2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA, United States (US)

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-3

Investigators and Study Centers: This study was conducted at 142 centers Australia, Canada, Europe, and the US. Centers and principal investigators are listed in Section 16.1.4.

Publications: None

Study Period: 11 September 2012 (first subject enrolled) to 30 August 2014 (data cutoff date for primary analysis).

Development Phase: 3

Objectives:

The key objectives of this study were as follows:

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

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

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 Objective:

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

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

Methodology: This was a double-blind, double-dummy, 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.

The study included a screening period, a 12-week, randomized, double-blind, placebo- and active-controlled phase (induction phase), a maintenance phase, and a long-term extension phase. In the induction phase, subjects were randomized in a 2:2:1:1 ratio to receive subcutaneous (SC) injections of 210 mg Q2W brodalumab, 140 mg Q2W brodalumab, ustekinumab (45 mg if ≤ 100 kg at the baseline visit, 90 mg if > 100 kg at the baseline visit), or matching 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. At the week-12 visit:

- Subjects originally randomized to either brodalumab arm were re-randomized (2:2:2:1) into the maintenance phase to receive brodalumab at 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 versus sPGA ≥ 1).
- Subjects originally randomized to ustekinumab continued to receive ustekinumab.
- Subjects originally randomized to receive placebo began receiving 210 mg Q2W brodalumab.
- 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 loading 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 at least 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 for all subjects, including those on ustekinumab. After week 16 subjects on ustekinumab remained on ustekinumab, even after qualifying for rescue. 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 re-randomized 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.

This report presents the results of the week-12 and week-52 efficacy endpoints, and available long-term efficacy through the data cutoff (30 August 2014); safety data are presented through week 52, as well as any available safety data through the data cutoff.

Number of Subjects Planned: 1800.

Number of Subjects Enrolled: 1881

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men and women who were ≥ 18 and ≤ 75 years of age at time of screening with stable, moderate to severe plaque psoriasis for at least 6 months before the first dose of the investigational product, with 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 (Section 16.1.1 of this report).

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

Brodalumab (Amgen Investigational Product)

During the blinded portion of the study, Amgen investigational product was administered as 2 blinded SC injections (1 x 1.0 mL [140 mg] and 1 x 0.5 mL [70 mg]) of brodalumab and/or matching placebo Q2W starting on day 1. Rescue treatment remained blinded until the study was unblinded (ie, subjects continued to received blinded Amgen investigational product and non-Amgen investigational product per dosing schedule of the maintenance phase, with administration of placebo as necessary to maintain the blind).

Brodalumab was administered to the abdomen, thigh, or upper arm. Brodalumab was supplied as a 140 mg/mL injectable solution (process 2 Amgen Thousand Oaks drug substance). Manufacturing batch numbers for brodalumab are provided in Section 16.1.6.

Ustekinumab (Non-Amgen Investigational Product)

During the induction phase all subjects received ustekinumab and/or placebo SC at day 1 and week 4. Subjects received ustekinumab (one 0.5-mL injection [45 mg] if ≤ 100 kg at the baseline visit and two 0.5-mL injections (90 mg) if > 100 kg at the baseline visit) or placebo, depending upon randomized arm.

During the maintenance phase of the study all subjects received ustekinumab and/or placebo at weeks 16, 28, and 40. Subjects received ustekinumab or placebo, depending upon randomized arm, with 1 injection for subjects ≤ 100 kg and 2 injections for those > 100 kg.

For subjects who received 2 injections of ustekinumab per dose, the 2 injections were to be administered in different body regions (upper arms, gluteal regions, thighs, or abdomen).

Ustekinumab was manufactured by [redacted] and was packaged and distributed by Amgen. Ustekinumab was procured in the US. Manufacturing batch numbers for ustekinumab are provided in Section 16.1.6.

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

Study Endpoints:

Co-primary (Brodalumab Arms Versus Placebo):

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

Primary (Brodalumab Versus Ustekinumab):

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

Key secondary (Brodalumab Arms Versus Placebo):

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

Key secondary (Brodalumab Versus 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, anti-brodalumab antibodies, and electrocardiograms.

Other endpoints included sPGA success (at other timepoints), time to sPGA success, PASI 75, PASI 90, and PASI 100 (at other timepoints), time to PASI response, percentage improvement in PASI, proportion of subjects achieving the responder definition of PSI, 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). Summary tables include a weight-based subgroup, which includes data for subjects who received brodalumab and were grouped by weight (ie, brodalumab 140 mg Q2W for subjects ≤ 100 kg and brodalumab 210 mg Q2W for subjects > 100 kg).

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 maintenance endpoints 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.

Following re-randomization at week 12, the maintenance endpoint (sPGA success at week 52) was tested sequentially between the brodalumab maintenance regimens at full alpha = 0.05.

At week 12, the dichotomous efficacy and patient-reported outcome (PRO) endpoints between the treatment arms, including the proportion of subjects achieving success on sPGA, the proportion of subjects achieving PASI 75 and PASI 100, and the proportion of subjects meeting the responder definition of PSI (total score ≤ 8, with no item scores > 1), 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 a stratified 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 17.0) 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) 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, systolic and diastolic blood pressures, respiration) 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 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.

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

Summary of Results:

Subject Disposition: A total of 1881 subjects were randomized into the study. Subject disposition for the induction phase is shown below:

			Brodalumab	
Number of Subjects	Placebo	Ustekinumab	140 mg Q2W	210 mg Q2W
Randomized	315	313	629	624
Received investigational product	313	313	626	622
Completed phase	301	303	604	608
Discontinued phase	14	10	25	16

Q2W = every 2 weeks
Source: Table 14-1.1.1

Subject disposition for the maintenance phase is shown below:

	Non-rerandomized at Week 12		Rerandomized at Week 12			
			Brodalumab			
Number of Subjects	Placebo/ 210 mg Q2W	Ustekinumab	140 mg Q8W	140 mg Q4W	140 mg Q2W	210 mg Q2W
Rerandomized	--	--	174	341	343	342
Non-rerandomized	298	301	--	--	--	--
Received IP	297	301	174	339	339	341
Completed phase	275	152	15	60	175	229
Discontinued phase	22	7	4	7	8	13
Entered rescue[a]	0	140	154	274	159	100

Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks
[a] Through week 52
Source: Table 14-1.1.2

Baseline Demographics:

Sex: 1288 men (68.5%); 593 women (31.5%)

Age: mean (range): 44.8 (18 to 75) years

Race: 1708 white (90.8%); 68 Asian (3.6%); 58 black or African American (3.1%); 29 other (1.5%); 8 native Hawaiian/other Pacific Islander (0.4%); 7 American Indian or Alaska native (0.4%); 3 multiple (0.2%)

Efficacy Results:

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

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

Comparison	Brodalumab		Placebo		
brodalumab vs placebo at week 12	n/N (%)	95% CI of %	n/N (%)	95% CI of %	Adjusted p-value
Primary efficacy endpoints					
PASI 75: 210 mg Q2W	531/624 (85.1)	(82.1, 87.8)	19/315 (6.0)	(3.7, 9.3)	<.001
sPGA success : 210 mg Q2W	497/624 (79.6)	(76.3, 82.7)	13/315 (4.1)	(2.2, 7.0)	<.001
PASI 75: 140 mg Q2W	435/629 (69.2)	(65.4, 72.7)	19/315 (6.0)	(3.7, 9.3)	<.001
sPGA success: 140 mg Q2W	377/629 (59.9)	(56.0, 63.8)	13/315 (4.1)	(2.2, 7.0)	<.001
Key secondary endpoints					
PASI 100: 210 mg Q2W	229/624 (36.7)	(32.9, 40.6)	1/315 (0.3)	(0.0, 1.8)	<.001
sPGA of 0: 210 mg Q2W	229/624 (36.7)	(32.9, 40.6)	1/315 (0.3)	(0.0, 1.8)	<.001
PASI 100: 140 mg Q2W	170/629 (27.0)	(23.6, 30.7)	1/315 (0.3)	(0.0, 1.8)	<.001
sPGA of 0: 140 mg Q2W	170/629 (27.0)	(23.6, 30.7)	1/315 (0.3)	(0.0, 1.8)	<.001
PSI responder: 210 mg Q2W	382/624 (61.2)	(57.3, 65.1)	20/315 (6.3)	(3.9, 9.6)	<.001
PSI responder: 140 mg Q2W	336/629 (53.4)	(49.4, 57.4)	20/315 (6.3)	(3.9, 9.6)	<.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; sPGA success = clear (0) or almost clear (1); Q2W = every 2 weeks
Adjusted p-values are based on a testing procedure consisting of a combination of parallel, sequential, and weighted Bonferonni-based recycling testing, which includes all primary and key secondary endpoint comparisons against placebo and ustekinumab, and are to be compared to a significance level of 0.05
NRI is used to impute missing data
Treatment groups are defined as planned treatment for the induction phase
Source: Table 14-4.32.1

Comparison With Ustekinumab, Primary and Key Secondary Endpoints:

Analysis results of the primary and key secondary endpoints are presented below.

Comparison brodalumab vs ustekinumab at week 12	Brodalumab n/N (%)	Brodalumab 95% CI of %	Ustekinumab n/N (%)	Ustekinumab 95% CI of %	Adjusted p-value
Primary efficacy endpoints					
PASI 100: 210 mg Q2W	229/624 (36.7)	(32.9, 40.6)	58/313 (18.5)	(14.4, 23.3)	<.001
PASI 100: weight-based	191/628 (30.4)	(26.8, 34.2)	58/313 (18.5)	(14.4, 23.3)	<.001
Key secondary endpoints					
PASI 100: 140 mg Q2W	170/629 (27.0)	(23.6, 30.7)	58/313 (18.5)	(14.4, 23.3)	0.007
PASI 75: 210 mg Q2W	531/624 (85.1)	(82.1, 87.8)	217/313 (69.3)	(63.9, 74.4)	0.007
PASI 75: weight-based	484/628 (77.1)	(73.6, 80.3)	217/313 (69.3)	(63.9, 74.4)	0.007

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; PASI = Psoriasis Area and Severity Index
Nominal p-value is based on Cochran-Mantel-Haenszel test stratified by total body weight at baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and adjusting for baseline values, without multiplicity adjustment
Weight-based = Subjects ≤ 100 kg at baseline randomized to 140 mg Q2W or > 100 kg at baseline randomized to 210 mg Q2W
Adjusted p-values are based on a testing procedure consisting of a combination of parallel, sequential, and weighted Bonferonni-based recycling testing, which includes all primary and key secondary endpoint comparisons against placebo and ustekinumab, and are to be compared to a significance level of 0.05
NRI is used to impute missing data
Treatment groups are defined as planned treatment for the induction phase
Source: Table 14-4.32.2

Maintenance Endpoint: sPGA Success (0 or 1) at Week 52

The percentage of subjects who achieved sPGA success at week 52 was 60.8% for subjects rerandomized to 210 mg Q2W, 44.9% for subjects rerandomized to 140 mg Q2W, 15.5% for subjects rerandomized to 140 mg Q4W, and 5.7% for subjects rerandomized to 140 mg Q8W. All comparisons for the maintenance endpoint were statistically significant based on the adjusted p-values ($p < 0.001$), with the 210 mg Q2W group achieving the highest rates of sPGA success at week 52.

Pharmacokinetic Results: Pharmacokinetic trough and intensive (week 10-12 and 20-22 for the substudy portion) samples were collected.

On weeks 10-12, after multiple SC injections of brodalumab in subjects with moderate to severe plaque psoriasis, C_{max} and AUC_{tau} increased greater than dose proportionally from the 140 mg Q2W to 210 mg Q2W dose. The mean C_{max} increased 2.8-fold and mean AUC_{tau} increased 2.6-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 10-12 and weeks 20-22.

Safety Results: During the induction phase, the most commonly reported (≥ 5%) adverse event in all treatment groups was nasopharyngitis. Other commonly reported (≥ 5%) are shown below. For the majority of subjects, these adverse events were reported by investigators as mild (grade 1).

	Placebo (N = 313) n (%)	Ustekinumab (N = 313) n (%)	Brodalumab 210 mg Q2W (N = 622) n (%)	Brodalumab 140 mg Q2W (N = 626) n (%)
All adverse events	152 (48.6)	168 (53.7)	353 (56.8)	329 (52.6)
Serious adverse events	3 (1.0)	2 (0.6)	9 (1.4)	10 (1.6)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Common adverse events (≥ 5% in any group)				
Nasopharyngitis	22 (7.0)	16 (5.1)	31 (5.0)	36 (5.8)
Upper respiratory tract infection	17 (5.4)	16 (5.1)	33 (5.3)	19 (3.0)
Headache	14 (4.5)	11 (3.5)	21 (3.4)	32 (5.1)
Arthralgia	10 (3.2)	6 (1.9)	36 (5.8)	25 (4.0)

N = Number of subjects who were randomized and received ≥ 1 dose of active investigational product;
n = Number of subjects reporting ≥ 1 occurrence of an adverse event; Q2W = every 2 weeks
Source: Table 14-6.1.1 and Table 14-6.2.4.1

Exposure-emergent adverse events through week 52 are summarized by the following groups.

- 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 started 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; these subjects were not rescued with 210 mg Q2W through week 52)
- 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 are formed from multiple randomized groups and account for rescue, and were defined based on the planned sequence of treatments. They are comprehensive, but are not unique since subjects in the "210 mg Q2W after ustekinumab" group are summarized in the "ustekinumab" group before they are rescued to 210 mg Q2W.

Overall subject-years of exposure and the most frequently reported exposure-emergent adverse events (per 100 subject-years) through week 52 are shown below. All other events occurred at < 10 per 100 subject-years. For the majority of subjects, these adverse events were reported by investigators as mild (grade 1). The most commonly reported adverse events through week 52 are consistent with those observed during the 12-week induction phase.

		Brodalumab				
		Variable Dose			Constant Dose	
	Ustekinumab (N = 313) n (r)	Ustekinumab/ 210 mg Q2W (N = 68) n (r)	Mixed Dosing[a] (N = 515) n (r)	140 mg Q2W / 210 mg Q2W (N = 428) n (r)	140 mg Q2W (N = 113) n (r)	210 mg Q2W (N = 489) n (r)
Subject-years	248.6	44.2	490.1	405.9	87.1	383.5
Nasopharyngitis	63 (25.3)	7 (15.8)	79 (16.1)	97 (23.9)	17 (19.5)	76 (19.8)
Headache	25 (10.1)	5 (11.3)	58 (11.8)	37 (9.1)	12 (13.8)	47 (12.3)
Arthralgia	27 (10.9)	6 (13.6)	58 (11.8)	67 (16.5)	18 (20.7)	62 (16.2)
Upper respiratory tract infection	63 (25.3)	7 (15.8)	88 (18.0)	60 (14.8)	7 (8.0)	64 (16.7)

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); Subj-yr = total subject years of exposure through week 52; Q2W = every 2 weeks
a Mixed dosing includes subjects originally randomized to either 140 mg Q2W or 210 mg Q2W who were rerandomized to either 140 mg Q4W or 140 mg Q8W.
Source: Table 14-6.9.1.6

During the induction phase, 12 brodalumab-treated subjects (1.0%), 2 ustekinumab-treated subjects (0.6%), and 3 subjects (1.0%) who received placebo had adverse events that led to withdrawal of investigational product. Arthralgia was the only event leading to withdrawal of investigational product that occurred in > 1 subject. Through week 52, there were 45 (3.2 per 100 subject-years) adverse events that led to withdrawal of investigational product in brodalumab-treated subjects; cardiac disorders was the most commonly reported system organ class of adverse events (0.6 events per 100 subject-years). The overall exposure-adjusted event rate for adverse events that led to withdrawal of investigational product (per 100 subject-years) through week 52 was 3.2 for all subjects who received at least 1 dose of brodalumab. The overall exposure-adjusted event rates for adverse events that led to withdrawal of investigational product (per 100 subject-years) were 3.9 in the constant 210 mg Q2W group, 5.7 in the constant 140 mg Q2W group, 3.9 in the combination 140 mg Q2W/210 mg Q2W group, 1.8 in the mixed dosing group, 0.0 in the 210 mg Q2W after ustekinumab group, and 2.8 in the ustekinumab group.

During the induction phase, the incidence of serious adverse events was 1.4% in the 210 mg Q2W group, 1.6% in the 140 mg Q2W group, 0.6% in the ustekinumab group, and 1.0% in the placebo group. The most commonly reported serious adverse event in subjects exposed to brodalumab was gastroenteritis (2 subjects, 0.2%). Through week 52, the exposure adjusted event rate (per 100 subject-years) of treatment-emergent serious adverse events for subjects exposed to brodalumab was 7.9. The overall exposure-adjusted event rates (per 100 subject-years) were 8.1 in the constant 210 mg Q2W group, 9.2 in the constant 140 mg Q2W group, 7.4 in the combination 140 mg Q2W/210 mg Q2W group, 8.0 in the mixed dosing group, 6.8 in the 210 mg Q2W after ustekinumab group, and 4.0 in the ustekinumab group. Myocardial infarction (6 events, 0.4 events per 100 subject-years) was the most frequently reported serious adverse event for subjects exposed to brodalumab through week 52.

No deaths occurred during the induction phase. A total of 5 deaths were reported through the data cutoff. Two subjects died while receiving investigational product; both deaths were reported by investigators as unrelated to investigational product. One subject died of cardiac arrest during treatment (day 275) with 210 mg Q2W and 1 subject died as the result of a [redacted] during treatment (day 123) with 140 mg Q2W. Two subjects died after the exposure period. One of these subjects died from hematophagic histiocytosis syndrome (140 mg Q2W in induction, 140 mg Q4W in maintenance, and 210 mg Q2W in the rescue phase), which occurred 55 days after the last dose of investigational product; 1 subject died from cardiac arrest (210 mg Q2W in

There were no clinically notable trends in vital sign or clinical laboratory results. Absolute neutrophil count was identified as a key laboratory assessment of interest in this study and neutropenia was an event of interest. One adverse event of neutropenia (1.1 per 100 subject-years) in the constant 140 mg Q2W group, 2 events (0.5 per 100 subject-years) in the combination of 140 mg Q2W/210 mg Q2W group, and 1 event (0.2 per 100 subject-years) in the mixed dosing group were grade 3 or higher.

A total of 1830 of 1881 subjects received brodalumab and were tested for anti-brodalumab antibodies. Of the 1684 subjects tested for antibodies after being exposed to brodalumab, 38 subjects (2.3%) developed binding anti-brodalumab antibodies after brodalumab administration through the data cutoff (30 August 2014). Sixteen subjects (1.0%) 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 through week 12 of this study show that brodalumab at 210 mg Q2W and 140 mg Q2W significantly improve efficacy response rates for all primary and secondary endpoints compared to placebo and ustekinumab. In addition, a higher proportion of subjects responded to treatment with 210 Q2W mg than with 140 mg Q2W mg.
- Brodalumab 210 mg Q2W and 140 mg Q2W increase response rates relative to 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).
- Statistically significant response rates were observed based on the adjusted p-values ($p < 0.001$) for the 210 mg Q2W group and weight based subgroup compared with ustekinumab for the primary endpoint PASI 100 at week 12 and the key secondary endpoint PASI 100 at week 12 in subjects randomized to 140 mg Q2W; the difference in response rate for PASI 75 at week 12 between the 210 mg Q2W group and the ustekinumab group was statistically significant based on the adjusted p-value ($p = 0.007$).
- A significantly higher proportion of subjects treated with both 210 mg Q2W and 140 mg Q2W met the PSI responder definition achieving 0 (not at all) or 1 (mild) compared to placebo at week 12.
- All protocol-specified comparisons for the maintenance endpoint sPGA success at week 52 were statistically significant based on the adjusted p-values ($p < 0.001$), with the 210 mg Q2W brodalumab regimen achieving significantly higher rates of sPGA success at week 52 than all other regimens evaluated.

Pharmacokinetics

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

Safety

- The most commonly reported adverse event occurring in ≥ 5% in any treatment group during the induction period was nasopharyngitis. Upper respiratory tract infection was reported for approximately 5.0% of subjects in the 210 mg Q2W, ustekinumab, and placebo groups. Headache was reported more frequently in the 140 mg Q2W group (5.1%) than in the other treatment groups. These events were also the most commonly reported through week 52.
- Through week 52, the exposure-adjusted event rate (per 100 subject-years) of serious adverse events was 7.9 for subjects exposed to brodalumab and 4.0 for subjects exposed to ustekinumab. The adverse event profile observed through week 52 was consistent with that observed during the induction phase.

- A total of 5 deaths were reported through the data cutoff. Three subjects died from cardiovascular events that investigators reported as unrelated to investigational product; all 3 subjects had relevant risk factors. One of these subjects was receiving 210 mg Q2W at the time of the event (cardiac arrest), 1 subject received his last dose of 210 Q2W 39 days before the event (cardiopulmonary failure), and 1 subject received his last dose of 210 mg Q2W 87 days before the event (cardiac arrest). One subject died from hematophagic histiocytosis syndrome, which was considered to be possibly related to investigational product; the subject received his last dose of 210 mg Q2W 55 days before the event. One subject died in a [redacted] and was receiving 140 mg Q2W at the time of the event.
- During the induction phase, 12 brodalumab-treated subjects (1.0%), 2 ustekinumab-treated subjects (0.6%), and 3 subjects (1.0%) who received placebo had adverse events that led to withdrawal of investigational product. Arthralgia was the only event leading to withdrawal of investigational product that occurred in > 1 subject. Through week 52, there were 45 (3.2 per 100 subject-years) adverse events that led to withdrawal of investigational product in brodalumab-treated subjects; cardiac disorders was the most commonly reported system organ class of adverse events (0.6 events per 100 subject-years).
- Through week 52, the exposure-adjusted rate (per 100 subject-years) for the oropharyngeal candidiasis AMQ was 10.5 in the all-brodalumab group and 6.4 in the ustekinumab group. No serious oropharyngeal candidiasis events were identified by AMQ.
- Through the data cutoff, 2 events mapping to the suicide-self-injury SMQ occurred in 2 subjects in the overall 210 mg Q2W group (rate of 0.1 events per 100 subject years). Neither event resulted in a completed suicide.
- Of subjects exposed to brodalumab, 16 (1.0%) 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.