

Title: 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

Brodalumab (AMG 827)

Amgen Protocol Number 20120103

EudraCT number 2012-000656-34

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Date: 20 February 2012
Amendment 1: 31 May 2012
Superseding Amendment 1: 3 December 2012
Amendment 2: 17 October 2013
Amendment 3: 26 March 2014

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Category	Value
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2	~0.5
3	~1
4	~2
5	~5
6	~10
7	~15
8	~25
9	~35
10	~45
11	~55
12	~65
13	~75
14	~85
15	100

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Protocol Synopsis

Title: 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

Study Phase: 3

Indication: Moderate to severe plaque psoriasis

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 (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 Objective

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

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Hypotheses: The first set of primary hypotheses of this study is that brodalumab at 210 mg Q2W and 140 mg Q2W will demonstrate superior efficacy compared with placebo in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects with success on sPGA and by the proportion of subjects with a PASI 75 at week 12.

The second set of primary hypotheses of this study is that brodalumab (at the 210 mg dosage and at the 140 mg dosage for subjects ≤ 100 kg with 210 mg dosage for subjects > 100 kg) will demonstrate superior ability to clear psoriasis compared with ustekinumab in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects attaining PASI 100 at week 12.

It is further hypothesized that subjects with moderate to severe plaque psoriasis who continue to receive brodalumab 210 mg Q2W or 140 mg Q2W will demonstrate superior response to those randomized to receive brodalumab at lower frequencies in the maintenance phase (140 mg Q4W and 140 mg Q8W), as measured by the proportion of subjects with success on sPGA at week 52.

Primary, Key Secondary, and Safety 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
 - 210 mg Q2W
 - 140 mg Q2W for subjects ≤ 100 kg and 210 mg Q2W for subjects > 100 kg

Key Secondary: brodalumab arms vs placebo

- PASI 100 at week 12
- sPGA 0 at week 12
- Psoriasis Symptom Inventory 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 and 210 mg Q2W for subjects > 100 kg

Maintenance (after rerandomization at week 12)

- sPGA success at week 52

Safety

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

Study Design

After the screening period, this study begins with a 12-week, double-blind, active comparator- and placebo-controlled induction phase. In this phase, subjects will be randomized in a 2:2:1:1 ratio to receive 210 mg Q2W brodalumab, 140 mg Q2W brodalumab, ustekinumab, or placebo (randomization will be stratified by baseline total body weight (≤ 100 kg; > 100 kg), by prior

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biologic use, and by geographic region; subjects with prior biologic use will be capped at 50% of the study population).

At the week 12 visit

- Subjects originally randomized to either brodalumab arm will be rerandomized (2:2:2:1) into the maintenance phase to receive brodalumab at 210 mg Q2W or 140 mg Q2W, every 4 weeks (Q4W), or every 8 weeks (Q8W). Rerandomization will be 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 will continue to receive ustekinumab.
- Subjects originally randomized to receive placebo will begin receiving 210 mg Q2W brodalumab.
- Subjects who do not attend their week 12 visit will not receive any further investigational product (IP).

At week 52, subjects who were originally randomized to ustekinumab will begin receiving 210 mg Q2W brodalumab.

At and after week 16, rescue treatment will be available according to the rules in [Section 6.3](#).

The entire study will be up to 271 weeks (approximately 5 years; includes up to 30 days for screening) in duration.

Original and rerandomized treatment assignments will remain blinded until all subjects reach week 52 or terminate the study, whichever comes first.

The safety of study participation will be evaluated on an ongoing basis through regular review of unblinded data by an independent Data Monitoring Committee. Major adverse cardiovascular events (defined as stroke, myocardial infarction, or cardiovascular death) will be adjudicated by an independent Cardiovascular Events Committee.

The overall study design is described by a [study schema](#) at the end of the protocol synopsis section.

Sample Size: 1800

Summary of Subject Eligibility Criteria: Subjects must have stable moderate to severe plaque psoriasis for at least 6 months. Subjects must be candidates to receive a biologic therapy for psoriasis, in the opinion of the investigator, according to regional labeling and must have psoriasis that involves body surface area $\geq 10\%$, PASI ≥ 12 , and sPGA ≥ 3 at screening and baseline visits. Subjects must have completed appropriate washout periods for drugs specified in [Section 4.2](#) and must be free of infections requiring systemic anti-infectives and of significant concurrent medical conditions as described in [Section 4.2](#). If applicable, women must be willing to use highly effective birth control.

For a full list of eligibility criteria, refer to [Section 4.1](#) and [4.2](#).

Investigational Product Dosage and Administration:

This is a double-blind, double-dummy study.

The Amgen IP is brodalumab (and placebo for brodalumab). The non-Amgen IP is ustekinumab (and placebo for ustekinumab). For additional detail on dosage and administration of both IPs, see [Section 6](#). Ustekinumab will be dosed according to its label (45 mg for subjects ≤ 100 kg and 90 mg for subjects > 100 kg).

Both IPs will be administered subcutaneously, according to the guidance in [Section 6](#). Doses should be withheld for absolute neutrophil count abnormalities, hepatotoxicity, or infections according to the rules in [Section 6.4](#). IPs should be permanently discontinued for certain adverse events (including significant or persistent absolute neutrophil count abnormalities) and for lack of effect ([Section 6.3](#), [Section 6.4.1](#), [Section 8.1](#)).

Until the blind is broken, subjects will receive placebo for brodalumab and/or ustekinumab, as needed, to maintain the blind.

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Induction

All subjects will receive 2 injections of Amgen IP at day 1 and weeks 1, 2, 4, 6, 8, and 10. These injections will be brodalumab and/or placebo for brodalumab, depending upon randomized arm.

All subjects will also receive non-Amgen IP at day 1 and week 4. These injections will be ustekinumab or placebo for ustekinumab, depending upon randomized arm.

- Subjects ≤ 100 kg at the baseline visit will receive one 0.5 ml injection of non-Amgen IP at day 1 and week 4.
- Subjects > 100 kg at the baseline visit will receive two 0.5 ml injections of non-Amgen IP at day 1 and week 4.

Maintenance

- All subjects will continue to receive Amgen and non-Amgen IP (2 injections of Amgen IP at weeks 12, 13, 14, 16, 17, 18 and every 2 weeks, non-Amgen IP [1 injection for subjects ≤ 100 kg at the baseline visit, 2 injections for subjects > 100 kg at the baseline visit] at weeks 16, 28, and 40).

Long-term extension

- All subjects will receive Amgen IP (Amgen IP at weeks 52, 53, 54, and every 2 weeks). Until the blind is broken, this will be 2 injections. After the blind is broken, subjects will receive 1 injection if receiving 140 mg or 2 injections if receiving 210 mg.

Rescue

Rescue treatment is available according to the rules in [Section 6.3](#)

Control Group: The initial phase of the study (the first 12 weeks) will be placebo-controlled. In this phase, the placebo control group will receive placebo at day 1 and weeks 1, 2, 4, 6, 8, and 10.

The first 52 weeks of the study will also be active-comparator-controlled. In this phase, the active comparator control group will receive ustekinumab at day 1 and weeks 4, 16, 28, and 40 (unless qualifying for rescue at week 16).

Procedures: At the screening visit, subjects will be dispensed an electronic hand-held diary device (eDiary) and instructions on its use to capture daily psoriasis symptoms using the Psoriasis Symptom Inventory. Subjects will complete the Psoriasis Symptom Inventory daily during the entire screening period and during the study, according to the schedule in [Appendix A](#).

Physical examination, medication and medical history, adverse event and concomitant medication assessment, vital signs measurement, electrocardiograms, tuberculosis test, urinalysis, and blood draw for serum chemistry and hematology analytes, C-reactive protein, pharmacokinetics, and anti-brodalumab antibody assay will be performed according to [Appendix A](#). Regular pregnancy tests will be performed in women of child-bearing potential. PASI, sPGA, involved body surface area assessment, Nail Psoriasis Severity Index, Dermatology Life Quality Index, work limitations, **Columbia-Suicide Severity Rating Scale, and Patient Health Questionnaire-8 depression scale** will be assessed periodically throughout the study according to [Appendix A](#).

Substudies/procedures that may require additional consent include

- Post-dose pharmacokinetic samples at additional timepoints for brodalumab pharmacokinetic analysis (according to the schedule in [Appendix A1](#))
- Lesional and non-lesional complete skin biopsies
- Photography
- Biomarker blood collection
- Pharmacogenetic analysis

Superseded

For a full list of study procedures, including the timing of each procedure, refer to [Section 7](#) and [Appendix A](#) and [Appendix A1](#).

Statistical Considerations

The primary analysis will occur after all subjects have completed their week 52 visit (or terminated from the study). This analysis will include induction phase co-primary endpoints that will include data through week 12, as well as maintenance endpoints that will include data through week 52. **Subsequent interim analyses may be performed as deemed necessary.** The final analysis for the study will occur after all subjects have completed the week 266 visit (or early terminated from the study).

The primary analysis will consist of two 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 will be 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). Within the placebo and ustekinumab families, the primary endpoints will be tested first. If the null hypothesis for any of the primary endpoints within a family is not rejected, all the subsequent hypotheses for the key secondary endpoints at week 12 within that family will not be tested. However, if the null hypotheses for the primary endpoints within a family are rejected, then the hypotheses corresponding to the key secondary endpoints at week 12 within that family will be tested sequentially at alpha = 0.01 (2-sided level) for the placebo family and alpha = 0.04 (2-sided) for the ustekinumab family. The order of the sequential testing for the key secondary endpoints is provided in [Section 10.6.2](#).

After rerandomization at week 12, the maintenance endpoint for sPGA success at week 52 will be tested at full alpha = 0.05 level (2-sided). The order of the sequential testing on the sPGA success at week 52 will be as follows: 210 mg Q2W brodalumab vs 140 mg Q8W brodalumab; 140 mg Q2W brodalumab vs 140 mg Q8W brodalumab; 210 mg Q2W brodalumab vs 140 mg Q4W brodalumab; 140 mg Q2W brodalumab vs 140 mg Q4W brodalumab; and 210 mg Q2W brodalumab vs 140 mg Q2W brodalumab.

The p-values for primary and key secondary comparisons will be adjusted for multiplicity, whereas the p-values for the analyses of other secondary and exploratory endpoints will be 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 Psoriasis Symptom Inventory, will be compared between the treatment arms using the Cochran-Mantel-Haenszel (CMH) test, adjusting for baseline total body weight (≤ 100 kg, > 100 kg), prior biologic use, geographic region, and baseline value group (\leq median, $>$ median; for sPGA-related endpoints, baseline sPGA = 3, 4, or 5 will be adjusted).

At week 52, dichotomous variables, including the proportion of subjects achieving success on sPGA, will be compared between the treatment arms using the CMH test adjusting for week 12 total body weight group (≤ 100 kg, > 100 kg), week 12 sPGA response (sPGA = 0, sPGA \geq 1), treatment received in the 12-week induction phase, and week 12 value group (\leq median, $>$ median for non sPGA-related endpoints).

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

Through week 12, missing categorical variables will be imputed as non-responders for dichotomous endpoints and worst-cases for ordinal endpoints, and missing continuous variables will be imputed by a multiple imputation technique. Various sensitivity analyses will be performed, including last-observation-carried-forward imputation and as-observed analysis. For maintenance phase endpoints after week 12 through week 52, missing categorical variables will be imputed as non-responders for dichotomous endpoints and worst-cases for ordinal endpoints, and missing continuous variables will be imputed by last-observation-carried-forward.

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For testing the maintenance endpoint (sPGA success at week 52), subjects who have an inadequate response at or before week 52 will be imputed as non-responders.

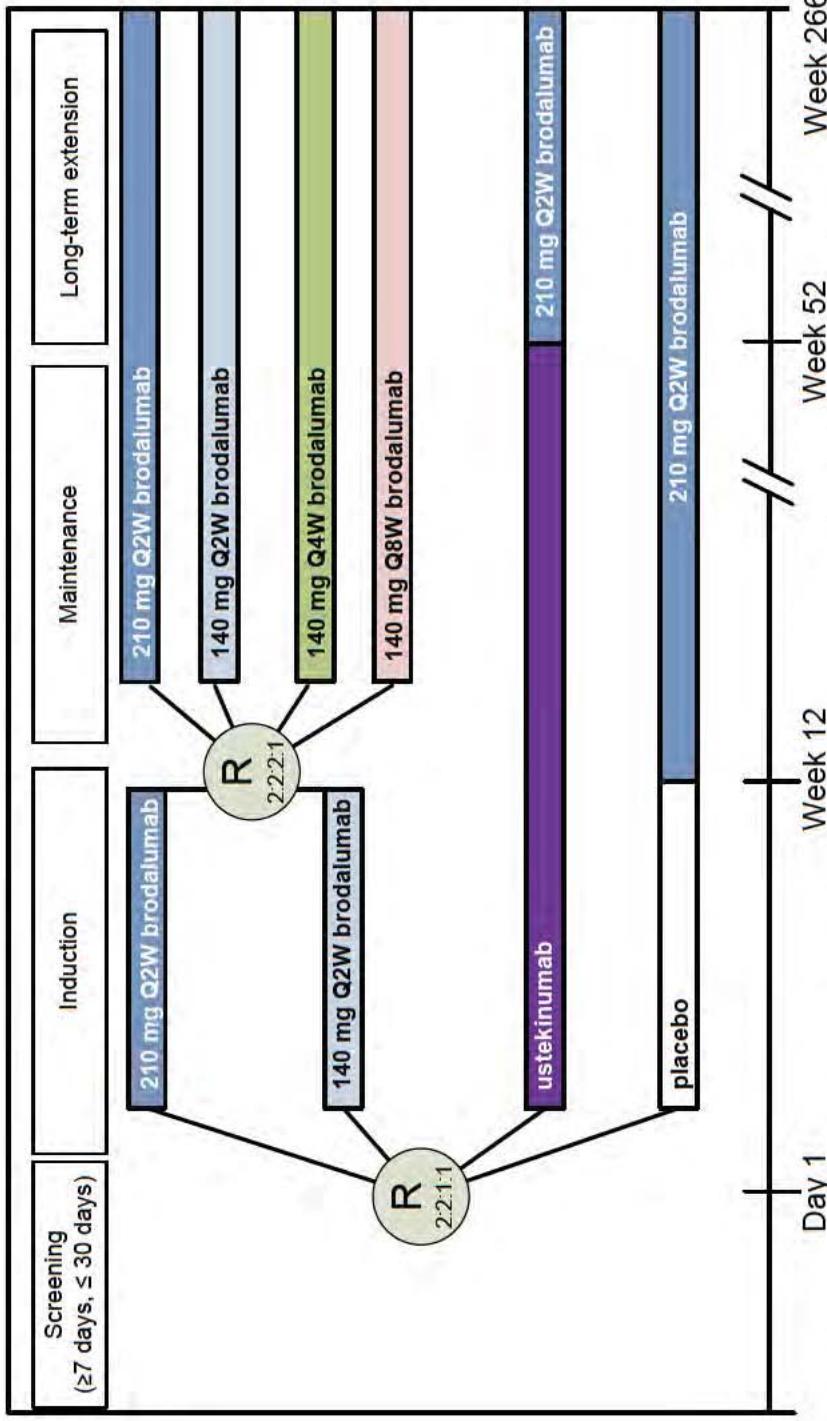
After week 52, analyses will be as observed.

For a full description of statistical analysis methods, refer to [Section 10](#).

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Study Design and Treatment Schema



R = randomization; Q2W = every 2 weeks (with an additional loading dose 1 week after initiation of brodalumab); Q4W = every 4 weeks; Q8W = every 8 weeks
Subjects will receive Amgen investigational product (IP; brodalumab and/or placebo for brodalumab) subcutaneously at day 1, weeks 1, 2, 4, 6, 8, 10, 12, 13, 14, 16, 17, 18 and every other week (with an additional dose at week 53). Subjects will also receive subcutaneous injections of non-Amgen IP (ustekinumab or a placebo for ustekinumab) at day 1 and weeks 4, 16, 28, and 40 (one 0.5 mL injection if ≤ 100 kg at baseline; two 0.5 mL injections if >100 kg at baseline).
Subjects can qualify for rescue treatment according to the rules in Section 6.1.

After the blind to original and rerandomized treatment assignment has been broken, an analysis to identify the most appropriate maintenance dosage(s) of brodalumab will be performed. Based upon the results of that analysis, an amendment may be pursued to change the dosage and/or frequency in some or all subjects.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
Amgen IP	Amgen investigational product (ie, brodalumab and/or brodalumab placebo)
ANC	absolute neutrophil count
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BSA	involved body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CMH	Cochran-Mantel-Haenszel
eC-SSRS	Electronic Self Rated Version, Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
day 1	date of the first dose of investigational product
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eDiary	electronic hand-held device used to collect daily information
end of study	the last clinical planned event for protocol-specified assessments
end of study for individual subject	the last day that procedures are conducted for an individual subject
FSH	follicle-stimulating hormone
ICH GCP	International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice
IEC	independent ethics committee
IL	Interleukin
IL-17R	interleukin-17 receptor
inadequate response	sPGA \geq 3 or persistent sPGA values of 2 over at least a 4-week period at or after week 16
IP	investigational product
IPIM	investigational product instruction manual
IRB	institutional review board
IVRS	interactive voice response system
NAPSI	Nail Psoriasis Severity Index

Abbreviation or Term	Definition/Explanation
Non-Amgen IP	Non-Amgen investigational product (ie, ustekinumab and/or ustekinumab placebo)
nonresponse	persistent sPGAs ≥ 3 over at least a 4-week period in a subject on continuous treatment for at least 12 weeks
PASI	Psoriasis Area and Severity Index
PHQ-8	Patient Health Questionnaire-8 depression scale
PPD	purified protein derivative (tuberculosis test)
primary completion	the last clinical planned event for protocol-specified assessments supporting the primary analysis (ie, the last subject has reached week 52 or terminated from the study)
Psoriasis Symptom Inventory responder definition	total score ≤ 8 , with no item scores > 1
Q2W	every 2 weeks (in this study, this regimen includes an additional loading dose 1 week after initiation of brodalumab)
Q4W	every 4 weeks
Q8W	every 8 weeks
RBC	red blood cell(s)
[REDACTED]	[REDACTED]
sPGA	static physician's global assessment
sPGA success	sPGA score of 0 (clear) or 1 (almost clear)
[REDACTED]	[REDACTED]
ULN	upper limit of normal
WBC	white blood cell(s)
WLQ	Work limitations questionnaire

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1. OBJECTIVES

1.1 Primary

1.1.1 Primary Placebo Family

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

1.1.2 Primary Ustekinumab Family

Compared with ustekinumab:

- To evaluate the efficacy of brodalumab (210 mg Q2W; and 140 mg Q2W for subjects ≤ 100 kg and 210 mg Q2W 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

1.2 Key Secondary

1.2.1 Placebo Family

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 (total score ≤ 8, with no item scores > 1) at week 12

1.2.2 Ustekinumab Family

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 Q2W for subjects > 100 kg), as measured by the proportion of subjects achieving PASI 75 at week 12

Superseded

1.3 Maintenance

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

1.4 Other Secondary

- To evaluate whether there is a weight threshold for the higher dose of brodalumab
- To evaluate the onset of response of brodalumab (210 mg Q2W; and 140 mg Q2W) in the induction phase
- To evaluate the effect of brodalumab (210 mg Q2W; and 140 mg Q2W) on psoriasis severity at all other timepoints
- To evaluate the effect of brodalumab (210 mg Q2W; and 140 mg Q2W) on nail disease at all timepoints
- To compare the efficacy of brodalumab and ustekinumab, as measured by
 - sPGA 0 at week 12 (210 mg Q2W; and 140 mg Q2W)
 - PASI 100 at week 52 (210 mg Q2W; and 140 mg Q2W)
 - PASI 75 at week 52 (210 mg Q2W; and 140 mg Q2W for subjects ≤ 100 kg with 210 mg Q2W for subjects > 100 kg)
 - sPGA 0, PASI 100, and PASI 75 at weeks 12 and 52 (140 mg Q2W for subjects below appropriate weight threshold and 210 mg Q2W for subjects above appropriate weight threshold)
- To evaluate the maintenance of response with each maintenance regimen, as measured by sPGA success at week 52 in subjects who had sPGA success at week 12
- To evaluate the effect of brodalumab (210 mg Q2W; and 140 mg Q2W) on patient-reported symptoms of psoriasis and other patient-reported outcomes at all other timepoints
- To characterize the pharmacokinetics of brodalumab after short- and long-term treatment

1.5 Safety

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

1.6 Exploratory

- To explore brodalumab population pharmacokinetics
- To explore brodalumab exposure/response relationship
- To explore the effect of treatment with brodalumab on laboratory parameters of interest (ie, inflammatory markers)
- To evaluate self-administration of brodalumab

Superseded

- To collect blood and biopsy samples for biomarker analysis (this part of the study is optional)
 - To investigate the effects of genetic variation in disease genes and drug target genes on psoriasis and/or subject response to brodalumab (this part of the study is optional)

2. BACKGROUND AND RATIONALE

2.1 Disease

Psoriasis is a common inflammatory skin disease occurring in 2% to 3% of the population worldwide ([National Psoriasis Foundation website](#)). Moderate to severe plaque psoriasis is, for most patients, a chronic, life-long condition. Currently approved therapies include topical agents (eg, corticosteroids), systemic therapies (eg, methotrexate, cyclosporine, retinoids), phototherapy, and biologics (eg, etanercept, infliximab, adalimumab, ustekinumab) ([Hsu et al, 2012](#); [Menter et al, 2008](#)). Many patients nevertheless remain untreated, do not respond to therapy, or suffer from toxicities associated with systemic or phototherapy.

2.2 Brodalumab Background

Interleukin (IL)-17 receptor A (IL-17RA) is a type I transmembrane receptor that is found on a wide variety of cell types including epithelial cells, endothelial cells, fibroblasts, chondrocytes, synovial cells, monocytes, neutrophils, and lymphocytes (Yao et al, 1997). IL-17A, IL-17F, IL 17A/F, and IL-25 stimulate cellular responses by interacting with IL-17RA. IL-17A, IL-17F, and IL-17A/F signal via a heteromeric IL-17RA/IL-17RC complex, whereas IL-25 signals via a heteromeric IL-17RA/IL-17RB complex (Rickel et al, 2008; Toy et al, 2006).

Brodalumab (AMG 827) is a human anti-IL-17RA monoclonal antibody that selectively targets human IL-17RA and antagonizes the effects of IL-17A, IL-17F, IL-17A/F, and IL-25. Interleukin 17RA blockade represents a novel mechanism to inhibit the inflammation and clinical symptoms associated with psoriasis.

For the most up-to-date information regarding brodalumab, including the efficacy and safety profile demonstrated in the phase 2 psoriasis study (Study 20090062), please consult the current copy of the Investigator's Brochure.

2.3 Ustekinumab Background

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. It is a marketed product for the treatment of moderate to

severe plaque psoriasis ([Stelara® prescribing information, September 2013](#);
[Stelara® summary of product characteristics, March 2014](#)).

For the most up-to-date information regarding ustekinumab, please consult the current local prescribing information.

2.4 Rationale

2.4.1 IL-17 in Psoriasis

There are many reports suggesting that T helper 17 cells, and the cytokines IL-17A and IL-17F, are dysregulated in psoriasis and thus may play an important role in skin inflammation ([Fujishima et al, 2010](#); [Kagami et al, 2010](#); [Zhang et al, 2010](#); [Johansen et al, 2009](#); [Ortega et al, 2009](#); [Watanabe et al, 2009](#); [Lowes et al, 2008](#); [Nograles et al, 2008](#)). There is also evidence that the elevated levels of IL-17 family cytokines often observed in patients with active psoriasis may be reduced in patients responding to therapies such as etanercept or ultraviolet radiation ([Coimbra et al, 2010](#); [Johnson-Huang et al, 2010](#); [Caproni et al, 2009](#); [Zaba et al, 2009](#); [Haider et al, 2008](#)).

2.4.2 Dose Justification

2.4.2.1 Induction Regimen

Selection of the induction doses for this study was based on safety, efficacy, and pharmacokinetic modeling from a dose-ranging phase 2 study in adult subjects with moderate to severe plaque psoriasis (Study 20090062).

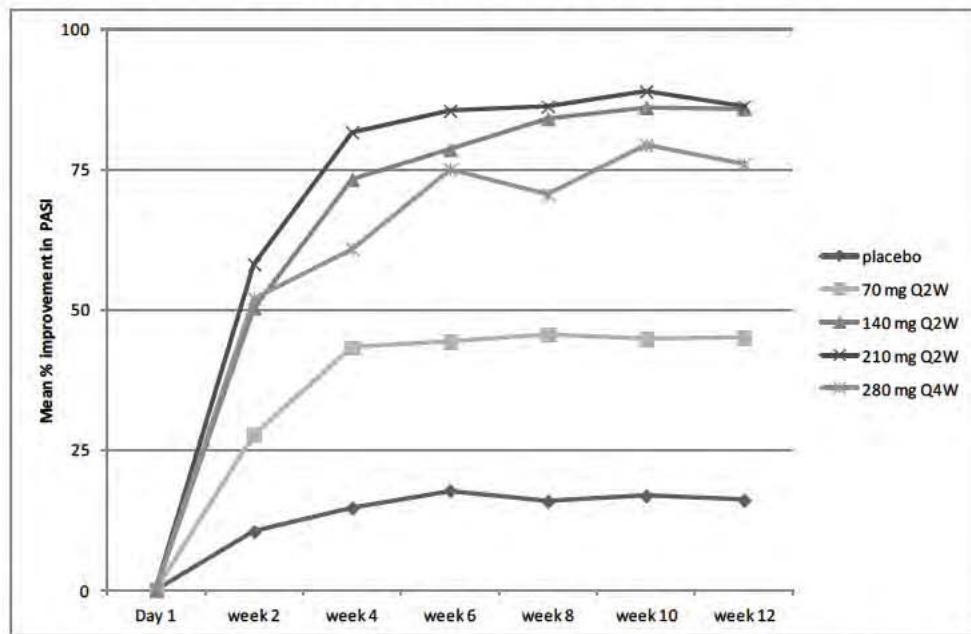
The dosages (all administered subcutaneously) in Study 20090062 were as follows:

- brodalumab 70 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 (“70 mg Q2W”)
- brodalumab 140 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 (“140 mg Q2W”)
- brodalumab 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 (“210 mg Q2W”)
- brodalumab 280 mg at day 1 and weeks 4 and 8 (every 4 weeks; “280 mg Q4W”)
- placebo

Brodalumab demonstrated substantial efficacy (Figure 1), with all dosages being statistically significantly better than placebo.

Superseded

Figure 1. Mean Percent Improvement in PASI in Study 20090062



PASI = Psoriasis Area and Severity Index; Q2W = "every 2 weeks" (day 1 and weeks 1, 2, 4, 6, 8, and 10); Q4W = "every 4 weeks" (day 1 and weeks 4 and 8).

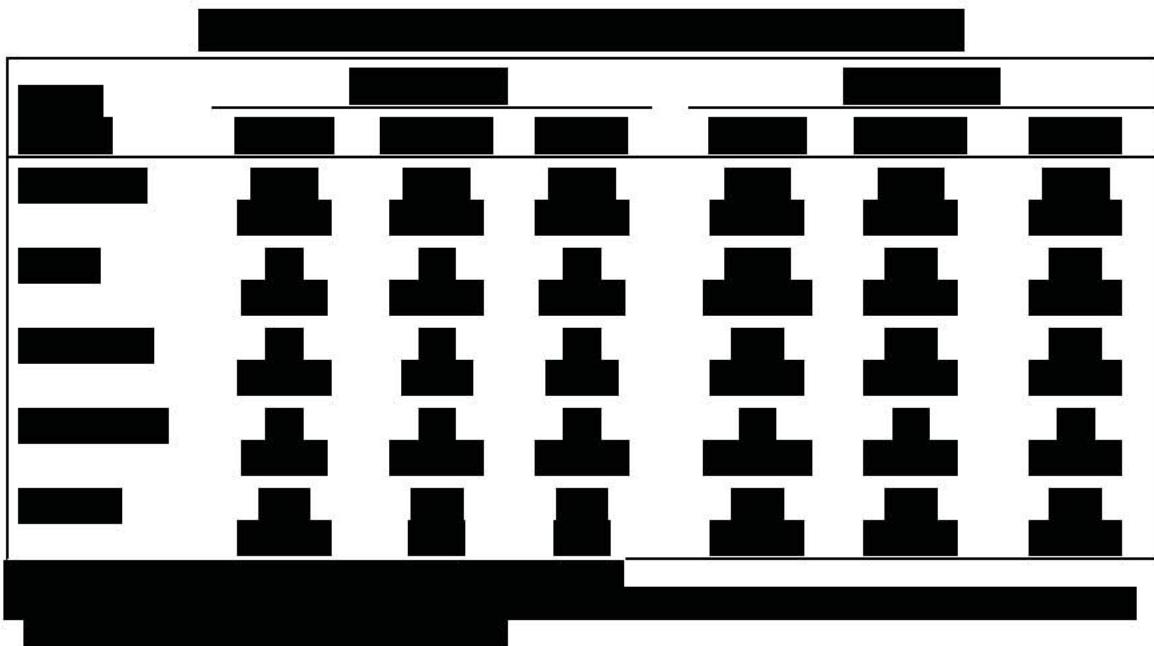
Moreover, a majority of subjects experienced clearance of disease (PASI 100) at the 210 mg Q2W dosage (Table 1).

Table 1. PASI 100 Response Rates at Week 12

	AMG 827				
	Placebo	70 mg Q2W	280 mg Q4W	140 mg Q2W	210 mg Q2W
Week 12	0/38	4/39	12/42	15/39	25/40
PASI 100 Response	(0.0%)	(10.3%)	(28.6%)	(38.5%)	(62.5%)

Non-Responder Imputation is used to impute missing data

PASI = Psoriasis Area and Severity Index; Q2W = "every 2 weeks" (day 1 and weeks 1, 2, 4, 6, 8, and 10); Q4W = "every 4 weeks" (day 1 and weeks 4 and 8).



Based on the results of the phase 2 study and the on-going open-label extension study, the risk:benefit ratios of the 140 mg and 210 mg dosages appear to be acceptable for continued development. Detailed information on the observed safety profile of brodalumab can be referenced in the Investigator's Brochure.

2.4.2.2 Maintenance Regimens

While the phase 2 study demonstrated that the 140 mg and 210 mg Q2W dosages gave near-maximal efficacy in an induction paradigm, maintenance of response with decreased frequency of administration or decreased doses was not studied. The goal of a maintenance regimen would be to provide ongoing, long-term maintenance of response with minimized exposure. The second phase of this study is therefore an evaluation and comparison of multiple maintenance regimens. The maintenance regimens being tested are 210 mg Q2W, 140 mg Q2W, 140 mg every 4 weeks (Q4W), and 140 mg every 8 weeks (Q8W; [Figure 2](#)).

Superseded



2.4.3 Neutropenia

Interleukin-17A is a regulator of granulopoiesis and neutrophil recruitment in mice under normal and inflammatory conditions (Smith et al, 2008). Smith and colleagues (2008) showed that IL-17RA deficient mice had reduced granulocyte colony-stimulating factor levels and neutrophil counts even with high levels of IL-17A and that IL-17A regulated blood neutrophil counts by inducing granulocyte colony-stimulating factor production, mainly in non-hematopoietic cells. In addition, a study conducted by von Vietinghoff and Ley (2008) showed that IL-17A stimulates granulocyte colony-stimulating factor secretion and that decreased levels of IL-17A and granulocyte colony-stimulating factor down-regulate neutrophil differentiation. Therefore, blocking such effects could potentially result in reduced neutrophil counts. Neutropenia has been reported with a molecule that targets IL-17A (5 subjects out of 75 treated with drug; Genovese et al, 2010).

Events of neutropenia have also been reported in clinical studies of brodalumab and neutropenia is an identified risk of brodalumab (Investigator's Brochure). In the phase 2 study of brodalumab in psoriasis, 2 adverse events of neutropenia were

reported (out of 158 subjects treated with drug). Both were grade 3 asymptomatic neutropenia, occurring in subjects receiving 210 mg Q2W AMG 827. In both cases, the abnormal laboratory values occurred at week 2 (the first measured time point after the first dose of investigational product [IP]). Both cases resolved after IP was withheld and without intervention. In the second case, the subject experienced a positive rechallenge with grade 3 neutropenia; IP was stopped and the subject's absolute neutrophil count (ANC) rapidly normalized.

To more fully define this phenomenon and provide the basis for future monitoring guidance (if necessary), each subject will be closely monitored, with rules provided for withholding and discontinuing IP ([Section 6.4.1](#)).

2.5 Clinical Hypotheses

The first set of primary hypotheses of this study is that brodalumab at 210 mg Q2W and 140 mg Q2W will demonstrate superior efficacy compared with placebo in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects with success on sPGA and by the proportion of subjects with a PASI 75 at week 12.

The second set of primary hypotheses of this study is that brodalumab (at the 210 mg dosage and at the 140 mg dosage for subjects ≤ 100 kg with 210 mg dosage for subjects > 100 kg) will demonstrate superior ability to clear psoriasis compared with ustekinumab in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects attaining PASI 100 at week 12.

It is further hypothesized that subjects with moderate to severe plaque psoriasis who continue to receive brodalumab 210 mg Q2W or 140 mg Q2W will demonstrate superior response to those randomized to receive brodalumab at lower frequencies in the maintenance phase (140 mg Q4W and 140 mg Q8W), as measured by the proportion of subjects with success on sPGA at week 52.

3. EXPERIMENTAL PLAN

3.1 Study Design

After the screening period, this study begins with a randomized, double-blind, placebo- and active-controlled phase.

Subjects will be randomized to receive brodalumab (140 or 210 mg dosages), ustekinumab, or placebo as described in [Section 5.1](#).

At the week 12 visit, subjects who were originally randomized to either of the brodalumab arms will be rerandomized ([Section 5.1](#)) to 1 of 4 maintenance regimens.

Superseded

Subjects originally randomized to placebo will begin receiving 210mg Q2W brodalumab.

Subjects originally randomized to ustekinumab will continue receiving ustekinumab.

At week 52, subjects originally randomized to ustekinumab will begin receiving 210 mg Q2W brodalumab.

Subjects may qualify for rescue according to the rules in [Section 6.3](#).

The entire study will be up to **271 weeks** (approximately 5 years; includes up to 30 days for screening) in duration. Original and rerandomized treatment assignments will remain blinded until all subjects reach week 52 or terminate the study, whichever comes first.

The overall study design is described by a [study schema](#) at the end of the protocol synopsis section.

The study endpoints are defined in [Section 10.1](#).

3.2 Number of Centers

The study will be conducted at approximately 200 centers in the United States, Europe, Canada, and Australia. Other regions may be added as needed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Approximately 1800 subjects will be enrolled into the study. Rationale for the sample size is provided in [Section 10.2](#).

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

Subjects will participate in the study for up to 271 weeks (includes up to 30 days for screening) or until

- the investigator's recommendation of discontinuation,
- Amgen's recommendation of discontinuation,
- the subject's decision to discontinue for any reason, or
- an administrative decision to close the study is made for any reason, including, but not limited to, no proven or insufficient efficacy demonstrated on the primary analysis.

The end of study for an individual subject will be the last day that procedures are conducted for an individual subject.

Superseded

3.4.2 End of Study

Primary completion is defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, the last subject has reached week 52 or ended the study).

The end of study is defined as when the last subject is assessed or receives an intervention for evaluation in the study (ie, the last subject has completed the safety follow-up).

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate, date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refused to participate).

Before any study-specific procedure, the appropriate written informed consent must be obtained (see [Section 11.1](#)).

4.1 Inclusion Criteria

- 4.1.1 Subject has provided informed consent.
- 4.1.2 Subject is ≥ 18 and ≤ 75 years of age at time of screening.
- 4.1.3 Subject has had stable moderate to severe plaque psoriasis for at least 6 months before first dose of IP (eg, no morphology changes or significant flares of disease activity in the opinion of the investigator).
- 4.1.4 Subject must be considered, in the opinion of the investigator, to be a suitable candidate for treatment with a biologic per regional labeling.
- 4.1.5 Subject has involved body surface area (BSA) $\geq 10\%$, PASI ≥ 12 , and sPGA ≥ 3 at screening and at baseline.
- 4.1.6 For women (except those surgically sterile or at least 2 years postmenopausal, with postmenopausal status confirmed by follicle-stimulating hormone [FSH] in the postmenopausal range): a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline.
- 4.1.7 Subject has no known history of active tuberculosis.

Superseded

4.1.8 Subject has a negative test for tuberculosis during screening defined as either:

- negative purified protein derivative (PPD) (< 5 mm of induration at 48 to 72 hours after test is placed)

OR

- negative Quantiferon test.

Subjects with a positive PPD and a history of Bacillus Calmette-Guérin (BCG) vaccination are allowed with a negative Quantiferon test.

Subjects with a positive PPD test (without a history of BCG vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have all of the following:

- no symptoms per tuberculosis worksheet provided by Amgen
- documented history of a completed course of adequate prophylaxis (per local standard of care)
- no known exposure to a case of active tuberculosis after most recent prophylaxis
- no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of IP.

4.2 Exclusion Criteria

Skin disease related

4.2.1 Subject diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (eg, eczema) that would interfere with evaluations of the effect of IP on psoriasis.

Other medical conditions

4.2.2 Subject has a planned surgical intervention between baseline and the week 52 evaluation.

4.2.3 Subject has an active infection or history of infections as follows:

- any active infection for which systemic anti-infectives were used within 28 days prior to first dose of IP
- a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first dose of IP
- recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject.

4.2.4 Subject has any systemic disease (eg, renal failure, heart failure, hypertension, liver disease, diabetes, anemia) considered by the investigator to be clinically significant and uncontrolled.

4.2.5 Subject has known history of Crohn's disease.

Superseded

- 4.2.6 Subject has known history of hepatitis B, hepatitis C, or human immunodeficiency virus.
- 4.2.7 Subject had myocardial infarction or unstable angina pectoris within the past 12 months prior to the first dose of IP.
- 4.2.8 Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
- 4.2.9 Subject has history of malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
- 4.2.10 Subject has any concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the subject.

Laboratory abnormalities

- 4.2.11 Subject has laboratory abnormalities at screening, including any of the following:
- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal
 - serum direct bilirubin ≥ 1.5 mg/dL (25.7 µmol/L)
 - white blood cell (WBC) count < 3.00 x 10³/µL
 - ANC < 2.00 x 10³/µL
 - any other laboratory abnormality, which, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

Washouts and non-permitted drugs

- 4.2.12 Subject has used topical therapy as follows:
- Super-potent or potent topical steroids or topical anthralin/dithranol within 28 days before first dose of IP
 - Any other formulation or potency of topical therapy within 14 days before first dose of IP (exception: upper mid-strength or lower potency topical steroids permitted on the face, axillae, and groin; bland emollients [without urea or alpha or beta hydroxy acids]; shampoo without steroids).
- 4.2.13 Subject has used the following within 28 days of first dose of IP: ultraviolet A light therapy (with or without psoralen); ultraviolet B light therapy; excimer laser; oral retinoids; methotrexate; cyclosporine; systemically administered calcineurin inhibitors; azathioprine; thioguanine; hydroxyurea; fumarates; or oral or parenteral corticosteroids including intramuscular or intraarticular administration (exception: otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses is permitted); other non-biologic systemic therapy for psoriasis.
- 4.2.14 Subject has received live vaccine(s) within 28 days of the first dose of IP (or longer, according to local requirements for ustekinumab [eg, 1 year in the United States for BCG vaccination]).

Superseded

4.2.15 Subject has used ustekinumab and/or anti-IL-17 biologic therapy ever or other experimental or commercially available biologic immune modulator(s) within 12 weeks prior to the first IP dose.

4.2.16 Subject currently is enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s).

4.2.17 Other investigational procedures are excluded.

General

4.2.18 Subject has known sensitivity to any of the products or components to be administered during dosing.

For women (except if surgically sterile or at least 2 years postmenopausal, with postmenopausal status confirmed by FSH in the postmenopausal range): not willing to use highly effective methods of birth control during treatment and for 15 weeks after the last dose (if discontinuing before week 52) or for 8 weeks after the last dose (if discontinuing at or after week 52).

4.2.19 For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 15 weeks after the last dose (if discontinuing before week 52) or for 8 weeks after the last dose (if discontinuing at or after week 52).

4.2.20 Subject will not be available for protocol required study visits or procedures, to the best of the subject's and investigator's knowledge.

4.2.21 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give informed consent and/or to comply with all required study procedures.

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see [Section 11.2](#)). A subject is considered enrolled once the subject has been randomized (has been assigned a randomization number) at baseline. All subjects must personally sign and date the informed consent form before commencement of study-specific procedures.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Superseded

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.1 Randomization

Subjects will be randomized at baseline to receive 210 mg brodalumab, 140 mg brodalumab, ustekinumab, or placebo in a 2:2:1:1 ratio via an interactive voice response system (IVRS). The randomization lists will be generated by Amgen using a permuted block design within each strata, based on total body weight at baseline (≤ 100 kg vs > 100 kg), prior biologic use (yes vs no), and geographic region (defined by country for non-US countries and by geographic region for the United States [US-West, US-Midwest, US-Northeast, US-South]). Subjects with prior use of biologics will be capped at no more than 50% of the global study population.

Each randomized subject will receive a single, unique randomization number at the first randomization.

Subjects who do not attend their week 12 visit will not receive any further IP. Subjects who were originally randomized to either brodalumab arm will be pooled and then rerandomized at the week 12 visit to receive 210 mg Q2W brodalumab, 140 mg Q2W brodalumab, 140 mg Q4W brodalumab, or 140 mg Q8W brodalumab in a 2:2:2:1 ratio via IVRS. The randomization lists will be generated by Amgen using a permuted block design within each strata, based on week 12 total body weight (≤ 100 kg vs > 100 kg), the subject's week 12 response (sPGA = 0 vs sPGA ≥ 1), and the subject's original randomized treatment group (210 mg Q2W vs 140 mg Q2W).

Each subject entering the maintenance testing phase of the study will receive a second, unique randomization number. While subjects originally randomized to either placebo or ustekinumab will not be rerandomized at week 12 (those originally randomized to the placebo arm will begin receiving 210 mg Q2W brodalumab and those who were originally randomized to ustekinumab will continue to receive ustekinumab), those assignments will be made through the rerandomization process to maintain the blind to original treatment.

Superseded

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for further management of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. Once a subject's treatment assignment is unblinded via IVRS, the subject will not be allowed to receive any further IP.

The principal investigator, or delegate, is strongly encouraged to contact the Amgen study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's electronic case report form (eCRF).

6. TREATMENT PROCEDURES

This is a double-dummy study.

The IP in this study will be brodalumab (and placebo for brodalumab) and ustekinumab (and placebo for ustekinumab). Brodalumab and/or placebo for brodalumab will be referred to as Amgen IP, and ustekinumab and/or placebo for ustekinumab will be referred to as non-Amgen IP. No subject will receive both brodalumab and ustekinumab at the same time.

Throughout the study, subjects will receive placebo (for brodalumab and/or ustekinumab) as needed to maintain the blind until it is broken. IP supply will be controlled by IVRS and box numbers will be assigned at each visit.

6.1 Amgen IP

Brodalumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Placebo will be presented in identical containers and stored/packaged the same as brodalumab during the blinded portion of the study.

An IP instruction manual (IPIM) containing detailed information regarding the storage, preparation, and administration of Amgen IP will be provided separately.

Overdose with brodalumab has not been reported. The effects of overdose of brodalumab are not known.

6.2 Non-Amgen IP

The non-Amgen IP in this study will be ustekinumab (and a placebo for ustekinumab). Ustekinumab will be dosed according to its label (45 mg for subjects ≤ 100 kg and 90 mg for subjects > 100 kg; [Stelara® prescribing information, September 2013; Stelara® summary of product characteristics, March 2014](#)).

Ustekinumab is manufactured by Janssen Biotech and will be packaged by Amgen and distributed using Amgen clinical study drug distribution procedures. Ustekinumab will be presented as 45 mg ustekinumab prefilled syringes; in addition to ustekinumab, each syringe also contains: L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg) to fill to a final volume of 0.5 mL ([Stelara® prescribing information, September 2013; Stelara® summary of product characteristics, March 2014](#)). Ustekinumab will be packaged in dispensing packs containing 1 prefilled syringe.

Placebo will be presented in identical containers and stored/packaged the same as ustekinumab during the blinded portion of the study.

Details regarding the storage, preparation, and administration of this drug are provided in the IPIM.

Single doses of ustekinumab up to 4.5 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity ([Stelara® prescribing information, September 2013; Stelara® summary of product characteristics, March 2014](#)). In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

6.3 Dosage, Administration, and Schedule

Induction Phase

All subjects will receive both Amgen IP and non-Amgen IP.

All subjects will receive 2 injections of Amgen IP (one 1.0 ml and one 0.5 ml) at day 1 and week 1, 2, 4, 6, 8, and 10. These injections will be brodalumab and/or placebo, depending upon randomized arm.

Superseded

All subjects will receive non-Amgen IP at day 1 and week 4. These injections will be ustekinumab or placebo, depending upon randomized arm.

- Subjects ≤ 100 kg at the baseline visit will receive one 0.5 ml injection of non-Amgen IP at day 1 and week 4.
- Subjects > 100 kg at the baseline visit will receive two 0.5 ml injections of non-Amgen IP at day 1 and week 4.

According to randomized arm, subjects will receive 210 mg brodalumab, 140 mg brodalumab, ustekinumab (45 mg if ≤ 100 kg at the baseline visit, 90 mg if > 100 kg at the baseline visit), or placebo.

Maintenance Phase

All subjects will continue to receive Amgen and non-Amgen IP.

All subjects will receive 2 injections of Amgen IP (one 1.0 mL and one 0.5 mL) at week 12, 13, 14, 16, 17, 18, and every other week.

All subjects will receive non-Amgen IP at weeks 16, 28, and 40. These injections will be ustekinumab or placebo, depending upon randomized arm.

- Subjects ≤ 100 kg at the baseline visit will receive one 0.5 ml injection of non-Amgen IP at weeks 16, 28, and 40.
- Subjects > 100 kg at the baseline visit will receive two 0.5 ml injections of non-Amgen IP at weeks 16, 28, and 40.

Starting at week 12, subjects who were originally randomized to placebo will receive 210 mg Q2W brodalumab. Subjects who were originally randomized to ustekinumab will continue receiving ustekinumab. At the week 12 visit, all subjects who were originally randomized to either of the brodalumab treatment arms will be rerandomized per [Section 5.1](#). In this phase, they will receive 210 mg Q2W brodalumab, 140 mg Q2W brodalumab, 140 mg Q4W brodalumab, or 140 mg Q8W brodalumab.

Subjects may qualify for rescue during the maintenance phase as described in the rescue section below.

Long-term Extension

All subjects will receive Amgen IP at weeks 52, 53, 54, and every other week.

Subjects on brodalumab will continue at their maintenance phase or rescue treatment dosage, as applicable.

Subjects who were on ustekinumab will begin 210 mg Q2W brodalumab at week 52.

Superseded

Subjects may qualify for rescue during the long-term extension as described in the rescue section below.

After the blind to original and rerandomized treatment assignment has been broken, an analysis to identify the most appropriate maintenance dosage(s) of brodalumab will be performed. Based upon the results of that analysis, an amendment may be pursued to change the dosage and/or frequency in some or all subjects.

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

| [REDACTED]
| [REDACTED]
| [REDACTED]

Rescue Treatment

Subjects qualify 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 can only qualify for rescue at scheduled study visits. After week 52, disease severity may also be assessed at unscheduled visits for study decision purposes (eg, qualification for rescue treatment); however, rescue treatment can only be initiated at the subject's next scheduled dose. To maintain a regular schedule of IP, rescue treatment cannot be initiated at week 17 or 53.

Rescue treatment will be blinded until the study is unblinded. Subjects qualifying for rescue will continue to receive Amgen IP and non-Amgen IP per the schedule described under "maintenance phase" and "long-term extension phase" above.

At week 16, any subject in the study who has an inadequate response is eligible for rescue with 210 mg Q2W brodalumab, regardless of treatment arm.

After week 16 but before week 52, subjects on brodalumab who qualify for rescue will receive 210 mg Q2W brodalumab; subjects on ustekinumab will continue to receive ustekinumab.

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Subjects who qualify for rescue at and after week 52 will receive 210 mg Q2W brodalumab.

Once they have been on rescue treatment for at least 12 weeks, subjects will be assessed for nonresponse. Nonresponse is defined as persistent sPGAs ≥ 3 over at least a 4-week period in a subject on continuous treatment for at least 12 weeks. Subjects who are nonresponders to rescue treatment should discontinue investigational product.

Administration

Through the week 26 visit and at the week 52, 53 and 54 visits, doses of IP must be given within ± 3 days from the scheduled dose date. Between week 28 and week 50 and from week 56 onwards, doses of IP must be administered ± 7 days from the scheduled dose date. Starting at week 28, any 2 consecutive doses of Amgen IP must be at least 7 days apart, with the exception of the weekly doses at weeks 52, 53, and 54. If that window is missed, that dose will not be administered. The next dose will be administered at the next scheduled dosing date. When an injection is to be administered on the same day as a study visit, it should not be administered until all other study visit procedures have been completed.

Non-Amgen IP will be administered via subcutaneous injection by a healthcare provider. Acceptable injection sites include the upper arms, gluteal regions, thighs, or abdomen. For subjects who are receiving 2 injections of non-Amgen IP per dose, the 2 injections should be administered in different body regions.

Amgen IP will be administered via subcutaneous injection to the abdomen, thigh, or upper arm. Subsequent injections of Amgen IP may be administered to the same body region. Amgen IP should not be administered in the same body region as non-Amgen IP at either the visit where both are given (eg, week 4) or for 2 weeks after non-Amgen IP was administered.

Through week 28, Amgen IP will be administered by a qualified staff member after all other study visit procedures have been completed, according to [Appendix A](#).

Starting at week 28 and up until week 52, subjects will self-administer Amgen IP every other week by subcutaneous injection (“self-administration” includes administration by a trained designated person). Before a subject may begin self-administration, it is the responsibility of the investigator to ensure that the subject or the subject’s designated person is trained to prepare and administer the injection. All subjects or their designated

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person will receive training and study tools designed to educate the subject on the proper storage and self-administration of Amgen IP. The completion of training on self-administration (or training to a designated person) will be recorded in the source documentation.

The first self-administered dose of Amgen IP must be administered in the office by the subject or the trained designated person. After the first self-administered dose, doses of Amgen IP will be administered by the subject or the trained designated person (in-office dosing is not required for Amgen IP; in-office dosing is required for non-Amgen IP).

Subjects will be supplied with a diary in which to record the date, time, and injection site of each dose of Amgen IP, whether the full dose was injected, and any potential adverse events and concomitant medications. Study site staff will review the diary with the subject at each clinic visit and transcribe all pertinent information onto the eCRF. The diaries will be retained at the study site as part of the source documentation once a subject has completed his/her study participation.

Starting at week 52, dosing of Amgen IP will again occur in the office (to maintain the blind while monitoring the initiation of brodalumab in subjects who were on ustekinumab). Self administration will begin again at week 64 and continue through the rest of the study.

The date, time, and administered volume of IP will be recorded on the individual subject's eCRF.

The subjects will be instructed in appropriate handling and storage of brodalumab.

Starting at week 28, supplies of Amgen IP will be dispensed according to [Appendix A](#) to subjects for self-administration. The site will ensure that each subject is supplied with all necessary materials required for self-administration.

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6.4 Dosage Adjustments and Rules for Withholding IP

6.4.1 ANC Abnormalities

ANC should be monitored and doses of all IPs withheld according to the following rules:

Site staff should review a subject's central laboratory values as soon as possible upon receipt (should be prior to the subject's next scheduled dose):

If the ANC is $< 1.00 \times 10^3/\mu\text{L}$, the subject should not be dosed and the subject should have a repeat complete blood count (CBC) through the central laboratory.

- During the periods of the study where Amgen IP is administered in the office, other visit procedures (including CBC) should be completed as scheduled but dosing should be held.
- During the periods of the study where the Amgen IP is self-administered, the subject should be contacted and instructed to hold the dose(s) and to return to the clinic as soon as possible for a repeat CBC.

If the subject's ANC at the repeat CBC is $\geq 1.00 \times 10^3/\mu\text{L}$, the subject may receive the scheduled dose (if within the dosing window).

If the ANC remains $< 1.00 \times 10^3/\mu\text{L}$ at the repeat CBC, the subject's next scheduled dose(s) must be held.

Treatment with IP should be permanently discontinued under the following scenarios:

- Subject has sustained episode of neutropenia ($\text{ANC} < 1.00 \times 10^3/\mu\text{L}$ at all measurements [must be at least 2] for ≥ 4 weeks).
- Subject has second episode of neutropenia ($\text{ANC} < 1.00 \times 10^3/\mu\text{L}$), following full recovery ($\text{ANC} \geq 1.00 \times 10^3/\mu\text{L}$).
- Subject's ANC is $< 0.50 \times 10^3/\mu\text{L}$.

6.4.2 Infections

The scheduled dose(s) of all IPs should not be administered if the subject has an infection for which systemic anti-infectives are indicated or the subject has signs and/or symptoms of an infection that, in the opinion of the investigator, warrant holding the dose. The dose(s) of all IPs should be delayed or withheld until the infection has resolved in the opinion of the investigator. If the dosing window is missed because of persistent infection, that dose should not be administered. The next dose should be administered at the next scheduled dosing date (unless the infection is still unresolved).

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6.4.3 Suicidal Ideation or Behavior

Suicidal ideation and behavior will be assessed using the electronic self rated version, Columbia-Suicide Severity Rating Scale (eC-SSRS). IP should be permanently discontinued according to the following rules:

- subject reports suicidal ideation after randomization, with severity of 4 or 5;
OR

- subject reports any suicidal behavior after randomization.

If any of these criteria are met the subject should be referred immediately to a mental health care professional for further evaluation.

6.4.4 Depression

Depression will be assessed using the eight-item version of the Patient Health Questionnaire depression scale (PHQ-8). Any subject who has a PHQ-8 total score of ≥ 10 should be referred immediately to a mental health care professional for further evaluation. IP should be permanently discontinued if the subject reports severe depression (PHQ-8 total score of ≥ 15).

6.4.5 General Guidance on Hepatotoxicity Stopping and Rechallenge Rules

A United States Food and Drug Administration Guidance exists for drug-induced liver injury. This guidance is general for all IPs, and its recommendations can be found in Appendix B. It provides criteria for withholding IP in the event that a subject develops signs or symptoms of hepatitis during a clinical trial.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.6](#).

6.6 Excluded Treatments During Study Period

The following concomitant therapies or treatments are prohibited throughout study participation. Subjects who require use of a prohibited medication should be discontinued from IP.

- ultraviolet A light therapy (with or without psoralen)
- ultraviolet B light therapy
- methotrexate
- mycophenolate mofetil

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- cyclophosphamide
- cyclosporine
- systemically administered calcineurin inhibitors
- azathioprine
- thioguanine
- oral retinoids
- hydroxyurea
- fumarates
- any biologic immune modulator, including but not limited to etanercept, alefacept, anakinra, adalimumab, infliximab, and IL-12/IL-23 inhibitor (other than ustekinumab as provided in this study)
- any other systemic therapy for psoriasis
- any investigational therapy other than brodalumab and ustekinumab (as provided in this study)

The therapies and medications listed below are allowed only according to the following guidance.

- topical therapy
 - through week 64:
 - use of upper mid-strength or lower potency topical steroids is allowed during the study on the face, axillae, and groin only; other topical therapies for psoriasis (eg, calcineurin inhibitors, vitamin D analogues, super-potent or potent topical steroids) are prohibited
 - Shampoos (without steroids) are permitted
 - Bland emollients (without urea or beta or alpha hydroxy acids) are permitted
 - after week 64:
 - topical therapy of any potency or formulation (eg, topical steroids, vitamin D analogues) is allowed on any body region

Application of topical therapies for psoriasis should not occur within a day prior to the visit.

- oral or parenteral corticosteroids including intramuscular or intraarticular
 - through week 64: use is not allowed (exception: otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses is permitted)
 - after week 64: use for up to 14 consecutive days is allowed for conditions other than psoriasis
- live vaccines
 - through week 55: use of live vaccines is not allowed
 - after week 55: if a live vaccine is needed, brodalumab must be discontinued at least 28 days prior to administration of the live vaccine. After administration of the live vaccine, brodalumab may be reinitiated at least 28 days later.
 - Note: live vaccines may be prohibited until later in the study according to local requirements for ustekinumab (eg, at least 1 year after the last dose of ustekinumab for subjects in the United States receiving BCG).

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7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and [Appendix A](#) can only be performed after obtaining informed consent. This includes any discontinuation of the subject's medication for the purpose of participation in this study.

All on-study visits and dosing should be scheduled from day 1 (date of the first dose of Amgen IP) on the study. It is very important that study procedures are performed at the timepoints stipulated below. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

With the exception of the informed consent, screening and re-screen visits, and dosing of IP (administered within the visit window), all study procedures for a visit must be performed on the same day. Any missed visits, tests not done, or examinations that are not performed must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments from prior visits should not be duplicated at subsequent visits.

7.1 Visit-specific Study Procedures

7.1.1 Screening

Informed consent must be obtained before completing any other screening procedure. After informed consent has been obtained, subjects will be screened in order to assess eligibility for study participation. The screening window is a maximum of 30 days; a subject must be in screening for at least 7 days. If a subject has not met all eligibility criteria at the end of the 30-day window the subject will be registered as a screen failure. Subjects who screen fail may be eligible to re-screen per [Section 7.1.2](#). Laboratory assessments used to determine subject eligibility may be repeated once for confirmation during each 30-day screening period before the subject is considered a screen failure.

The following procedures will be completed for all subjects during the screening period:

- informed consent
- medical / medication history
- physical examination (includes height and weight)
- vital signs
- disease assessments
 - PASI
 - sPGA
 - BSA

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- laboratory assessments
 - PPD or Quantiferon
 - hematology
 - chemistry
 - FSH, if applicable
 - serum pregnancy test, if applicable
 - urinalysis
- chest radiograph and tuberculosis worksheet (if the subject has a positive PPD or positive or indeterminate Quantiferon test)
- serious adverse events
- distribution of electronic hand-held device (eDiary) and instructions on its use for collection of daily Psoriasis Symptom Inventory

The Psoriasis Symptom Inventory will be completed daily during screening.

7.1.2 Re-screening

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to re-screen twice for a total of 3 screenings. Re-screen subjects must first be registered as screen failures in IVRS and subsequently registered as re-screens.

Subjects will retain the same subject identification number assigned at the original screening. Subjects will continue to complete the Psoriasis Symptom Inventory daily during re-screening. A subject must be in re-screening for at least 7 days.

Subjects re-screening within the original 30-day screening window only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. If a subject fails to meet eligibility after re-screening once within the original 30-day screening window, the subject may not re-screen again until 30 days after the re-screening date.

Subjects re-screening after the original 30-day screening window has ended must be re-consented and repeat all screening procedures, except the PPD test, Quantiferon test, and/or chest radiograph if negative at the first screening. If the first re-screen is performed after the original screening window has ended, a new 30-day screening window will begin. If the final re-screen is within the 30 days following the first re-screen, only the assessment(s) that did not meet eligibility at the first re-screen need to be repeated.

Superseded

7.1.3 Baseline

Once a subject has met the screening eligibility criteria, the following baseline procedures will be completed:

- patient-reported outcomes
 - Psoriasis Symptom Inventory (completed daily)
 - Dermatology Life Quality Index (DLQI)
 - Work limitations questionnaire (WLQ)
- disease assessments
 - PASI (baseline eligibility assessment)
 - BSA (baseline eligibility assessment)
 - sPGA (baseline eligibility assessment)
 - Nail Psoriasis Severity Index (NAPSI)
- adverse events (see [Section 9](#))
- concomitant medications
- physical examination (includes weight and waist circumference)
- electrocardiogram
- vital signs
- laboratory assessments
 - hematology
 - chemistry
 - C-reactive protein
 - urinalysis
 - urine pregnancy test, if applicable
 - anti-brodalumab antibodies
 - brodalumab pharmacokinetics
 - biomarker blood samples (for consenting subjects)
 - biomarker lesional skin biopsy samples (for consenting subjects)
 - non-lesional skin biopsy samples (for consenting subjects)
- photography (for consenting subjects)
- randomization
- Amgen and non-Amgen IP administration (may be completed up to 3 days after randomization)

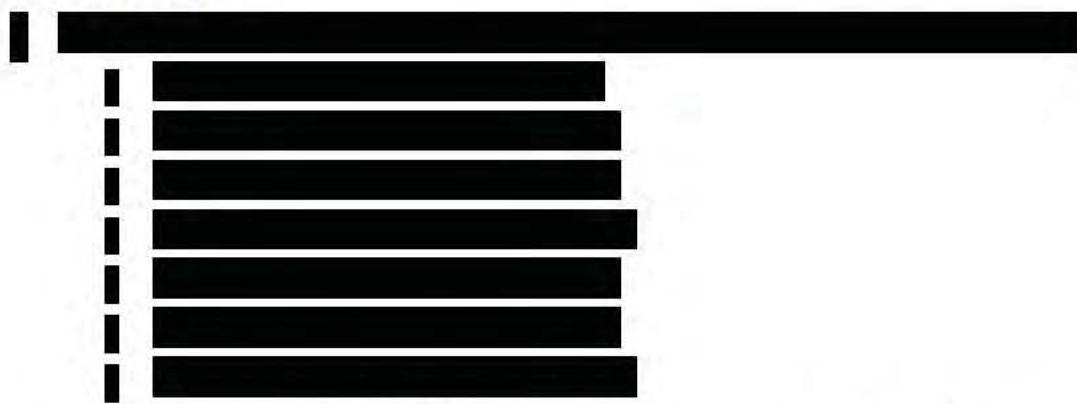
The date of the first dose of Amgen IP is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date.

Superseded

7.1.4 Week 1 to Week 26

Visits will occur per the schedule of assessments ([Appendix A](#)). On-study visits may be completed within \pm 3 days of the target visit date. The following procedures will be completed at each visit, unless otherwise specified:

- patient-reported outcomes
 - Psoriasis Symptom Inventory (completed daily until the week 24 visit)
 - DLQI (weeks 2, 4, 8, 12, 16, 20, and 24)
 - WLQ (weeks 12 and 24)
- disease assessments
 - PASI
 - BSA
 - sPGA
 - NAPSI (weeks 12 and 24)
- concomitant medications
- adverse events
- physical examination (includes weight; weeks 12 and 24)
- vital signs
- electrocardiogram (week 24)
- laboratory assessments
 - hematology
 - chemistry (weeks 4, 8, 12, 16, 20 and 24)
 - urinalysis (weeks 4, 8, 12, 16, 20 and 24)
 - urine pregnancy test, if applicable (weeks 4, 8, 12, 16, 20 and 24)
 - C-reactive protein (weeks 12 and 24)
 - anti-brodalumab antibodies (weeks 4, 12, and 24)
 - brodalumab pharmacokinetics (pre-dose samples; weeks 1, 2, 4, 6, 10, 12, 20, 22 and 24)



- biomarker blood samples (for consenting subjects; weeks 1, 12, and 13)

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- biomarker lesional skin biopsy samples (for consenting subjects; weeks 2, 4, and 12)
- biomarker non-lesional skin biopsy samples (for consenting subjects; week 12)
- photography (for consenting subjects; weeks 4, 12 and 24)
- retrieval of eDiary (week 24)
- rerandomization (week 12 only)
- Amgen IP administration
- non-Amgen IP administration (week 4 and 16)

7.1.5 Week 28 to Week 52

The week 28 to week 48 visits will occur per the schedule of assessments ([Appendix A](#)) and may be completed within \pm 7 days of the target visit date. The week 52 visit will occur per the schedule of assessments ([Appendix A](#)) and may be completed within \pm 3 days of the target visit date. The following procedures will be completed at each visit unless otherwise specified:

- patient-reported outcomes
 - Psoriasis Symptom Inventory (completed daily following the week 48 visit until the week 52 visit)
 - DLQI
 - WLQ (weeks 36 and 52)
- eC-SSRS
- PHQ-8
- disease assessments
 - PASI
 - BSA
 - sPGA
 - NAPSI (weeks 36 and 52)
- physical examination (includes weight; weeks 36 and 48; week 48 includes waist circumference)
- electrocardiogram (week 48)
- concomitant medications
- adverse events
- vital signs
- laboratory assessments
 - hematology
 - chemistry
 - C-reactive protein (week 48)

Superseded

- urinalysis
 - urine pregnancy test, if applicable
 - anti-brodalumab antibodies (weeks 48 and 52)
 - brodalumab pharmacokinetics (weeks 48 and 52)
 - biomarker lesional skin biopsy sample (for consenting subjects; week 52)
 - distribution eDiary (week 48)
 - retrieval of eDiary (week 52)
 - Amgen IP administration (week 28 dose should be administered in the office by the subject or the designated person per [Section 6.3](#) to demonstrate competence; week 52)
 - non-Amgen IP administration (weeks 28 and 40)
 - Amgen IP dispensing for self administration (weeks 28, 32, 36, 40, 44, and 48)
 - photography (for consenting subjects; week 52)
- 

7.1.6 Week 53 to Week 68

The week 53 and 54 visits will occur per the schedule of assessments ([Appendix A](#)) and may be completed within \pm 3 days of the target visit date. The week 56 to week 64 visits will occur per the schedule of assessments ([Appendix A](#)) and may be completed within \pm 7 days of the target visit date. The following procedures will be completed at each visit (**week 52 to week 60**), unless otherwise specified:

- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - PASI (weeks 54, 56, 60, and 62)
 - BSA (weeks 54, 56, 60, and 62)
 - sPGA (weeks 54, 56, 60, and 62)
- physical examination (includes weight; week 60)
- concomitant medications
- adverse events
- vital signs

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- laboratory assessments
 - hematology
 - chemistry
 - urinalysis
 - urine pregnancy test, if applicable (weeks 56, 60, and 64)
 - anti-brodalumab antibodies (week 62)
 - brodalumab pharmacokinetics (week 62)
- Amgen IP administration (weeks 53, 54, 56, 58, 60, and 62; must be administered in office)
- Amgen IP dispensing for self administration (week 64)

The following procedures will be completed at week 68.

- eC-SSRS
- PHQ-8
- urine pregnancy test, if applicable

7.1.7 Week 72 to Week 260

Visits will occur per the schedule of assessments ([Appendix A](#)). On-study visits may be completed within \pm 7 days of the target visit date. The following procedures will be completed at each visit, unless otherwise specified:

- eC-SSRS [every 4 weeks (weeks 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, and 260)]
- PHQ-8 [every 4 weeks (weeks 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, and 260)]
- disease assessments
 - PASI
 - BSA
 - sPGA
 - NAPSI (weeks 72, 96, 120, 144, 168, 192, 216, and 240)
- physical examination (includes weight; weeks 96, 144, and 192 include waist circumference)
- concomitant medications
- adverse events
- vital signs
- electrocardiogram (week 96, 144, and 192)

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- laboratory assessments
 - hematology
 - chemistry
 - urinalysis
 - urine pregnancy test and distribution of test kits, if applicable
 - C-reactive protein (weeks 72, 96, 120, 144, 168, 192, 216, and 240)
 - anti-brodalumab antibodies (weeks 72, 84, 96, 108, 120, 144, 168, 192, 216, and 240)
 - brodalumab pharmacokinetic samples (weeks 72, 84, 96, 108, 120, 144, 192, and 240)
- Amgen IP dispensing for self administration

7.1.8 Week 264/Early Termination

The week 264 visit should be completed within \pm 7 days of the target visit date. Subjects ending the study prior to week 264 will be asked to complete an early termination visit.

The following procedures apply to the week 264 and early termination visits:

- patient-reported outcomes (early termination only [only for subjects who terminate the study before week 52])
 - Psoriasis Symptom Inventory
 - DLQI
 - WLQ
- eC-SSRS
- PHQ-8
- disease assessments
 - PASI
 - BSA
 - sPGA
 - NAPSI
- concomitant medications
- adverse events
- physical examination (includes weight and waist circumference)
- electrocardiogram
- vital signs
- laboratory assessments
 - hematology
 - chemistry
 - urinalysis

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- urine pregnancy test, if applicable
- C-reactive protein
- anti-brodalumab antibodies
- brodalumab pharmacokinetics

7.1.9 Week 266/Safety Follow-up

Subjects will complete a safety follow-up at week 266. If subjects early terminate, a safety follow-up visit should occur approximately 30 days after the last dose of IP. In the event that a subject has had investigational product withheld (for a protocol specified reason) for greater than 30 days before the decision to early terminate occurs, the safety follow-up visit should occur as soon as possible after the decision has been made to early terminate. The visit may be conducted by telephone. The following will be collected per the Schedule of Assessments ([Appendix A](#)):

- concomitant medications
- adverse events

7.2 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in [Section 7.1](#).

7.2.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent form before any study specific procedures are performed ([Section 11.1](#)).

Depending on site and IRB/IEC requirements, substudies/procedures that may require a separate informed consent form include:

- Post-dose pharmacokinetic samples at additional timepoints for brodalumab pharmacokinetic analysis (according to the schedule in [Appendix A1](#))
- Lesional and non-lesional complete skin biopsies
- Photography
- Biomarker blood collection
- Pharmacogenetic analysis

7.2.2 Medical History

The subject's complete medical and surgical history, including alcohol and tobacco use history, will be obtained prior to enrollment and recorded on the eCRF. Diagnosis dates for psoriasis and psoriatic arthritis (if applicable) will also be collected.

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7.2.3 Medication History

The subject's history of all medications taken within the 3 months prior to screening will be recorded on the eCRF. In addition to this, the subject's psoriasis- or psoriatic arthritis-specific medication history, including biologic and non biologic systemic therapy, phototherapy, and/or topical therapy at any time in the subject's history will be recorded on the eCRF. The reason for discontinuing methotrexate, PUVA, cyclosporine or prior biologic therapies will be collected.

7.2.4 Physical Examination

The screening physical examination will be a complete physical examination including height and weight. Height should be recorded with the subject standing without shoes. Weight should be recorded with the subject without shoes. Breast, genital, and rectal examinations are not required at any study visit unless specific evaluation is warranted. Physical examination findings at screening should be recorded on the medical and surgical history eCRF. The physical examination at subsequent study visits will consist of an interim examination to monitor for any changes and will also include weight. Waist circumference will also be measured at specific visits in [Section 7.1](#) and [Appendix A](#).

To measure the subject's waist circumference, a tape measure should be placed around the subject's bare abdomen just above the hip bone (iliac crest) while the subject is standing. The tape should be placed parallel to the floor and held with enough tension that it remains closely fitted to the body, but does not compress the skin. The measurement should be taken after the subject has exhaled.

Any clinically significant changes in physical examination, per the investigator's opinion, should be recorded on the adverse event eCRF.

7.2.5 Vital Signs

Vital signs will be obtained with the subject in the seated position and should include body temperature, blood pressure, and pulse. Subjects should be in a seated position for at least 5 minutes before taking vital sign measurements.

7.2.6 Chest Radiographs

If applicable, the chest radiograph will include anterior/posterior or posterior/anterior and lateral views. The radiograph should be read by a radiologist or per local requirements.

7.2.7 Electrocardiogram

A standard 12-lead electrocardiogram will be obtained after the subject has been supine for at least 3 minutes and prior to blood samples being drawn. Standard

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electrocardiogram machines will be provided to the site and should be used for all study-related electrocardiogram requirements. The PI or designated physician will review all electrocardiograms. Electrocardiograms will be transferred electronically to a central reader for analysis per Amgen instructions. The signed, original electrocardiogram tracing will be retained with the subject's source document.

7.2.8 Patient-reported Outcomes

The following assessments will be completed by the subject and should be completed prior to any other procedure at the applicable visit. eDiaries and ePRO tablets will be provided to the sites.

7.2.8.1 Psoriasis Symptom Inventory

Subjects will use an eDiary to record their daily psoriasis symptoms using the Psoriasis Symptom Inventory, a psoriasis-specific patient-reported outcome measure that has been developed on the basis of a literature review, in-depth physician interviews, psoriasis patient focus groups, and cognitive interviews. The Psoriasis Symptom Inventory consists of eight psoriasis-specific items. Subjects will be requested to rate the severity of their symptoms in the last 24 hours from 'not at all' to 'very severe,' ranging from 0 to 4. Total scores range from 0 to 32 with higher scores indicating worse symptoms. The Psoriasis Symptom Inventory takes about 3 minutes to complete.

Site staff will train the subject on the proper use of the eDiary at the screening visit. Subjects should be instructed to complete the Psoriasis Symptom Inventory once per day. The eDiary will be completed in the evening within a specified time window; for the early termination visit only, the Psoriasis Symptom Inventory may be completed earlier in the day.

7.2.8.2 DLQI

Health related quality of life will be evaluated using the DLQI, a skin disease-specific instrument that has been validated for use in patients with psoriasis ([Finlay and Khan, 1994](#)). The DLQI takes about 2 minutes to complete.

7.2.8.3 WLQ

WLQ measures the on-the-job impact of chronic health problems and treatment. The WLQ is a 25-item questionnaire examining 4 domains: time management, physical demands, mental-interpersonal demands and output demands. It has a recall period of 2 weeks. WLQ also includes a separate 4-question Time Loss module to determine the

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percentage of productivity lost due to work absences. It takes approximately 10 minutes to complete the WLQ questionnaire and the Time Loss module.

7.2.8.4 Electronic Self Rated Version, Columbia-Suicide Severity Rating Scale (eC-SSRS)

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior ([Mundt et al, 2010; Posner et al, 2011](#)). Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eC-SSRS defines five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS takes approximately 3 to 10 minutes to complete.

7.2.8.5 Patient Health Questionnaire-8 (PHQ-8)

The PHQ-8 is a validated and widely used eight-item version of the Patient Health Questionnaire depression scale designed to clinically assess patients for symptoms and signs of depression ([Kroenke and Spitzer, 2002; Kroenke et al, 2009](#)). The PHQ-8 takes approximately 3 minutes to complete.

7.2.9 Disease Assessments

The assessor who performs the following assessments will be a healthcare professional who has been certified as trained by Amgen. If possible, each subject should have their assessments done by the same assessor throughout the study. Extra care should be taken to ensure that the same assessor performs the baseline and week 12 assessments. If necessary, study visits may be rescheduled within the specified window to accommodate when the specific assessor will be available.

7.2.9.1 PASI

The PASI score (0 to 72) is a calculation of plaque qualities, including induration, erythema, and desquamation, and the area involved with psoriasis. The assessor will score plaque qualities (0 to 4) and area of involvement (0 to 6) for each of 4 body areas: head and neck, upper extremities, trunk, and lower extremities. Higher scores indicate more severe and/or extensive psoriasis.

7.2.9.2 BSA Involvement

The BSA numerical score (0% to 100%) is completed by the same assessor performing the PASI assessments and will be used to measure the assessor's assessment of the proportion of the subject's total BSA involved with psoriasis.

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7.2.9.3 sPGA

The sPGA scale (0 [clear] to 5 [severe]) is completed by the same assessor performing the PASI assessments and is designed to evaluate the assessor's global assessment of the subject's psoriasis based on severity of induration, scaling, and erythema.

7.2.9.4 NAPSI

The NAPSI scale is an objective, numeric, and reproducible grading system for nail psoriasis that incorporates the many different features of nail psoriasis. For assessments in this study (including selection of target nail), a nail is graded using the NAPSI scale by first dividing the nail with imaginary horizontal and vertical lines into 4 quarters. The following 8 clinical features of nail psoriasis are then scored based on the number of quarters in which the feature is present (0 to 4) to arrive at a NAPSI score of 0 to 32 for each nail:

- pitting
- leukonychia
- red spots in lunula
- nail plate crumbling
- oil drop (salmon patch) discoloration
- onycholysis
- nail bed hyperkeratosis
- splinter hemorrhages

In randomized subjects with nails involved with psoriasis, each nail will be scored at baseline to determine the worst nail (ie, the nail with the highest NAPSI score). Those subjects whose worst nail has a minimum NAPSI score of 6 at baseline will have this nail (the target nail) followed for the remainder of the study. If multiple nails have the same worst score, only 1 target nail will be followed.

7.2.10 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of urine pregnancy, PPD, and Quantiferon (may be done by central or local laboratory). The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, urinalysis, C-reactive protein, and any other laboratory tests required. Urine pregnancy and PPD testing, if applicable, will be performed locally. The results of this testing will be maintained in the source documents at the site. Amgen or designee will be responsible for brodalumab pharmacokinetics, anti-brodalumab antibody, biomarker development and

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pharmacogenetic assessments and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment).

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. All blood samples will be obtained by venipuncture before IP administration. The date and time of sample collection will be recorded in the source documents at the site.

Specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples are listed below ([Table 4](#)).

Table 4. Analytes

Chemistry	Urinalysis	Hematology and Differential	Other Labs
Sodium	Specific gravity	RBC	C-reactive protein (high sensitivity)
Potassium	pH	RBC Morphology	Anti-brodalumab antibody
Chloride	Blood	Hemoglobin	Serum beta hCG ^a
Bicarbonate	Protein	Hematocrit	Quantiferon ^b
Total protein	Glucose	Platelets	Brodalumab Pharmacokinetics
Albumin	Bilirubin	WBC	FSH ^b
Adjusted calcium	Leukocyte esterase	Differential	
Magnesium	Ketones	• Bands/stabs	
Phosphorus	Microscopic(Reflex testing if abnormal)	• Eosinophils	
Glucose		• Basophils	
BUN		• Lymphocytes	
Creatinine ^c		• Monocytes	
Uric acid		ANC	
Total bilirubin			
Direct bilirubin			
Alk phos			
AST			
ALT			

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell; FSH=follicle-stimulating hormone.

Note: Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

^a For all women, except those surgically sterile or at least 2 years postmenopausal confirmed by FSH

^b If applicable

^c Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Modification of Diet in Renal Disease formula

Any blood, urine, or tissue samples collected according to the Schedule of Assessments ([Appendix A](#)) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical

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methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

If informed consent is provided by the subject, Amgen may do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the inflammatory conditions, the dose response and/or prediction of response to IP, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

7.2.10.1 Anti-brodalumab Antibody

Blood samples will be collected from all subjects for the measurement of anti-brodalumab binding antibodies. [REDACTED]

Term	Percentage (%)
Climate change	85
Global warming	92
Green energy	88
Sustainable development	95
Environmental protection	82
Recycling	80
Energy efficiency	88
Organic food	60

7.2.10.2 Brodalumab Pharmacokinetics

Samples will be collected, processed, frozen, and shipped per the central laboratory manual.

[REDACTED]

[REDACTED]

[REDACTED]

7.2.10.2.1 Main Pharmacokinetic Study (All Subjects)

Blood samples for brodalumab pharmacokinetic analysis will be collected from all subjects prior to dosing as shown in the schedule of assessments ([Appendix A](#)).

7.2.10.2.2 Brodalumab Pharmacokinetic Substudy (Optional; Additional Consent Required)

The pharmacokinetic substudy has a target enrollment of at least 12% (approximately 190 subjects). These subjects will be required to visit the study site for additional blood draws at the post-dose timepoints shown in the brodalumab pharmacokinetic substudy schedule of assessments ([Appendix A1](#)).

7.2.10.3 Urine Pregnancy

Urine pregnancy tests for women who are not surgically sterile or at least 2 years post menopausal (confirmed by FSH) will be performed locally. On visits where required, urine pregnancy tests must be performed prior to dosing with IP. In between scheduled study visits after week 64, subjects will perform urine pregnancy testing monthly. If a urine pregnancy test is positive, IP must be held; if pregnancy is confirmed, then IP must be discontinued.

7.2.10.4 PPD

The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. The test will be read per [Section 4.1.8](#). PPD test kits will not be provided by the sponsor and must be procured locally.

7.2.11 Photography of Psoriasis (Optional; Additional Consent Required)

7.3 Biomarker Development and Pharmacogenetic Studies

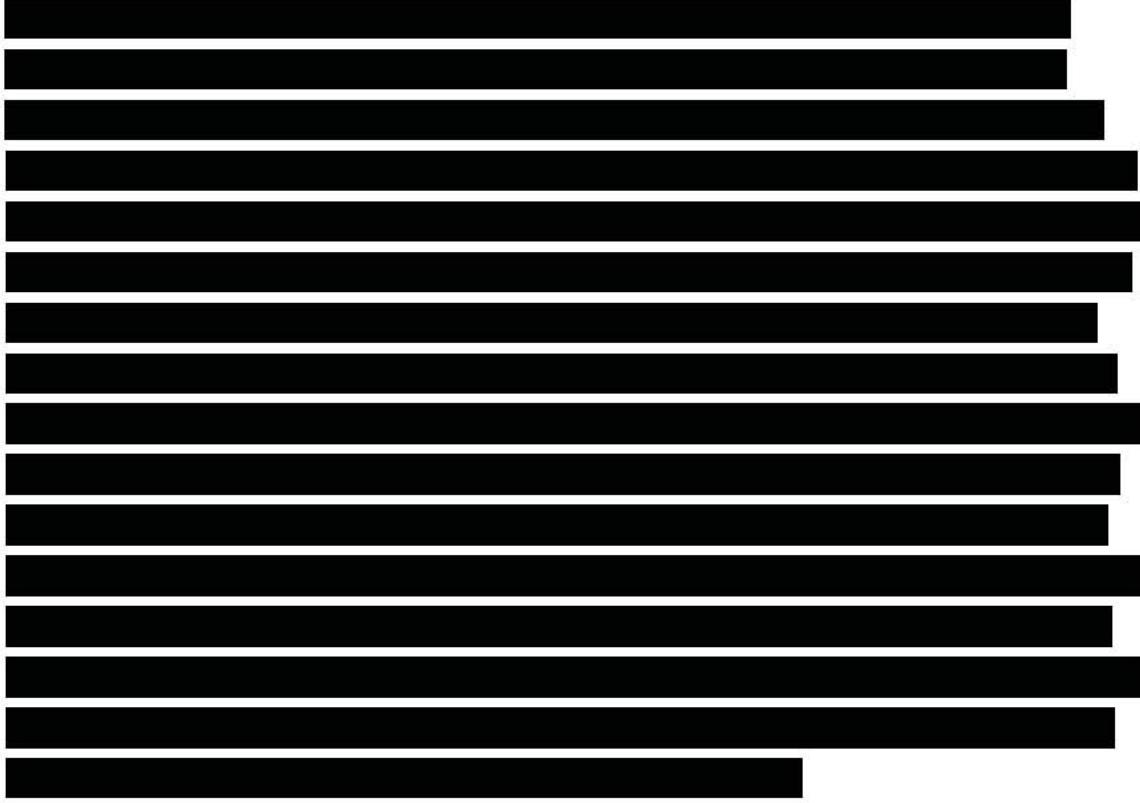
7.3.1 Biomarker Development

Biomarker Blood Samples (Optional; Additional Consent Required)

Tissue Samples (Optional; Additional Consent Required)

7.3.2 Pharmacogenetic Studies (Optional; Additional Consent Required)

7.3.3 Sample Storage and Destruction



8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation; subject data up to withdrawal of consent will be included in the analysis of the study. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Withdrawal of partial consent means that the subject does not wish to take protocol-specified product(s) any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures). Subjects may decline to continue receiving protocol-specified product(s) at any time during the study. If a subject declines to continue receiving protocol-specified product(s) or is discontinued from protocol-specified therapy(ies) for a protocol-specified

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reason, the investigator will discuss with the subject the appropriate procedures for withdrawal from protocol-specified therapy(ies) and must discuss with the subject the options for continuation of the Schedule of Assessments ([Appendix A](#)) and collection of data, including endpoints and adverse events. The investigator should document the change to the Schedule of Assessments ([Appendix A](#)) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, and from review of the medical records).

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Reasons for removal from protocol-specified product(s) or observation might include:

- partial withdrawal of consent
- withdrawal of full consent
- administrative decision by the investigator or Amgen
- subject missed the week 12 visit
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; (see [Appendix C](#)).
- ineligibility
- significant protocol deviation
- subject noncompliance
- adverse event – examples of adverse events where IP should be discontinued include:
 - malignancy (except basal cell or squamous cell carcinoma of the skin and cervical intraepithelial neoplasia)
 - tuberculosis
 - serious opportunistic infection
 - Crohn's disease
 - hepatotoxicity as detailed in [Section 6.4.3](#)
- ANC values as detailed in [Section 6.4.1](#)
- subject is not responding to IP ([Section 6.3](#))
- subject's treatment assignment is unblinded via IVRS for the future management of the subject
- other safety concern by the investigator or Amgen

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- suicidal ideation (severity of 4 or 5) or any suicidal behavior after randomization based on an assessment with the eC-SSRS
- severe depression after randomization, defined as a total score of ≥ 15 based on an assessment with the PHQ-8

8.2 Replacement of Subjects

Subjects who withdraw or are removed from the study will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event. The worsening of psoriasis, the disease under study, should only be reported as an adverse event if it is clinically significant worsening.

9.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization through the end of the subject's study participation are reported using the applicable eCRF (eg, Adverse Event Summary eCRF).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution,
- severity (and/or toxicity per protocol),
- assessment of relatedness to IP, and
- action taken

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The adverse event severity grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4. The severity grading scale used in this study is described in [Appendix B](#).

The investigator must assess whether the adverse event is possibly related to the IP. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the IP?

For serious adverse events, the investigator must assess whether the serious adverse event is possibly related to any study mandated procedure. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may be related to any study activity or procedure?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator’s judgment) should not be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) should be recorded as the adverse event.

The investigator’s clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject, or subject’s parent/legal guardian, may also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject should be encouraged to undergo, at a minimum, an end-of-study assessment.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

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An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event”. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury (see [Appendix B](#) for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention. **Suicidal behavior and suicidal ideation (severity 4 or 5) should be reported as serious adverse events.**

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 “life threatening” CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator’s judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the subject’s medical record.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of IP or the subject’s last study visit, whichever is later, are recorded in the subject’s medical record and are submitted to Amgen. The serious adverse event must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event.

If the electronic data capture system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator’s knowledge of the event. See [Appendix E](#) for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For electronic data capture studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the electronic data capture system when the system is again available.

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New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator should notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specific product [REDACTED]

[REDACTED]
[REDACTED] the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of event. Report pregnancy on the Pregnancy Notification Worksheet ([Appendix C](#)). As this reporting only occurs in the case of pregnancy, it is not included in the schedule of assessments.

If a lactation case occurs while the female subject is taking protocol-required therapies and for an additional [REDACTED] after the discontinuing ustekinumab or [REDACTED] after discontinuing brodalumab, report the lactation case to Amgen as specified below.

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Any lactation case should be reported to Amgen's global Lactation Surveillance Program within 24 hours of the investigator's knowledge of the event. Report a lactation case on the Lactation Notification Worksheet ([Appendix D](#)).

9.4 Major Adverse Cardiovascular Events

If a suspected major adverse cardiovascular event (defined as stroke, myocardial infarction, or cardiovascular death) occurs in a subject, the principal investigator may be requested to provide additional information (eg, onset and duration of symptoms) to the Cardiovascular Events Committee for adjudication. As this reporting only occurs in cases where additional information is needed, it is not included in the schedule of assessments.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 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
 - 210 mg Q2W
 - 140 mg Q2W for subjects ≤ 100 kg and 210 mg Q2W for subjects > 100 kg

Key Secondary: brodalumab arms vs placebo

- PASI 100 at week 12
- sPGA of 0 at week 12
- Psoriasis Symptom Inventory responder definition (total score ≤ 8, with no item score > 1) 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 and 210 mg Q2W for subjects > 100 kg
- **Maintenance (after rerandomization at week 12)**
- sPGA success at week 52

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Other Secondary

- time to sPGA success in the initial 12-week phase
- time to PASI response (PASI 75, 90, and 100) in the initial 12-week phase
- sPGA of 0 at week 12
- PASI 100 at week 52
- PASI 75 at week 52
- sPGA success at week 52 in subjects who had sPGA success at week 12
- sPGA success at measured timepoints
- sPGA of 0 (clear) at measured timepoints
- PASI 75 and 100 at other measured timepoints
- PASI 50 and 90 at measured timepoints
- % PASI improvement at measured timepoints
- absolute PASI score at measured timepoints
- involved BSA at measured timepoints
- NAPSI at measured timepoints
- patient-reported outcomes at measured timepoints
- Psoriasis Symptom Inventory
 - DLQI
 - WLQ
- pharmacokinetic endpoints

Safety

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

Exploratory

- brodalumab population pharmacokinetic models
- brodalumab population exposure/response relationships
- C-reactive protein
- within-subject difference in PASI improvement 4 weeks before and 4 weeks after self-administration in subjects rerandomized to and staying on the same dosage of brodalumab
- subject incidence of injection site reactions during the 24 weeks before and the 24 weeks after self-administration in subjects rerandomized to and staying on the same dosage of brodalumab
- effects of genetic variation in disease genes and drug target genes on psoriasis and/or subject response to brodalumab

10.1.2 Analysis Data Sets

10.1.2.1 Full Analysis Set

The full analysis set will be used to carry out the primary analysis of the study. The full analysis set will consist of all randomized subjects at the initial randomization. Subjects will be analyzed according to their initial randomized treatment group. Analyses for demographics, baseline characteristics, efficacy, and PRO endpoints will utilize this analysis set.

10.1.2.2 Efficacy Analysis Set

10.1.2.2.1 Induction Phase

The efficacy evaluable subset for the 12-week double-blind induction phase is the full analysis set, which includes all randomized subjects regardless of receipt of investigational product. Subjects will be analyzed according to their initial randomized treatment group.

10.1.2.2.2 Maintenance Phase (Rerandomized Subjects)

The efficacy evaluable subset for the maintenance phase for rerandomized subjects includes only those subjects who are rerandomized at week 12. Subjects will be analyzed according to the rerandomized treatment group. Analyses for demographics, disease characteristics, and maintenance phase efficacy and PRO endpoints for rerandomized subjects will utilize this analysis set.

10.1.2.2.3 Maintenance Phase (Comparisons with Ustekinumab)

The efficacy evaluable subset for the maintenance phase for comparisons between the rerandomized brodalumab treatment arms and ustekinumab includes subjects rerandomized to brodalumab at 210 mg Q2W or 140 mg Q2W at week 12 plus subjects in the full analysis set initially randomized to ustekinumab who have assessments at or after week 12. Subjects will be analyzed according to the rerandomized treatment for the rerandomized subjects and the initial randomized treatment for the ustekinumab subjects.

10.1.2.2.4 Maintenance Phase (Subjects Initially Randomized to Placebo)

The efficacy evaluable subset for the maintenance phase for subjects who were initially randomized at baseline to placebo includes subjects in the full analysis set who have assessments at or after week 12. Subjects will be analyzed according to the initial randomized treatment. Summaries of efficacy and PRO endpoints for the maintenance phase will utilize this analysis set.

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10.1.2.2.5 Rescue Treatment Following Inadequate sPGA Response Before Week 52

The efficacy evaluable subset for subjects with an inadequate sPGA response before week 52 includes all subjects who receive at least 1 dose of rescue treatment following inadequate sPGA response before week 52. Subjects will be analyzed according to the rescue treatment received, in addition to their rerandomized treatment group (for rerandomized subjects) or initial randomized treatment (for non-rerandomized subjects).

10.1.2.2.6 Long-Term Extension (After Week 52)

The efficacy evaluable subset after week 52 includes all subjects who have assessments after week 52.

10.1.2.3 Safety Analysis Set

The safety analysis set will consist of all randomized subjects who received at least 1 dose of IP. Subjects will be analyzed according to the treatment group as randomized. Safety data will be further investigated and sensitivity analysis may be performed by group as treated, if the randomized treatment differs from actual treatment.

10.1.2.3.1 Induction Phase

The safety evaluable subset for the 12-week double-blind induction phase consists of all randomized subjects (at the initial randomization) who receive at least one dose of investigational product. Subjects will be analyzed according to the initial treatment group as randomized. As supportive analysis, safety tables may be provided as treated.

10.1.2.3.2 Maintenance Phase (Rerandomized Subjects)

The safety evaluable subset for the maintenance phase for rerandomized subjects includes only those subjects who are rerandomized at week 12 who receive at least 1 dose of investigational product following rerandomization. Subjects will be analyzed according to the rerandomized treatment group. As supportive analysis, safety tables may be provided as treated.

10.1.2.3.3 Maintenance Phase (Non-Rerandomized Subjects)

The safety evaluable subset for the maintenance phase for subjects who were initially randomized at baseline to the placebo or ustekinumab treatment arms includes all subjects in these arms who receive at least one dose of investigational product during the maintenance phase at or after week 12. Subjects will be analyzed according to the initial randomized treatment. As supportive analysis, safety tables may be provided as treated.

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10.1.2.3.4 Rescue Treatment Following Inadequate sPGA Response Before Week 52

The safety evaluable subset for subjects with an inadequate sPGA response before week 52 includes all subjects who receive at least one dose of rescue treatment following inadequate sPGA response before week 52. To accurately reflect the safety experience of subjects who receive rescue treatment following inadequate sPGA response, all events reported during this phase will be summarized separately from the events reported during the maintenance phase. Subjects will be analyzed according to the rescue treatment received, in addition to their rerandomized treatment group (for rerandomized subjects) or initial randomized treatment (for non-rerandomized subjects). As supportive analysis, safety tables may be provided as treated.

10.1.2.3.5 Through Week 52

The safety evaluable subset for safety analyses through week 52 consists of all subjects who receive at least one dose of investigational product during this period. Subjects will be analyzed according to the initial treatment group as randomized. As supportive analysis, safety tables may also be provided as treated.

10.1.2.3.6 Long-Term Extension (After Week 52)

The safety evaluable subset for long-term safety analyses after week 52 includes all randomized subjects who receive at least one dose of investigational product after week 52.

10.1.2.4 Per Protocol Analysis Set

10.1.2.4.1 Week 12 Per Protocol Set

For the analysis of the week 12 endpoints, the per protocol analysis set will include all randomized subjects who complete the initial 12 week treatment and who did not significantly deviate from the protocol through the 12-week induction phase.

10.1.2.4.2 Week 52 Per Protocol Set

For the analysis of the week 52 endpoints, the per protocol analysis set will include all rerandomized subjects who complete the treatment in the maintenance phase and did not significantly deviate from the protocol during the maintenance phase. Further details of the per protocol analysis set will be described in the statistical analysis plan. The per protocol analysis sets may be used to perform sensitivity analyses on the primary, key secondary, and maintenance phase endpoints.

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10.1.2.5 Systemic Agent Failure or Contraindication Analysis Set

The systemic agent failure or contraindication analysis set will consist of all subjects who failed to respond to, were intolerant to, or have a contraindication to at least 1 of the following therapies: methotrexate, cyclosporine, and PUVA.

10.1.2.6 Brodalumab Pharmacokinetic Analysis Set

[REDACTED]

10.1.2.7 Antibody Analysis Set

[REDACTED]

10.1.2.8 Biomarker Analysis Set

[REDACTED]

10.1.3 Covariates and Subgroups

Efficacy endpoints may have covariate analyses run to assess which covariates had influence on the endpoint. The possible covariates to be adjusted for are

- prior use of systemic or photo therapies (Yes, No)
- prior use of biologic psoriasis therapies (Yes, No)
- prior use of anti-tumor necrosis factor biologic (Yes, No)
- number of prior biologic psoriasis therapy failures
- number of prior systemic therapies
- baseline PASI score (used in the primary analysis)
- baseline BSA involvement
- geographic regions
- sex (male, female)
- age
- race/ethnicity
- baseline body mass index
- baseline total body weight
- disease duration

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Efficacy endpoints may be analyzed by subgroups of

- prior use of systemic or photo therapies (Yes, No)
- prior use of biologic psoriasis therapies (Yes, No)
- prior use of anti-tumor necrosis factor biologic (Yes, No)
- failure of prior biologic psoriasis therapies (Yes, No)
- baseline PASI score (\leq median, $>$ median)
- baseline BSA involvement (\leq median, $>$ median)
- baseline body mass index groups ($\leq 35 \text{ kg/m}^2$, $> 35 \text{ kg/m}^2$)
- baseline total body weight groups
- geographic regions
- sex (male, female)
- age (< 65 , ≥ 65)
- race/ethnicity
- concomitant topical steroid use (Yes, No)
- concomitant topical therapy use (Yes, No)
- psoriatic arthritis history (Yes, No)
- disease duration (\leq median, $>$ median)
- anti-brodalumab antibody status (presence, absence)
- prior failure of systemic agent or contraindication (Yes, No)

Key safety data may be examined by subgroups of

- age (< 65 , ≥ 65)
- sex (male, female)
- race/ethnicity
- prior use of systemic or photo therapies (Yes, No)
- prior use of biologic psoriasis therapies (Yes, No)
- prior use of any psoriasis therapy (Yes, No)
- concomitant topical steroid use (Yes, No)
- concomitant topical therapy use (Yes, No)
- baseline body mass index ($\leq 35 \text{ kg/m}^2$, $> 35 \text{ kg/m}^2$)
- baseline total body weight
- disease duration (\leq median, $>$ median)
- baseline disease severity (\leq median PASI, $>$ median PASI or sPGA 3, 4, 5)
- anti-brodalumab antibody status (presence, absence)
- prior failure of systemic agent or contraindication (Yes, No)

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10.2 Sample Size Considerations

This study will have two families of sets of null hypotheses (brodalumab vs placebo and brodalumab vs ustekinumab) concerning the primary and key secondary endpoints. The sample size of 1,800 is needed to provide at least 90% power to detect the difference in the PASI 75 comparisons of brodalumab (210 mg Q2W; and 140 mg Q2W for subjects ≤ 100 kg with 210 mg Q2W for subjects > 100 kg) vs ustekinumab within the ustekinumab family of primary and key secondary endpoints. In addition, the stated multiple testing procedure employed to test the two families of hypotheses will have an overall family-wise type-1 error rate maintained at 5%, and the sample size will provide marginal power of 90% or more for each pair of null and alternative hypotheses. The two families of null hypotheses will be tested in parallel at alpha = 0.01 (2-sided) and 0.04 (2-sided) for the brodalumab vs placebo and the brodalumab vs ustekinumab families, respectively. Within each family, null hypotheses will be tested sequentially in the pre-specified order, as stated in [Section 10.6.2](#).

The sample size is driven by the following assumptions regarding the endpoints based on study 20090062 and other cited evidence.

Family of Hypotheses Based on Comparisons with Placebo

For the co-primary endpoints, based on study 20090062 we assume a PASI 75 response rate of 82.5% for 210 mg Q2W brodalumab, 77% for 140 mg Q2W brodalumab, and 10% for placebo. For sPGA success, we assume a response rate of 77% for 210 mg Q2W brodalumab, 72% for 140 mg Q2W brodalumab, and 10% for placebo. For the key secondary endpoints, we assume a PASI 100 response rate of 62% for 210 mg Q2W brodalumab, 38% for 140 mg Q2W brodalumab, and 10% for placebo, and we further assume the same response rates for sPGA clear (0). For the key secondary endpoint of Psoriasis Symptom Inventory responder definition, we assume a response rate of 85% for both the 140 mg Q2W brodalumab and 210 mg Q2W brodalumab groups and 10% for placebo.

Family of Hypotheses Based on Comparisons with Ustekinumab

For the primary endpoints, based on study 20090062, we assume a PASI 100 response rate of 62% for 210 mg Q2W brodalumab and a weight-based PASI 100 response rate of 55% (60% for subjects ≤ 100 kg on 140 mg Q2W brodalumab and 46% for subjects > 100 kg on 210 mg Q2W brodalumab) for brodalumab. For ustekinumab (45 mg for subjects ≤ 100 kg and 90 mg for subjects > 100 kg), we assume a PASI 100 response rate of 16% (17% for subjects ≤ 100 kg and 15% for subjects > 100 kg). For the key

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secondary endpoints, based on study 20090062, we assume a PASI 100 response rate of 38% for 140 mg Q2W brodalumab, a PASI 75 response rate of 82.5% for 210 mg Q2W brodalumab, and a weight-based PASI 75 response rate of 82.5% (89% for subjects ≤100 kg on 140 mg Q2W brodalumab and 69% for subjects > 100 kg on 210 mg Q2W brodalumab) for brodalumab. For ustekinumab (45 mg for subjects ≤ 100 kg and 90 mg for subjects > 100 kg), we assume a PASI 100 response rate of 16% (17% for subjects ≤100 kg and 15% for subjects >100 kg) and a PASI 75 response rate of 72.5% (73.5% for subjects ≤ 100 kg and 70.5% for subjects > 100 kg) (Lebwohl et al, 2010; Leonardi et al, 2008; Papp et al, 2008).

The assumptions for the primary and key secondary endpoints are summarized in Table 5.

Table 5. Powering Assumptions

	Placebo	Ustekinumab	Brodalumab		
			140 mg ≤ 100kg,	210 mg	210 mg > 100kg
PASI 75	10%	72.5%	77%	82.5%	82.5%
sPGA success	10%	--	72%	77%	--
PASI 100	10%	16%	38%	62%	55%
sPGA clear (0)	10%	--	38%	62%	--
Psoriasis Symptom Inventory responder definition	10%	--	85%	85%	--

PASI = Psoriasis Area and Severity Index; sPGA = static physician's global assessment

Using a logistic regression model adjusted by total body weight group, with alpha = 0.01 (2-sided), the sample sizes of 600 subjects in the 210 mg Q2W brodalumab group, 600 subjects in the 140 mg Q2W brodalumab group, and 300 subjects in the placebo group, will provide more than 90% power to detect the difference in all the comparisons within the placebo family of co-primary and key secondary endpoints. Similarly, using a logistic regression model adjusted by total body weight group, with alpha = 0.04 (2-sided), a total of 600 subjects in the 210 mg Q2W brodalumab group, 600 subjects in the 140 mg Q2W brodalumab group, and 300 subjects in the ustekinumab group will provide more than 90% power to detect the difference in all the PASI 100 comparisons within the ustekinumab family of primary and key secondary

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endpoints. For the PASI 75 comparisons within the ustekinumab family of primary and key secondary endpoints, the sample size will provide power to detect a treatment difference of at least 90%.

For the maintenance phase, under a 15% annual dropout, we assume 1,152 subjects (of the total N = 1,200 initially randomized to either brodalumab arm at baseline) will be rerandomized at week 12. We further assume that the overall sPGA of 0 or 1 success rate at week 52 for the 210 mg Q2W brodalumab group is 70%, for the 140 mg Q2W brodalumab group is 55%, for the 140 mg Q4W brodalumab group is 40%, and for the 140 mg Q8W brodalumab group is 25%. Under these assumptions, the power to detect a difference between the proportion of responders between 210 mg Q2W vs 140 mg Q8W, 140 mg Q2W vs 140 mg Q8W, 210 Q2W vs 140 mg Q4W, 140 mg Q2W vs 140 mg Q4W, and 210 mg Q2W vs 140 mg Q2W treatment groups at week 52 will be more than 90%, at alpha = 0.05 (2-sided).

10.3 Study Oversight

10.3.1 Data Monitoring Committee

A Data Monitoring Committee will be convened to monitor the brodalumab phase 3 program; membership, meeting frequency, and other details will be defined in the Data Monitoring Committee charter. The Data Monitoring Committee is an independent, multidisciplinary group comprising medical and statistical representatives. The committee will review unblinded data at the scheduled Data Monitoring Committee meetings.

Additionally, safety monitoring will occur in an ongoing fashion by the Amgen global safety team.

10.3.2 Cardiovascular Events Committee

An independent Cardiovascular Events Committee will be used to adjudicate any major adverse cardiovascular events that may be reported ([Section 9.4](#)). Membership and logistics are defined per the Cardiovascular Events Committee charter.

10.4 Access to Individual Subject Treatment Assignments by Amgen or Designees

Unblinding of treatment assignment can occur at any time as needed for safety reasons ([Section 5.2](#)).

The original randomization and the second randomization for the maintenance phase will remain blinded to all subjects, investigators, and Amgen Clinical Study Team until the

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data through week 52 are finalized, at which time an unblinded analysis of all data through week 52, including the primary endpoint, will be performed.

The Data Monitoring Committee will review unblinded data at the scheduled Data Monitoring Committee meetings.

Staff associated with tracking and assaying and analyzing brodalumab pharmacokinetic samples may have access to the pharmacokinetic-related information only. Similarly, staff analyzing biopsies may have access to biomarker-related information only. Such staff will not be blinded to the treatment assignments in this study.

10.5 Interim Analysis and Early Stopping Guidelines

The primary analysis will occur after all subjects have completed their week 52 visit (or terminated from the study). This analysis will include induction phase co-primary endpoints that will include data through week 12, as well as maintenance endpoints that will include data through week 52. A statement of study objectives will be made based on this primary analysis.

The randomization of the 12-week induction phase and the randomization of the maintenance phase of the study will be unblinded when all continuing subjects reach week 52.

Subsequent interim analyses may be performed as deemed necessary.

The final analysis for the study will occur after all subjects have completed their week 266 visit (or early terminated from the study).

In addition to the analyses described above, after week 52, on an annual basis or until an administrative decision is made to close the study, summary tables of safety and efficacy will be produced for use in the annual report and to support publications, if warranted. Corresponding subject listings will be provided.

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

Baseline demographics and disease characteristics will be summarized descriptively.

The daily assessment of the Psoriasis Symptom Inventory will be analyzed as a weekly average.

Summary descriptive statistics by treatment group will be provided. For categorical endpoints, the descriptive statistics will contain the frequency and percentage. For

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continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum.

All statistical tests will be 2-sided. For comparisons in the placebo family of endpoints and ustekinumab family of endpoints, the significance level will be 0.01 and 0.04, respectively. Following rerandomization at week 12, the endpoints during the maintenance phase (sPGA success at week 52) will be tested at full alpha = 0.05.

Details of all statistical methods will be provided in the statistical analysis plan.

10.6.2 Efficacy Endpoints

The efficacy analysis through week 52 will be based on the randomized treatment assignment regardless of the actual treatment received during the study.

For analyses for the induction phase, total body weight at baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), and geographic region (US will be split into US-West, US-Midwest, US-Northeast, US-South; other countries will not be split) will be used as stratification factors. Geographic regions with an insufficient number of subjects to have complete randomization across all strata may be combined. Details will be provided in the statistical analysis plan. For analyses for the rerandomized groups in the maintenance phase, week 12 total body weight (≤ 100 kg, > 100 kg), week 12 sPGA response (sPGA = 0, sPGA ≥ 1), and treatment received in the 12-week induction phase will be used as stratification factors.

At week 12, dichotomous variables, including the proportion of subjects achieving success on the sPGA, the proportions of subjects achieving PASI 75 and PASI 100, and the proportion of subjects achieving the responder definition of Psoriasis Symptom Inventory, will be compared between the treatment arms using the Cochran-Mantel-Haenszel (CMH) test, adjusted by the relevant baseline stratification factors and baseline value group (\leq median, $>$ median; for sPGA-related endpoints, baseline sPGA = 3, 4, or 5). At week 52, the CMH test adjusting for relevant week 12 stratification factors and week 12 value group (\leq median, $>$ median for non sPGA-related endpoints) will be used.

Continuous variables, including % PASI improvement, will be compared between the treatment arms using a stratified analysis of covariance (ANCOVA) model with relevant baseline or week 12 values as covariates, or a stratified Wilcoxon rank sum test (van Elteren test), depending on the normality of the data. As a sensitivity analysis, a mixed-effects model with a random intercept will be applied to compare mean

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post-baseline % PASI improvement between the treatment groups through week 12. The mixed model will include treatment group, week, treatment-by-week interaction, and baseline covariates including the baseline PASI score as fixed effects.

To allow for an assessment of differences between the 140 mg Q2W and 210 mg Q2W brodalumab groups by body weight, a pre-specified analysis of primary efficacy endpoints (sPGA success and PASI 75 rates at week 12) by 10-kg increments (eg, 51 to \leq 60 kg, 61 to \leq 70 kg) will be conducted. If an “inflection point” at a specific weight threshold exists, the efficacy of brodalumab compared with ustekinumab will be evaluated based on the weight threshold. This analysis will also be performed in a pooled fashion for studies 20120102, 20120103, and 20120104.

For Psoriasis Symptom Inventory, an additional analysis will be performed based on Psoriasis Symptom Inventory total score of 0 (best possible score). This analysis will be performed at week 12 to compare treatment groups using a logistic regression model, adjusting for baseline Psoriasis Symptom Inventory total score and the relevant baseline stratification factors. Cumulative distribution curves for Psoriasis Symptom Inventory total score improvement from baseline at week 12 will be generated by treatment group.

For DLQI, the main analysis will be a mean change in total score from baseline at week 12 and additional analyses will include the proportion of subjects with at least 5-point improvement in total score, a total score of 0, and a total score of 0/1 at week 12. For WLQ, the main analysis will be a mean change from baseline at week 12 for each domain score. Descriptions of how each instrument is scored and details of additional analyses will be provided in the statistical analysis plan.

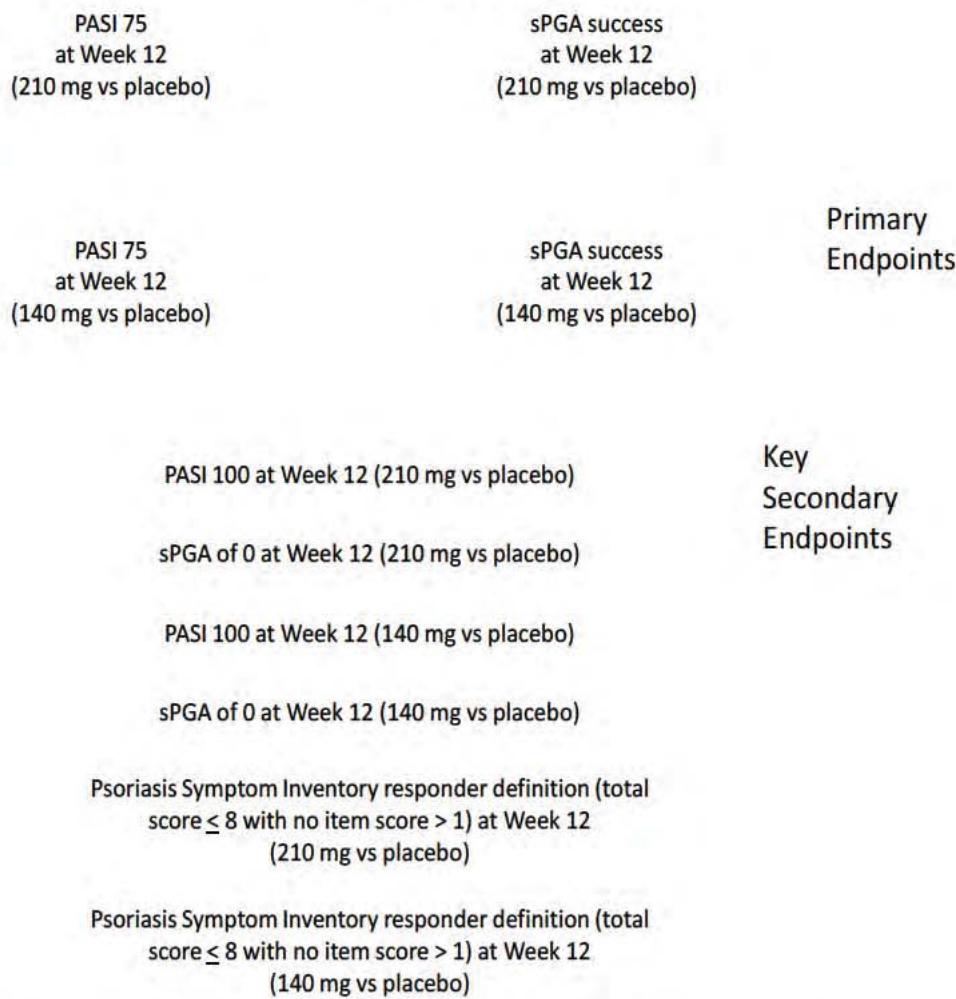
Time to event endpoints in the initial 12-week phase will be analyzed using a log-rank test with stratifications.

During the 12-week induction phase, to maintain the 2-sided family-wise type-1 error rate at 5%, a combination of parallel and sequential testing will be 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). Within the placebo and ustekinumab families, the primary endpoints will be tested first. If the null hypothesis for any of the primary endpoints within a family is not rejected, all the subsequent hypotheses for the key secondary endpoints at week 12 within that family will not be tested. However, if the null hypotheses for the primary endpoints within a

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family are rejected, then the hypotheses corresponding to the key secondary endpoints at week 12 within that family will be tested sequentially at alpha = 0.01 (2-sided) for the placebo family and alpha = 0.04 (2-sided) for the ustekinumab family. The sequential order of the endpoints in each family is shown in [Figure 3](#) and [Figure 4](#).

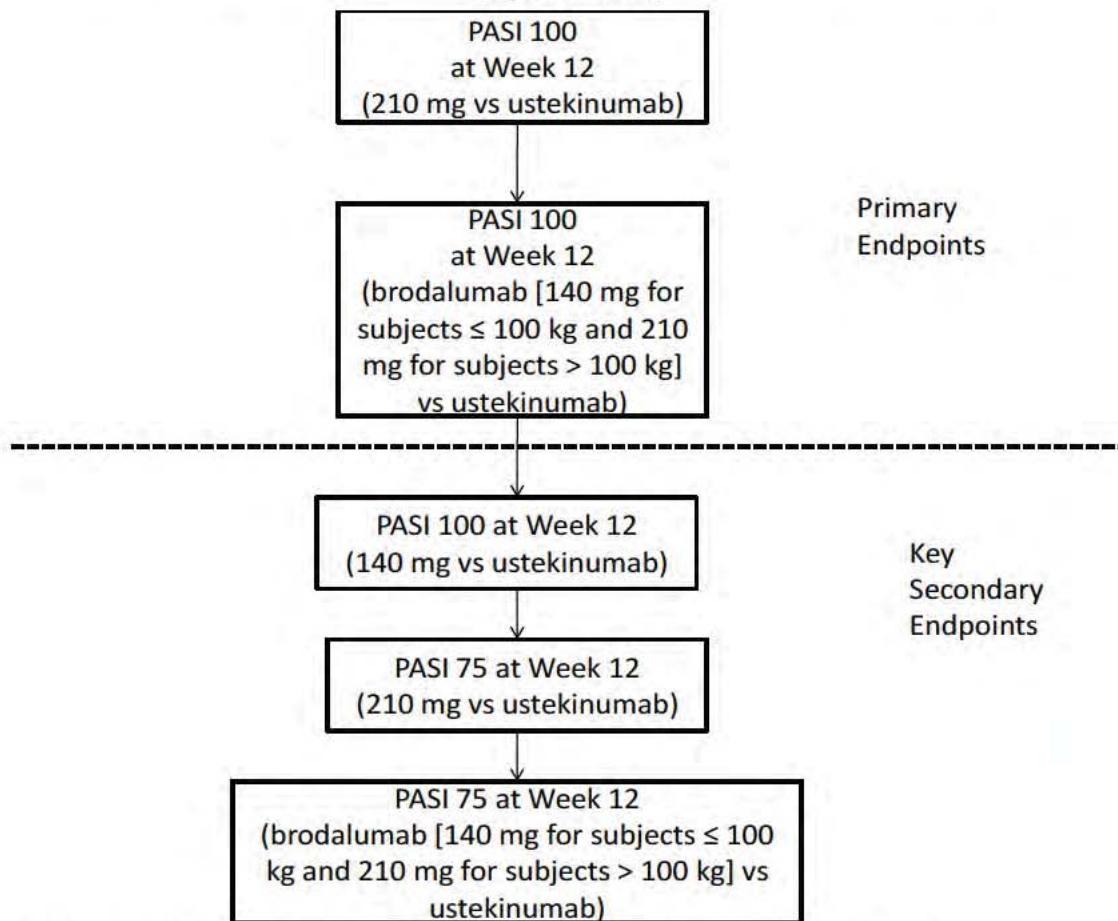
Figure 3. Family of Hypotheses Based on Comparisons With Placebo (alpha = 0.01)



PASI = Psoriasis Area and Severity Index; sPGA = static physician's global assessment

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**Figure 4. Family of Hypotheses Based on Comparisons With Ustekinumab
(alpha = 0.04)**



PASI = Psoriasis Area and Severity Index; sPGA = static physician's global assessment

After rerandomization, we consider testing of the maintenance endpoints for sPGA success at week 52 to be separate from the primary analysis testing of the primary and key secondary endpoints at week 12. Therefore, the maintenance endpoints for sPGA success at week 52 will be sequentially tested at full alpha = 0.05 level (2-sided), independent of prior testing results for the primary analysis at week 12 (Shih et al, 2003; Berger, 2004). The order of the sequential testing on the sPGA success at week 52 will be as follows:

- sPGA success at week 52 (210 mg Q2W vs 140 mg Q8W)
- sPGA success at week 52 (140 mg Q2W vs 140 mg Q8W)
- sPGA success at week 52 (210 mg Q2W vs 140 mg Q4W)
- sPGA success at week 52 (140 mg Q2W vs 140 mg Q4W)
- sPGA success at week 52 (210 mg Q2W vs 140 mg Q2W)

The p-values for the analyses of other secondary endpoints will be nominal without adjusting for multiplicity.

As a supportive secondary analysis, the effects of geographic region and geographic region by treatment interaction will be assessed for the primary endpoints. Additional details will be provided in the statistical analysis plan.

Through week 12, missing categorical variables will be imputed as non-responders for dichotomous endpoints and worst-cases for ordinal endpoints, and missing continuous variables will be imputed by a multiple imputation technique. The details for handling of missing data for patient reported outcomes, including the Psoriasis Symptom Inventory are specified in the statistical analysis plan.

Various imputation methods will be performed as sensitivity analyses, including as-observed analysis and last-observation-carried-forward.

After week 12, analyses for subjects receiving placebo during the induction phase and initiating 210 mg Q2W brodalumab during the maintenance phase will be as observed.

For the maintenance phase analyses of all other subjects after week 12 through week 52, the following will be done:

- For missing values, dichotomous variables will be imputed as non-responders, ordinal variables will be imputed with the worst case, and continuous variables will be imputed using last observation carried forward. Sensitivity analyses will be performed using as-observed analysis.
- For testing the maintenance endpoint (sPGA success at week 52), subjects who have an inadequate response at or before week 52 will be categorized as non-responders.
- To summarize all other endpoints for subjects rerandomized to 140 mg Q2W brodalumab, 140 mg Q4W brodalumab or 140 mg Q8W brodalumab at week 12, who have an inadequate response at or after week 16 (and before week 52) or subjects who were randomized to ustekinumab and qualified for rescue at week 16: Subjects will be categorized as non-responders for dichotomous variables for subsequent visits up to week 52. For continuous variables, the value at the visit at which an inadequate response is seen will be carried forward for subsequent visits up to week 52.
- To summarize all other endpoints for subjects rerandomized to 210 mg Q2W brodalumab at week 12 who have an inadequate response at or after week 16 (and before week 52) or subjects who were randomized to ustekinumab and qualified for rescue after week 16 (and before week 52): There will be no consequent categorization as non-responders for dichotomous variables for subsequent visits up to week 52, as no change in treatment will occur. For continuous variables, the value at the visit at which an inadequate response is seen will not consequently be carried forward for subsequent visits up to week 52, as no change in treatment will occur.

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- As a sensitivity analysis, to summarize all other endpoints: subjects who had an inadequate response at or after week 16 and before week 52 will be categorized as non-responders for dichotomous variables for subsequent visits up to week 52. For continuous variables, the value at the visit at which an inadequate response is seen will be carried forward for subsequent visits up to week 52.

After week 52, all data will be analyzed as observed.

A simulation study was conducted to ensure efficacy results are not driven by the method of handling missing data if there is differential pattern of dropout. Details of this analysis are provided in the statistical analysis plan. The reasons for dropout and patterns of missing data may be examined, and further analyses to account for informative dropouts may be used as sensitivity analyses. Efficacy analyses may be based on the week 12 rerandomized treatment assignment or the actual treatment received. Details of these analyses, including multiple imputation methodology, will be provided in the statistical analysis plan.

10.6.3 Safety Endpoints

The Medical Dictionary for Regulatory Activities will be used to code all adverse events to a system organ class and a preferred term. During the first 52 weeks of the study, all safety data will be summarized using subject incidence and exposure-adjusted event rates. After week 52, exposure-adjusted event rates will be summarized by brodalumab treatment exposure and treatment received at the time of event. All statistical methods for analyses after week 52 will be pre-specified prior to the week 52 primary analysis in a supplemental statistical analysis plan.

The subject incidence and exposure-adjusted event rates of adverse events will be summarized for all treatment emergent, grade 2 and above, serious, treatment related, serious treatment related, those leading to withdrawal of investigational product, those leading to study discontinuation, fatal, and of special interest. Subject incidence of adverse events of interest will also be summarized according to their categories. The events of interest search list is a living document and will be updated in response to the emerging safety profile of brodalumab.

Subject incidence of all treatment emergent, grade 2 and above, serious, treatment related, serious treatment related, those leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

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Summaries of treatment emergent and treatment-related treatment-emergent adverse events occurring in at least 1% of the subjects in any treatment arm, serious, and serious treatment-related adverse events will be provided by preferred term in descending order of frequency.

Key safety data including all adverse events, serious adverse events, serious infectious events, all investigational product related adverse events, and investigational product related serious adverse events may be examined by the subgroups listed in [Section 10.1.3](#).

10.6.4 Additional Analyses

Shift tables of the worst on-study laboratory toxicity based on CTCAE relative to baseline will be tabulated by treatment group. Subject listings of grade 2 and above laboratory toxicities will be provided. Vital signs will be summarized by study week and treatment group. The presence or absence of antibodies to brodalumab will be tabulated.

Descriptive summaries of the primary efficacy endpoint, key secondary efficacy endpoints, or safety endpoints may be provided by covariates specified in [Section 10.1.3](#), as deemed necessary.

Induction and maintenance endpoints will also be evaluated in a pooled fashion across identical studies 20120103 and 20120104. Analyses of relevant subpopulations (eg, TNF failures) will be performed in a pooled fashion across studies 20120102, 20120103, and 20120104.

Rebound, defined as $\geq 125\%$ of baseline PASI score at any measurement between weeks 12 and 24 (only in subjects randomized to a lower dose or frequency into the maintenance phase), will be summarized if present ([Gordon et al, 2002](#)).

For population pharmacokinetic models and exposure/response modeling, data from this study will be used; additional analyses may be performed, if feasible, with these data combined with data from other studies (phase 1 through 3).

The number of subjects who are randomized, rerandomized, receive study drug, and complete the study will be provided.

Additional analyses are planned to evaluate efficacy, adverse events, and anti-brodalumab antibodies in subjects who switch from Amgen IP (TO) to Amgen IP (RI). Analyses will be conducted between subjects who receive Amgen IP (RI) and those who remain on Amgen IP (TO); and within subjects who receive Amgen IP (RI)

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during the period prior to and after the switch from Amgen IP (TO). For the efficacy analyses, sPGA, PASI, and BSA involvement will be evaluated, and descriptive summaries of these measures will be provided. For the safety analyses, subject incidence will be analyzed for adverse events, and the presence or absence of antibodies will be tabulated. Details of the analyses related to the Amgen IP (RI) will be provided in the statistical analysis plan.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IPs are administered.

The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject.

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of IP.

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The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

Term	Percentage (%)
Global warming	98
Green energy	95
Sustainable development	92
Clean water	90
Renewable energy	88
Carbon footprint	85
Recycling	82
Biodiversity	80
Organic food	78
Eco-friendly	75
Green technology	72
Climate change	68
Energy efficiency	65
Waste reduction	62
Green building	58
Green products	55
Green infrastructure	52
Green economy	48
Green space	45
Green transportation	42
Green architecture	38
Green design	35
Green products	32
Green infrastructure	28
Green economy	25
Green space	22
Green transportation	18
Green architecture	15
Green design	12
Green products	8
Green infrastructure	5
Green economy	2
Green space	1
Green transportation	0

11.4 Pharmacogenetics Confidentiality (For Subjects who Consent to the Pharmacogenetic Substudy Only)

A series of five horizontal black bars of varying lengths, decreasing from left to right. The first bar is the longest, followed by a slightly shorter one, then a very short one, then another slightly longer one, and finally the shortest bar on the far right.

physician, or other third parties, except as specified in the informed consent.

11.5 Investigator Signatory Obligations

A horizontal bar chart with five categories on the y-axis: "All Americans", "Blacks", "Latinos", "Asian Americans", and "Middle Eastern Americans". The x-axis represents a percentage scale from 0% to 100%. Each category has a corresponding horizontal bar that is completely blacked out, indicating no visible data.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Term	Percentage (%)
Climate change	100
Global warming	98
Green energy	95
Sustainable development	92
Environmental protection	88
Green economy	85

12.2 Study Documentation and Archive

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Term	Percentage (%)
Green energy	95
Carbon footprint	92
Sustainable development	90
Renewable energy	88
Eco-friendly	85
Green economy	50
Climate change	78
Green technology	75
Organic food	72
Green building	68
Green products	65
Green infrastructure	62
Green transportation	58
Green jobs	55
Green investment	52
Green economy	50

12.3 Study Monitoring and Data Collection

The Amgen representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

A horizontal row containing five solid black rectangular bars. The bars are positioned at different horizontal levels. From left to right: the first bar is narrow; the second is wide; the third is very narrow; the fourth is wide; and the fifth is very narrow.

12.4 Language

Electronic CRFs must be completed in English.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

12.5 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the [Uniform Requirement for Manuscripts Submitted to Biomedical Journals](#) (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.6 Compensation



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14. APPENDICES

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Appendix A. Schedule of Assessments
Screening through week 52

Study Visit-Week	Scr	BL	1	2	4	6	8	10	12	13	14	16	17	18	20	22	24	26	28	32	36	40	44	48	52
Informed consent	X																								
Patient-reported outcomes																									
Distribute eDiary	X																								
Retrieve eDiary																									
Psoriasis Symptom Inventory																									
DLQI		X																							
WLQ		X																							
General and safety assessments																									
Medical / Medication history	X																								
Physical examination (includes weight)	X ^a	X ^b																							
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events / Con medis	X ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X																								
Photography ^d	X		X																						
eC-SSRS																									
PHQ-8																									
Disease assessments																									
PASI / BSA / SPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPSI		X																							

Footnotes are defined on next page

Scr = screening; BL = baseline; PASI = Psoriasis Area and Severity Index; BSA = involved body surface area; sPGA = static physician's global assessment;
NAPSI = nail psoriasis severity index; DLQI = Dermatology life quality index; WLQ = Work Limitations Questionnaire

a Includes height.

b Includes waist circumference.

c Report serious adverse events that occur after signing informed consent form. Non-serious adverse events are reported as medical history prior to randomization.
d For consenting subjects only.

Screening through week 52, cont.

Study Visit-Week	Scr	BL	1	2	4	6	8	10	12	13	14	16	17	18	20	22	24	26	28	32	36	40	44	48	52
Laboratory assessments																									
PPD or Quantiferon	X																								
Chest Xray/TB worksheet	X ^e																								
Serum pregnancy test ^f	X																								
Follicle-stimulating hormone ^g	X																								
Urine pregnancy test ^f	X																								
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry / Urinalysis	X	X																							
C-reactive protein	X																								
Anti-brodalumab antibodies	X																								
Brodalumab pharmacokinetic sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biomarker blood sample ^{d,g}	X	X																							
Biomarker lesional biopsy samples ^d	X	X	X																						
Biomarker non-lesional biopsy samples ^d	X																								
Investigational Product																									
Amgen IP admin ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Non-Amgen IP admin ⁱ	X																								
Amgen IP dispense ⁱ																									

Footnotes are defined on next page

Scr = screening; BL = baseline; PPD = purified protein derivative (tuberculosis test); TB = tuberculosis.

^d For consenting subjects only.

^e Only for subjects with a positive tuberculosis test (ie, positive PPD or positive or indeterminate Quantiferon).

^f If applicable.

^g For subjects who also consent to pharmacogenetic studies, DNA extracted from the biomarker blood samples will be used.

^h The first self-administered dose must be administered in the office by the subject or the designated person to demonstrate competence.

ⁱ Subjects who do not attend their week 12 visit will not receive any further IP.

		Week 53 through end of study																								
Study Visit-Week		53	54	56	58	60	62	64	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264 / early term	266 Safety Follow-up
Subject-completed assessments																										
Psoriasis Symptom Inventory																										
DLQI																										
WLQ																										
General and safety assessments																										
Physical examination (includes weight)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^b	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^b	
Adverse events / Con meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^k	
Electrocardiogram																										X
eC-SSRS		X	X	X	X	X	X	X																		X
PHQ-8		X	X	X	X	X	X	X																		X
Disease assessments																										
PASI / BSA / sPGA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NAPSI																										X
Laboratory assessments																										X
Urine pregnancy test ^f																										X
Hematol / Chem / Urinal		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein																										X
Anti-brodalumab antibodies																										X
Brodalumab pharmacokinetic sample																										X
Investigational Product																										X
Amgen IP admin		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Amgen IP dispense																										X

Scr = screening; BL = baseline; DLQI = Dermatology Life Quality Index; WLQ = Work Limitations Questionnaire; PASI = Psoriasis Area and Severity Index; sPGA = static physician's global assessment; NAPSI = nail psoriasis severity index; SF_i = Hematology; chem = chemistry.

^b Includes waist circumference.
^f If applicable, includes dispensing kits for self-testing between study visits.

^j Early termination only, only for those subjects who terminate the study before week 52.
^k May be conducted by telephone.

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

The adverse event grading scale used will be the CTCAE version 4.0. As of the protocol date, the CTCAE is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

General United States Food and Drug Administration Guidance on Hepatotoxicity Stopping and Rechallenge Rules

As noted in [Section 6.4.3](#), a United States Food and Drug Administration Guidance exists for drug-induced liver injury. This guidance is general for all investigational and marketed products and is synopsized here as a reference. It provides criteria for reporting and withholding IP in the event that a subject develops signs or symptoms of hepatotoxicity during a clinical trial.

Criteria for Permanent Withholding of IP(s) due to Potential Hepatotoxicity

IP(s) should be discontinued permanently and the subject should be followed for possible drug-induced liver injury, if ALL of the criteria below are met:

- total bilirubin > 2x the upper limit of normal (ULN) or international normalized ratio (INR) > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- AND no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or total bilirubin values include, but are not limited to:
 - Obstructive gall bladder or bile duct disease
 - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
 - Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
 - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
 - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements

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- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
- Autoimmune hepatitis
- Nonalcoholic steatohepatitis or other "fatty liver disease"

It should be noted that some of the circumstances above may nevertheless warrant discontinuation of IP(s) ([Section 8](#)) without requiring assessment for drug-induced liver injury.

Criteria for Conditional Withholding of IP(s) due to Potential Hepatotoxicity

For subjects that do not meet the criteria for permanent withholding of IP outlined above and have no underlying liver disease and eligibility criteria requiring normal transaminases and total bilirubin at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of IP:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for \geq 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)

- OR: total bilirubin > 3x ULN at any time
- OR: alkaline phosphatase > 8x ULN at any time

IP(s) should be withheld pending investigation into alternative causes of drug-induced liver injury. If IP is withheld, the subject should be followed according to recommendations above for possible drug-induced liver injury. Rechallenge may be considered if an alternative cause is discovered and the laboratory abnormalities resolve to normal or baseline.

Criteria for Rechallenge of IP(s) after Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen.

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If signs or symptoms recur with rechallenge, then IP(s) should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation should never be rechallenged.

Reporting

To facilitate appropriate monitoring for signals of drug-induced liver injury, cases of concurrent AST/ALT and total bilirubin and/or INR elevation that require permanent withholding of IP require the following:

- The event should be reported to Amgen as a serious adverse event within 24 hours following the investigator's knowledge of the event (ie, before additional etiologic investigations have been concluded).
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities should be completed and sent to Amgen.

Other events of hepatotoxicity and potential drug-induced liver injury should be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.

Additional Clinical Assessments and Observation

All subjects in whom IP is withheld (either permanently or conditionally) due to potential drug-induced liver injury or who experience AST/ALT elevations > 3x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that should be performed during this period include:

Additional Clinical Assessments and Observation that are required:

- Repeat liver chemistries within 24 to 48 hours (ALT, AST, ALP, total and direct bilirubin and INR)
 - In cases of total bilirubin > 2x ULN or INR > 1.5 retesting should be performed every 24 hours until laboratory abnormalities improve.
 - In cases of AST/ALT much greater than 3x ULN and when total bilirubin is normal, repeat liver enzyme and serum bilirubin test two or three times weekly.
 - Testing frequency may decrease if the abnormalities stabilize or the IP has been discontinued AND the subject is asymptomatic
- Follow the subject and the laboratory tests (ALT, AST, total bilirubin, INR) until all laboratory abnormalities return to baseline or normal. The "close observation period" should continue for a minimum of 4 weeks after drug discontinuation.
- If liver tests (ALT or AST) are elevated for greater than 48 hours without a clear etiology, the following tests should be performed as appropriate to determine the etiology of the elevation of the liver tests.

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- Obtain CBC with differential to assess for eosinophilia.
- Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis.
- Obtain serum acetaminophen (paracetamol) levels.
- Obtain a more detailed history of:
 1. Symptoms and prior history of concurrent diseases.
 - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting, and fever.
 2. Exposure to environmental and/or industrial chemical agents.
 3. Prior and/or concurrent use of alcohol, recreational drugs, and special diets.
 4. Concomitant use of medication (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms.
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear.
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected.
- Initiate viral hepatitis evaluation (serologies for hepatitis A,B,C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of drug-induced liver injury including but not limited to: nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtain hepatology consult.
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and total bilirubin elevation that require permanent withholding of IP.

The potential drug-induced liver injury event and additional information such as medical history, concomitant medications, and laboratory results must be captured in corresponding CRFs.

