 52. Most were transient and none were temporally associated with serious infections.

- One subject in the placebo treatment group met laboratory criteria for potential Hy's law (ALT/AST > 3x ULN, total bilirubin > 2x ULN, and ALP ≤ 2X ULN at same visit) during the induction phase and 1 subject (brodalumab 140 mg Q2W/140 mg Q4W/210 mg Q2W) met the criteria after week 52 during the open-label extension phase. Both subjects had alternative etiologies for the elevations, and therefore are not considered cases of Hy's law.
- The profile of treatment-emergent adverse events was similar for subjects who switched to ARI product at week 52 and those who remained on ATO product.

Pharmacokinetics

- C_{max} and AUC_{tau} increased greater than dose proportionally from the brodalumab 140 mg Q2W to 210 mg Q2W dose on weeks 10 to 12. Mean C_{max} and AUC_{tau} values were generally similar on weeks 20 to 22 compared with weeks 10 to 12 for each respective brodalumab dosing regimen.

Anti-brodalumab antibodies

- Samples from 34 brodalumab subjects (2.0%) tested positive for binding anti-brodalumab antibodies after brodalumab administration through the data cutoff. Neutralizing anti brodalumab antibodies were not detected in samples from any subjects. No impact of anti-brodalumab antibodies on subject safety was observed.