

Product:	Brodalumab
Protocol Number:	20120103
Protocol 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
Author(s):	[REDACTED]
Statistical Analysis Plan (SAP) Version Number: #.#	2.0
SAP Version Date: DD-MON-YYYY	07-OCT-2014
Signatures and dates required for all relevant staff. Signature confirms the SAP has been reviewed and is acceptable in its present form.	
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[REDACTED] [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

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STATISTICAL ANALYSIS PLAN

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

Protocol Number 20120103

Version: 2.0
Date: 07 October 2014
Authors: [REDACTED]

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Table of Abbreviations

Abbreviation	Definition
AE	Adverse event
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
ANCOVA	Analysis of Covariance
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
AUC	Area under the curve
BMI	Body Mass Index
BSA	Body Surface Area
CMH	Cochran-Mantel-Haenszel
CRP	C-Reactive Protein
CTCAE	Common Toxicity Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
eCRF	Electronic Case Report Form
eC-SSRS	Electronic Self Rated Version, Columbia-Suicide Severity Rating Scale
EOI	Event of Interest
EOS	End Of Study
ET	Early Termination
IP	Investigational Product
IPD	Important Protocol Deviation
IVRS	Interactive Voice Response System
Inadequate response	sPGA \geq 3 or persistent sPGA values of 2 over at least a 4-week period at or after week 16
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NAPSI	Nail Psoriasis Severity Index
NRI	Non-Responder Imputation
PASI	Psoriasis Area and Severity Index
PASI 50	A 50% or greater improvement from baseline in PASI score
PASI 75	A 75% or greater improvement from baseline in PASI score
PASI 90	A 90% or greater improvement from baseline in PASI score
PASI 100	A 100% improvement from baseline in PASI score
PHQ-8	Patient Health Questionnaire-8 depression scale

Abbreviation	Definition
PK	Pharmacokinetics
PKDM	Pharmacokinetics and Drug Metabolism
PRO	Patient Reported Outcome
Q2W	Every 2 weeks (in this study, this regimen includes an additional loading dose 1 week after initiation of brodalumab)
Q4W	Every four weeks
Q8W	Every eight weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SIE	Serious Infectious Episode
sPGA	Static Physician Global Assessment of Psoriasis
sPGA success	sPGA score of 0 or 1 (clear or almost clear)
WHODRUG	World Health Organization Drug dictionary
WLQ	Work Limitations Questionnaire

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **amendment** for brodalumab study 20120103 dated **26 March 2014**. The scope of this plan includes the primary, interim, and final analyses that are planned and will be executed by the Biostatistics department or designee unless otherwise specified eg, standard PK tables may be provided by PKDM.

2. Objectives

2.1 Primary

2.1.1 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

2.1.2 Primary Ustekinumab Family

Compared with ustekinumab:

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

2.2 Key Secondary

2.2.1 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

2.2.2 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

2.3 Maintenance

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

2.4 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

2.5 Safety

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

2.6 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
- [REDACTED]
- [REDACTED]
- 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)

3. Study Overview

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 Protocol Section 5.1.

At their week 12 visit, subjects who were originally randomized to either of the brodalumab arms will be rerandomized (Protocol Section 5.1) to 1 of 4 maintenance regimens. Subjects originally randomized to placebo will begin receiving 210 mg 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 Protocol Section 6.3.

The entire study will be up to 271 weeks (approximately 5 years; includes up to 30 days of 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 4](#) of this SAP.

3.2 Sample Size

This study will have 2 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 2 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 2 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 10.5.1](#).

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 (total score ≤ 8 with no item scores > 1), 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 \leq 100 kg and 15% for subjects $>$ 100 kg). For the key 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 \leq 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 \leq 100 kg and 90 mg for subjects $>$ 100 kg), we assume a PASI 100 response rate of 16% (17% for subjects \leq 100 kg and 15% for subjects $>$ 100 kg) and a PASI 75 response rate of 72.5% (73.5% for subjects \leq 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 below:

	Placebo	Ustekinumab	Brodalumab		
			140 mg	210 mg	140 mg \leq 100kg, 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%	--

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 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 mg 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).

4. 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 with 210 mg Q2W for subjects > 100 kg

Key Secondary: brodalumab vs placebo

- PASI 100 at week 12
- sPGA of 0 at week 12
- Psoriasis Symptom Inventory responder definition (total score ≤ 8, with no item scores > 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 with 210 mg Q2W for subjects > 100 kg

Maintenance (after rerandomization at week 12)

- sPGA success at week 52

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

5. Hypotheses and/or Estimation

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.

6. Definitions

6.1 Basic Definitions

Interactive Voice Response System (IVRS)

The IVRS system is used to:

- assign subjects to randomized treatment
- manage brodalumab, ustekinumab, and placebo drug supply at the site and track subject study termination data

Investigational Product (IP)

brodalumab, ustekinumab, or placebo

Rescue Treatment

Subjects qualify for rescue treatment at or after week 16 with an inadequate response (defined as the case of a single sPGA of ≥ 3 or persistent sPGA values of 2 over at least a 4-week period). Rescue treatment will be blinded until the study is unblinded.

At week 16, any subject in the study who has an inadequate response is eligible for rescue with 210 mg Q2W brodalumab, regardless of prior treatment arm. After week 16 through week 52, subjects on brodalumab who qualify for rescue will receive 210 mg Q2W brodalumab; subjects on ustekinumab will continue to receive ustekinumab.

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

Last Observation Carried Forward (LOCF) Imputation

A method of imputation where missing post-baseline efficacy data will be carried forward from the last non-missing post-baseline value for that endpoint

LOCF After Inadequate Response Imputation

A method of imputation where data after qualification for rescue treatment due to inadequate response will be carried forward from the last non-missing value for that endpoint taken at the same visit, and prior to or on the date of qualification for rescue treatment due to inadequate response. For subjects who qualify for rescue treatment due to inadequate response at study weeks 17/18, or 22, or 26, the DLQI assessment from week 16, or 20, or 24, respectively, will be carried forward through week 52. This imputation only applies to subjects not initially randomized to placebo, who have an inadequate response on or after week 16 and through week 52.

LOCF After Treatment Change Imputation

A method of imputation where data after a protocol-specified treatment change after qualifying for rescue will be carried forward from the last non-missing post-baseline value for that endpoint taken at the same planned visit, prior to or on the date of qualification for rescue that results in a planned treatment change. For subjects who qualify for a planned treatment change due to rescue at study weeks 17/18, or 22, or 26, the DLQI assessment from week 16, or 20, or 24, respectively, will be carried forward through week 52.

Multiple Imputation (MI)

A method of imputation where a set of values will be imputed for each missing observation of efficacy data instead of a single value, representing the uncertainty in the correct value to impute

Non-responder Imputation (NRI)

A method of imputation where missing dichotomous ("yes or no") efficacy data will be imputed as a non-responder

NRI After Inadequate Response Imputation

A method of imputation where dichotomous efficacy data after qualification for rescue will be imputed as non-responder. This imputation only applies to subjects not initially randomized to placebo, who have an inadequate response on or after week 16 and through week 52.

NRI After Treatment Change Imputation

A method of imputation where dichotomous efficacy data after a protocol-specified treatment change after qualifying for rescue will be imputed as

non-responder. This imputation does not apply to subjects initially randomized to placebo.

6.2 Study Points of Reference

Study Baseline

The last non-missing measurement for the endpoint of interest taken before the first dose of investigational product for the initial randomization (for Psoriasis Symptom Inventory, the weekly average of the 7 days prior to the first dose of investigational product will be the baseline value). In cases where baseline measurements are taken on the same day as IP and no times are reported, it will be assumed that these measurements are taken prior to IP being administered. For subjects who are randomized but not dosed after the initial randomization, the baseline of the study is defined as the last non-missing measurement prior to the initial randomization.

Maintenance Phase Baseline

The planned week 12 measurement for the endpoint of interest.

Rescue Phase Baseline (Through Week 52)

The measurement for the endpoint of interest taken at the same visit and prior to or on the date at which a subject qualifies for rescue through week 52.

The baseline only applies to subjects not initially randomized to placebo, who have an inadequate response on or after week 16 and through week 52.

Rescue Phase Baseline (After Week 52)

The measurement for the endpoint of interest taken at the same visit and prior to or on the date at which a subject qualifies for rescue after week 52. This baseline only applies to subjects who qualify for rescue treatment due to an inadequate response after week 52.

Study Day 1

The first day of investigational product administration or the date of initial randomization for subjects who do not receive any dose of investigational product in this study

Study Day

Study day is defined as the number of days from Study Day 1.

Before Study Day 1:

$$\text{Study Day} = (\text{Date of Interest} - \text{Date of Study Day 1})$$

After Study Day 1:

$$\text{Study Day} = (\text{Date of Interest} - \text{Date of Study Day 1}) + 1$$

Therefore, the day prior to study day 1 is -1

6.3 Study Dates

End of Study Date

The end of study date is the date recorded on the End of Study page of the electronic Case Report Form (eCRF) for an enrolled subject

Enrollment (Initial Randomization) Date

The date on which a subject is assigned to one of the induction phase randomized treatments through the IVRS

Rerandomization Date

The date on which a subject is assigned to one of the treatment groups in the maintenance phase through IVRS. This date only applies to those subjects who are rerandomized **into** the maintenance phase.

First Dose Date Following Initial Randomization

The date on which a subject is administered the first dose of investigational product during the study (following the initial randomization). This date is also referred to as Study Day 1, and it may or may not be the same as the initial randomization date.

First Dose Date Following Rerandomization

The date on which a subject is administered the first dose of investigational product following rerandomization

Informed Consent Date

The date on which the subject signs the informed consent

Last Dose Date

The date on which a subject is administered the last dose of investigational product

6.4 Study Time Intervals

Screening Period

The period during which subjects are evaluated for eligibility according to the inclusion/exclusion criteria specified in the protocol, after signing the informed consent form **and before enrollment date**

On-Study Period

The time from the enrollment date to the end of study date, inclusive

Induction Phase

This phase starts when a subject receives the first dose of investigational product through the completion of the week 12 sPGA assessment, or **Study Day 91, whichever comes first.** For subjects who are not dosed with investigational product following randomization, the phase starts when the subject is randomized into the study.

Maintenance Phase

During the maintenance phase, subjects initially randomized to 210 mg Q2W brodalumab or 140 mg Q2W brodalumab will be rerandomized at week 12 to one of four brodalumab maintenance regimens. For these subjects who are rerandomized at week 12, the maintenance phase starts when a subject receives the week 12 dose of investigational product following rerandomization. If a subject does not receive the week 12 dose of investigational product after rerandomization, this phase begins at the date of rerandomization.

All subjects initially randomized to placebo or ustekinumab will not be rerandomized; subjects initially randomized to placebo will initiate 210 mg Q2W brodalumab (at week 12) and subjects initially randomized to ustekinumab will continue receiving ustekinumab. For these subjects, the maintenance phase starts when a subject receives the week 12 dose of investigational product following the week 12 sPGA assessment. For non-rerandomized subjects who do not receive the week 12 dose of investigational product, the maintenance phase begins on the week 12 sPGA assessment date.

The maintenance phase continues until the week 52 dose date. If the subject does not have a week 52 dose, the maintenance phase will continue until the week 52 sPGA assessment, post-week 52 sPGA or vital signs assessment, post-week 52

dose, the date at which subject qualifies for rescue, or Study Day 371, whichever comes first. For analysis of subjects initially randomized to placebo and initiating brodalumab during the maintenance phase, subjects will not be able to qualify and enter the rescue phase, and the maintenance phase will continue until the week 52 dose date. If the subject does not have a week 52 dose date, the maintenance phase will continue until the week 52 sPGA assessment, post- week 52 sPGA or vital signs assessment, post-week 52 dose, or Study Day 371, whichever comes first.

Rescue Treatment Phase (through week 52)

The phase starts when a subject qualifies for rescue treatment and continues until the week 52 dose date. If the subject does not have a week 52 dose, the rescue phase will continue until the week 52 sPGA assessment, post-week 52 sPGA or vital signs assessment, post-week 52 dose, or Study Day 371, whichever comes first. The phase only applies to subjects not initially randomized to placebo, who have an inadequate response on or after week 16 and through week 52.

Long-term Extension (starting at week 52)

The phase starts when a subject receives the first dose of investigational product at week 52. For subjects who do not receive the investigational product at week 52, the long-term extension phase begins on the week 52 sPGA assessment date, post-week 52 sPGA or vital signs assessment, post-week 52 dose, or Study Day 371, whichever comes earliest.

The long-term extension phase will continue through the end of the study at week 266 or until the assessment at which the subject qualifies for rescue treatment after week 52 (for subjects who have not already qualified for rescue treatment through week 52), whichever occurs first.

After week 52, subjects who were receiving brodalumab up to week 52 will continue at their maintenance phase dosage (until rescue treatment is initiated) or rescue treatment dosage, as applicable. Subjects who were receiving ustekinumab up to week 52 will begin treatment with 210 mg Q2W brodalumab (first dose at week 52).



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Rescue Treatment Phase (after week 52)

The phase starts at the visit the subject qualifies for rescue treatment after week 52 through the end of the study. This phase only applies to those subjects who qualified for rescue treatment after their week 52 sPGA assessment.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study Visit

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study visit as follows. Note that the visit windows for statistical analysis are different from the targeted study windows defined in Section 18.0 of the ETO Business Requirements.

The actual visit date is allowed to fall within a specified interval of the target day; this is to prevent the presence of gaps between study visit weeks.

In general if more than 1 actual visit (including the unscheduled visits, ie, CPEVENT = 'UNSCHED') falls within the same defined window, the closest visit to the target day (ie, scheduled visit week $x 7 + 1$) will be considered for analysis. If 2 actual visit dates are at the same distance from the target day, the later visit will be considered for analysis. The visit windows will not include unscheduled laboratory assessments or laboratory assessments/vital sign data collected as part of investigation of drug-induced liver injury.

The rules above for selecting a visit from multiple ones within the same visit window are not applicable when one of the multiple visits in the same window is the visit at which a subject qualifies for rescue treatment. In this case, the visit at which the subject qualifies for rescue will be considered for analysis, even if there is another visit closer to the target day.

In addition, the rules above for selecting a visit from multiple ones within the same visit window are not applicable to retest values of lab data. If the lab measurement is a retest, the retest value (the last observation within the same visit window) will be chosen.

Adverse events will be attributed to a phase based on AE start date as follows:

Phase	Start Date	End Date
Induction	Study Day 1	Min(End of Induction phase, Start of Maintenance Phase – 1, EOS)
Maintenance	First IP date in Maintenance phase	Min(End of Maintenance phase, Start of Rescue Treatment phase – 1, Start of Long-Term Extension – 1, EOS)
Rescue Treatment (through week 52) ^a	First IP date in Rescue Treatment phase (through week 52)	Min(End of Rescue Treatment phase through week 52, Start of Long-Term Extension – 1, EOS)
Long-Term Extension (starting at week 52)	First IP date in Long-Term Extension	Min(Rescue Treatment phase after week 52 – 1, EOS)
Rescue Treatment (after week 52) ^b	First IP date in Rescue Treatment phase (after week 52)	EOS

^a Applies only to subjects receiving rescue treatment through week 52.

^b Applies only to subjects receiving rescue treatment after week 52.

Treatment emergent adverse events which occur on or after first dose of investigational product within a phase and prior to the beginning of the next phase will be attributed to that phase.

6.5 Study Disposition

Completing Induction Phase

Subjects are defined as completing the induction phase if they have a non-missing sPGA assessment at Study Day >78.

Completing Maintenance Phase

Subjects initially randomized to placebo are defined as completing the maintenance phase if they have a non-missing sPGA or vital signs assessment at Study Day >351.

All other subjects are defined as completing the maintenance phase if they have a non-missing sPGA or vital signs assessment at Study Day >351, without qualifying for rescue treatment through week 52.

Completing Rescue Treatment Phase (through week 52)

Subjects are defined as completing the rescue treatment phase (through week 52) if they qualify for rescue treatment through week 52 and they have a non-missing sPGA or vital signs assessment at Study Day >351.

Completing Study

Subjects are defined as completing study if they complete 264 weeks of study evaluations. This will be derived from the date on the eCRF end of study page.

Early Termination (ET) From Study

Subjects are defined as early terminators from the study if they do not complete the study. This will be derived from the date on the eCRF end of study page.

Enrolled

Individuals are considered enrolled if they have been assigned a randomization number. Enrolled individuals are referred to as “subjects”.

Exposed to Investigational Product

Subjects are defined as exposed if they receive at least 1 dose of investigational product

On-Study

Subjects are considered on-study when they have enrolled and have not had an end of study date

6.6 Arithmetic Calculations

Age at Enrollment Date

Number of whole years from a subject’s birth date to the enrollment date. For partial birth dates, age will be taken to be collected age provided on the demographics eCRF.

Body Mass Index (BMI)

The weight (kg) of the subject divided by square of the height (m)

Duration of Psoriasis

The number of years between the date of diagnosis (DXDT) and Study Day 1

If Month or Day of the DXDT is missing, follow the formula below to calculate the duration:

Observed portion	Missing portion	Formula to Calculate Duration
Year, Month, Day		(DAY 1 – DXDT + 1)/365.25
Year, Month	Day	[Year(DAY 1)-Year(DXDT)]+ [Month(DAY 1)-Month(DXDT)]/12 *if duration equals 0, add 1 month or 1/12 years (this is to avoid a disease duration of 0)
Year	Month, Day	[Year(DAY 1)-Year(DXDT)] *if duration equals 0, add 1 month or 1/12 years (this is to avoid a disease duration of 0)

Exposure-Adjusted Event Rate

The exposure-adjusted event rate is defined as the total number of events reported in a given time period of exposure divided by total patient-years of exposure in that period. This rate can be multiplied by a factor of 100 to give rate per 100 patient-years.

Patient Years on Drug

The number of days between the first dose date and the last dose date, inclusive, in a given time period divided by 365.25 summed over all subjects within a treatment group

Percent Change From Baseline

The change from baseline divided by baseline and multiplied by 100:

$$(\text{Post-baseline Value} - \text{Baseline Value}) / \text{Baseline Value} * 100$$

If the baseline value is 0, then the percent change from baseline is set to “missing” (or ‘.’).

Percent Improvement From Baseline

The improvement from baseline divided by baseline and multiplied by 100:

$$(\text{Baseline Value} - \text{Post-baseline Value}) / \text{Baseline Value} * 100$$

If the baseline value is 0, then the percent improvement from baseline is set to “missing” (or ‘.’).

Psoriasis Symptom Inventory Weekly Average

The weekly average is defined as the sum of the daily assessments from all entries from the previous 7 days divided by the number of assessments available. The PSI weekly average will only be calculated if there are at least 4 entries within

the last 7 days. If a subject has multiple PSI entries on a single day, only the latest record from that day will be chosen to use in the derivation of the weekly average. If all records from the same date occurred at the same time, the entry with the worst response (highest) will be used in the derivation of the weekly average.

Subject Incidence

The subject incidence for a given event in a given time period is defined as the number of subjects with at least 1 reported occurrence of the event divided by the number of subjects who entered that period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

6.7 Definitions of Study Endpoints

Body Surface Area (BSA) of Psoriasis Involvement

A measurement of psoriasis involvement, given as the assessor's assessment of the proportion of the subject's total body surface area involved with psoriasis

Dermatology Life Quality Index (DLQI)

A skin disease-specific instrument to evaluate health related quality of life ranging from 0 (best possible score) to 30 (worst possible score). The DLQI has been validated for use in patients with psoriasis.

A 5-point improvement from baseline at a specific visit will be defined as a clinically meaningful change ([Khilji et al, 2002](#)). Only subjects with a baseline DLQI total score of 5 or greater will be analyzed for a 5-point improvement from baseline.

DLQI score of 0 or 1 is defined as having no effect at all on a subject's life at a specific visit.

DLQI score of 0 is defined as a best possible score at a specific visit.

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 five subtypes of behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS was implemented after all subjects had been enrolled in the study and was limited to those who had not discontinued prior to implementation, so analyses of prospectively collected data will be evaluated based on a retrospective assessment of prior history of suicidal ideation or behavior.

Exposure Emergent Adverse Event

An exposure-emergent AE is defined as an event that occurs after the first active dose of investigational product (IP) or an event that is already present prior to the initiation of active IP but worsens in either intensity or frequency after the initiation of active IP and prior to the last active dose plus the planned dosing frequency.

Inadequate Response

A sPGA score of 3 (or higher), or persistent sPGA values of 2 over at least a 4-week period at or after week 16

Infectious Event

An event recorded on the Adverse Events eCRF that is coded to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class “Infections and Infestations.”

Injection Site Reaction

An event coded to the MedDRA high level term of “Injection Site Reactions”

Nail Psoriasis Severity Index (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 one target nail will be followed.

Psoriasis Area and Severity Index (PASI)

Assessment of psoriasis (score 0 to 72) based on severity of erythema, induration, and desquamation as well as area of involvement. **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.

PASI 50 Response

A 50% or greater improvement from baseline in PASI score

PASI 75 Response

A 75% or greater improvement from baseline in PASI score

PASI 90 Response

A 90% or greater improvement from baseline in PASI score

PASI 100 Response

A 100% improvement from baseline in PASI score

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 was implemented after all subjects had been enrolled in the study and was limited to those subjects who had not yet discontinued, so analyses will be based prospective collection of data without a baseline assessment.

Percentage of Work Productivity Lost Due to Work Absences

A ratio of total missed work hours to total usual work hours in a 2-week time frame. The 4-item WLQ Work Absence Module is used to attain this measure.

Psoriasis Symptom Inventory

A psoriasis-specific patient-reported outcome measure that has been developed based on literature review, in-depth physician interviews, and psoriasis patient focus groups and cognitive interviews. The Psoriasis Symptom Inventory assesses the severity of 8 psoriasis related symptoms and produces a total score. Subjects are 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 daily assessment of the Psoriasis Symptom Inventory will be analyzed as a weekly average. **Exploratory analyses on the Psoriasis Symptom Inventory may also be done on the daily assessment scores.**

Psoriasis Symptom Inventory Responder Definition

The Psoriasis Symptom Inventory responder definition is a total score ≤ 8 , with no item scores > 1 .

This definition of Psoriasis Symptom Inventory Total Score responder was established based on clinical interpretation of the response scales, the psychometric properties of the Psoriasis Symptom Inventory, and by evaluating sensitivity and specificity based on PASI, sPGA, and DLQI responses. [Appendix F](#) provides data in support of the responder definition.

The Psoriasis Symptom Inventory score of 0 and 50% or greater percent improvement in the Psoriasis Symptom Inventory score will also be evaluated. The Psoriasis Symptom Inventory score of 0 is the best possible score at a specific visit and indicates psoriasis symptoms rated by the subject as not at all severe.

Serious Adverse Event

An adverse event that is fatal, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent/significant disability, is a congenital anomaly/birth defect, or other medically important serious event

Static Physician's Global Assessment (sPGA)

Assessor's global assessment of the subject's psoriasis (scale: 0 [clear] to 5 [very severe]) based on severity of plaque elevation, scaling, and erythema

sPGA Success (Clear or Almost Clear) Status

A score of 0 (clear) or 1 (almost clear) on the sPGA assessment

Treatment Emergent Adverse Event

A treatment emergent AE is defined as an event that occurs after the initiation of the investigational product (IP) or an event that is already present prior to the initiation of the IP but worsens in either intensity or frequency after the initiation of the IP **and prior to the end of study date.**

Work Limitations Questionnaire (WLQ)

WLQ measures the impact of chronic health problems and treatment on work-related outcomes. The WLQ is a 25-item questionnaire that contains 4 domains: time management, physical demands, mental-interpersonal demands and output demands. The WLQ has a recall period of the past 2 weeks. WLQ also contains a 4-question Work Absence module to determine the percentage of productivity lost due to work absences.

Responses to the 25 items are combined into four work limitation scales. These capture the multi-dimensionality of job roles (most jobs involve numerous tasks). They also reflect an important characteristic of many health problems, which is that they may result in limitations in performing some activities but not others.

The WLQ's **Time Management scale** (Question 1) contains 5 items addressing difficulty performing a job's time and scheduling demands. The 6-item **Physical Demands scale** (Question 2) covers a person's ability to perform job tasks that involve bodily strength, movement, endurance, coordination and flexibility. The **Mental/Interpersonal Demands Scale** (Questions 3 and 4) has 9 items. Six items pertain to difficulty performing cognitive job tasks and/or tasks involving the processing of sensory information. Three items address a person's problems interacting with people on-the-job. The fourth scale is the **Output Demands scale** (Question 5). It contains 5 items concerning decrements in a person's ability to meet demands for quantity, quality, and timeliness of completed work.

Scale scores range from 0 (limited none of the time) to 100 (limited all of the time) and represent the reported amount of time in the prior 2 weeks respondents were limited on-the-job.

Work Limitations Questionnaire (WLQ) Productivity Loss Score

The WLQ Productivity Loss Score indicates the percentage decrement in work output due to health problems. It is computed using the 4 WLQ scale scores.

Work Limitations Questionnaire (WLQ) Work Absence Module

The WLQ Work Absence Module is a 4-question time loss module to determine the percentage of productivity lost due to work absences.

7. Analysis Subsets

7.1 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, regardless of receipt of investigational product. 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. The procedure to handle missing data for subjects who provide no data or follow-up information after randomization will be discussed in [Section 9.3](#) and [Appendix C](#).

7.2 Efficacy Analysis Set

7.2.1 Efficacy Analysis Set – Maintenance Phase

The maintenance phase efficacy analysis set includes both the efficacy evaluable subsets for maintenance phase (rerandomized subjects) and maintenance phase (non-rerandomized subjects).

7.2.2 Efficacy Analysis Set – 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, as well as a combination of the initial randomized treatment and the rerandomized treatment group. Analyses for demographics, disease characteristics, and maintenance phase efficacy and PRO endpoints for rerandomized subjects will utilize this analysis set. The procedure to handle missing data for subjects who provide no data or follow-up information after rerandomization will be discussed in [Section 9.3](#) and [Appendix C](#).

7.2.3 Efficacy Analysis Set – Maintenance Phase (Non-Rerandomized Subjects)

The efficacy evaluable subset for the maintenance phase for non-rerandomized subjects includes subjects in the full analysis set initially randomized at baseline to ustekinumab or placebo who have the planned week 12 assessment. Subjects will be analyzed according to a combination of the initial randomized treatment and planned treatment during the maintenance phase. Analyses for demographics, disease characteristics, and maintenance phase efficacy and PRO endpoints for non-rerandomized subjects will utilize this analysis set. After week 12, for the subjects initially randomized to placebo, all efficacy and PRO analyses for the maintenance phase will be as observed, and will be summarized descriptively. For subjects initially randomized to ustekinumab, the procedure to handle missing data for subjects who provide no data or follow-up information after week 12 will be discussed in [Section 9.3](#) and [Appendix C](#).

7.2.4 Efficacy Analysis Set – Rescue Treatment Phase Through Week 52

The efficacy evaluable subset for subjects with an inadequate response through week 52 includes all subjects (excluding subjects initially randomized to placebo) who qualify for rescue treatment due to inadequate response through week 52. Subjects will be analyzed according to a combination of the rescue treatment and treatment during the maintenance phase.

7.2.5 Efficacy Analysis Set – Rescue Treatment Phase Through Week 52 (Rerandomized Subjects)

This efficacy analysis set includes only rerandomized subjects who qualify for rescue treatment following inadequate response through week 52. Subjects will be analyzed according to a combination of the rescue treatment and treatment during the induction and maintenance phases.

7.2.6 Efficacy Analysis Set – Long-Term Extension

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

7.2.7 Efficacy Analysis Set – Rescue Treatment Phase After Week 52

The efficacy evaluable subset for subjects who require rescue treatment after week 52 includes all subjects who qualify for rescue treatment after week 52.

7.3 Safety Analysis Set

The safety analysis set for on study safety analyses will consist of all randomized subjects who received at least one dose of investigational product. 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.

7.3.1 Safety Analysis Set – Maintenance Phase

The maintenance phase safety analysis set includes both the safety evaluable subsets for maintenance phase (rerandomized subjects) and maintenance phase (non-rerandomized subjects).

7.3.2 Safety Analysis Set – 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 one dose of investigational product following rerandomization. Subjects will be analyzed according to the rerandomized treatment group, **as well as a combination of the initial randomized treatment and the rerandomized treatment group**. As supportive analysis, safety tables may be provided as treated.

7.3.3 Safety Analysis Set – 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 on or after week 12. Subjects will be analyzed according to a combination of the initial randomized treatment and treatment during the maintenance phase. As supportive analysis, safety tables may be provided as treated.

7.3.4 Safety Analysis Set – Rescue Treatment Phase Through Week 52

The safety evaluable subset for subjects with an inadequate response through week 52 includes all subjects (excluding subjects initially randomized to placebo) who receive at least one dose of rescue treatment following inadequate response through week 52. To accurately reflect the safety experience of subjects who receive rescue treatment following inadequate 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 a combination of the rescue treatment received and**

treatment during the maintenance phase. As supportive analysis, safety tables may be provided as treated.

7.3.5 Safety Analysis Set – Rescue Treatment Phase Through Week 52 (Rerandomized Subjects)

This safety analysis set includes only rerandomized subjects who qualify for rescue treatment due to inadequate response through week 52 and receive at least one dose of rescue treatment. Subjects will be analyzed according to a combination of the rescue treatment and treatment during the induction and maintenance phases.

7.3.6 Safety Analysis Set – Through Week 52

The safety evaluable subset for the safety analyses during the initial 52 weeks of study consists of all subjects who receive at least one dose of active investigational product. Subjects will be analyzed according to a collapsed treatment group defined by their planned sequence of treatments as defined below in section 10.6.1. As supportive analysis, safety tables may also be provided as treated.

7.3.7 Safety Analysis Set – Long-Term Extension

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 on or after week 52.

7.3.8 Safety Analysis Set – Rescue Treatment Phase After Week 52

The safety evaluable subset for subjects who require rescue treatment after week 52 includes all subjects who receive at least one dose of rescue treatment due to inadequate response after week 52.

7.3.9 Safety Analysis Set –Brodalumab Exposure

The safety evaluable subset for brodalumab exposure includes all subjects who receive at least one dose of brodalumab. Subjects will be analyzed according to a collapsed treatment group based on the proportion of doses after the subject's first active dose of investigational product that were of a particular dose as defined in section 10.6.1.

7.4 Per Protocol Analysis Sets

7.4.1 Week 12 Per Protocol Analysis Set

For the analysis of the week 12 endpoints, the per protocol analysis set will include all randomized subjects who receive all scheduled treatment doses as defined in the

protocol through week 10, and did not significantly deviate from the protocol through the 12-week induction phase. Subjects will be excluded from the week 12 per protocol analysis set for the following protocol deviations:

- Use of proscribed medication (as defined in section 6.6 of the protocol) in the induction phase.
- Missing any dose of active investigational product (Amgen or non-Amgen IP) through week 10.
- Received treatment other than that which the subject was randomized through week 10.
- Subject and/or investigator was inadvertently unblinded to subject's treatment during the induction phase.
- Subject did not meet minimum disease severity for inclusion in the study (sPGA < 3, BSA<10% or PASI < 12 at baseline).
- Subject does not have a valid sPGA assessment between Study Days 78-91.
- Subject had baseline or week 12 efficacy assessments performed by non-certified individual.

The week 12 per protocol analysis set may be used to perform sensitivity analyses on the primary, co-primary, and key secondary endpoints.

7.4.2 Week 12-52 Per Protocol Analysis Set

The week 12-52 per protocol analysis set will include all non-rescued subjects who did not significantly deviate from the protocol from the start of the maintenance phase through week 52, as well as subjects qualifying for rescue through week 52 who did not significantly deviate from the protocol prior to qualifying for rescue. Subjects will be excluded from the week 12-52 per protocol analysis set for the following protocol deviations:

- Use of proscribed medication (as defined in section 6.6 of the protocol) during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase prior to the week 52 sPGA assessment if the subject is not rescued through week 52.
- Missing more than 20% of active doses of Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.
- Missing more than 2 consecutive active doses of Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.

- Missing the last active dose of Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.
- Missing any active dose of non-Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.
- Received treatment other than that which the subject was randomized (or rerandomized) during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase prior to the week 52 sPGA assessment if the subject is not rescued through week 52.
- Subject and/or investigator was inadvertently unblinded to the subject's treatment during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase prior to the week 52 sPGA assessment if the subject is not rescued through week 52.
- Subject did not meet minimum disease severity for inclusion in the study (sPGA < 3, BSA<10% or PASI < 12 at baseline).
- Subject's sPGA was incorrectly entered during the maintenance phase such that it may impact the rescue treatment assigned to the subject prior to the subject's week 52 sPGA assessment.
- Subject was rescued early (not due to sPGA IVRS entry error)
- Subject with missing rescue sPGA assessment does not have a valid sPGA assessment between Study Day 351-371.

The week 12-52 per protocol analysis set may be used to perform sensitivity analyses on the maintenance phase endpoint sPGA success at week 52.

7.4.3 Week 52 Per Protocol Analysis Set

The per protocol analysis set for the first 52 weeks of the study will include all non-rescued subjects who did not significantly deviate from the protocol during the first 52 weeks of the study, as well as subjects qualifying for rescue who did not significantly deviate from the protocol prior to qualifying for rescue. Subjects will be excluded from the week 52 per protocol analysis set for the following protocol deviations:

- Use of proscribed medication (as defined in section 6.6 of the protocol) prior to experiencing inadequate response, or prior to the week 52 sPGA assessment if the subject is not rescued through week 52.
- Missing any dose of active investigational product (Amgen or non-Amgen IP) through week 10.
- Missing more than 20% of active doses of Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.

- Missing more than 2 consecutive active doses of Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.
- Missing the last active dose of Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.
- Missing any active dose of non-Amgen investigational product during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase if the subject is not rescued through week 52.
- Received treatment other than that which the subject was randomized (or re-randomized) during the maintenance phase prior to experiencing inadequate response, or during the maintenance phase prior to the week 52 sPGA assessment if the subject is not rescued through week 52.
- Subject and/or investigator was inadvertently unblinded to the subject's treatment prior to experiencing inadequate response, or prior to the week 52 sPGA assessment if the subject is not rescued through week 52.
- Subject did not meet minimum disease severity for inclusion in the study (sPGA < 3, BSA<10% or PASI < 12 at baseline)
- Subject's sPGA was incorrectly entered during the maintenance phase such that it may impact the rescue treatment assigned to the subject prior to the subject's week 52 sPGA assessment
- Subject was rescued early (not due to sPGA IVRS entry error)
- Subject with missing rescue sPGA assessment does not have a valid sPGA assessment between Study Day 351-371.
- Subject had baseline or week 12 efficacy assessments performed by non-certified individual.

The week 52 per protocol analysis set may be used to perform sensitivity analyses on the maintenance phase endpoint sPGA success at week 52.

7.5 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 one of the following therapies: methotrexate, cyclosporine, and PUVA.

7.6 Brodalumab Pharmacokinetic Analysis Set



7.7 Antibody Analysis Set



8. 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), **when the study is unblinded**. This analysis will include induction phase primary and key secondary endpoints that will include data through week 12, as well as maintenance **and rescue** phase endpoints that will include data through week 52. **In addition, safety and efficacy data after week 52 but prior to the cutoff may be summarized.**

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.

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. A Cardiovascular Events Committee will be used to **adjudicate** any major adverse cardiovascular events that may be reported, per the Cardiovascular Events Committee charter.

Additionally, safety monitoring will occur in an ongoing fashion by the Amgen Global Safety Team.

9. Data Screening and Acceptance

9.1 General Principles

Data screening will be performed periodically during the conduct of the study in a blinded fashion. The objective of periodic data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. Any questionable values or situations will be reported to Clinical Data Management for review or confirmation.

9.2 Data Handling and Electronic Transfer of Data

Clinical data from this study will be stored in an electronic data capture (EDC) system, RAVE. The database will be subjected to edit checks outlined in the Data Management Plan (DMP). All datasets to be used for planned analyses will be received from Amgen's

Clinical Data Management department. Details will be provided in the DMP and Data Transfer Plan (DTP).

9.3 Handling of Missing and Incomplete Data

Subjects may be missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing.

Through week 12, missing efficacy data will be imputed as described in [Section 9.3.3](#).

After week 12, analyses of subjects who were initially randomized to placebo will be “as observed” and missing efficacy data of all other subjects will be imputed as described in [Section 9.3.3](#).

After week 52, analyses for all subjects will be “as observed.”

9.3.1 Missing Dates

If the start date of an adverse event or medication is completely missing, it will be assumed that the event or medication started before enrollment. If the stop date and continuing flag for an on-study adverse event or medication are both completely missing, it will be assumed that the event or medication stopped after the end of study date.

	Missing	Imputation	Exception
Start date (AE, concomitant medication, phototherapy)	Day	01	Default to Study Day 1 if an event starts the same year and month as Study Day 1 (and end date is after first dose of IP or concomitant medication/AE is ongoing/not resolved)
	Day/Month	01JAN	Default to Study Day 1 if an event started the same year as Day1 (and end date is after first dose of IP or concomitant medication/AE is ongoing/not resolved)
Stop date (concomitant medication and phototherapy only)	Day	Last day of the month	Default to the End of Study Date if the concomitant medication stopped the same year and month as the End of Study Date. For ongoing subjects, default to the planned analysis cut-off date if the concomitant medication stopped the same year and month as the planned analysis cut-off date
	Day/Month	31DEC	Default to the End of Study Date if the concomitant medication stopped the same year as the End of Study Date. For ongoing subjects, default to the planned analysis cut-off date if the concomitant medication stopped the same year as the planned analysis cut-off date

Missing years will not be imputed under any conditions.

9.3.2 Missing Baseline Evaluation

Missing baseline evaluations will not be imputed.

9.3.3 Missing Post-baseline Efficacy and Safety Evaluations

A simulation study was conducted to examine the impact of various methods for missing data handling, based on data from the completed phase 2 psoriasis study (20090062).

The simulation study summary report is provided in [Appendix A](#).

For simplicity, we only simulated data for subjects randomized to 140 mg Q2WK brodalumab and placebo in the simulation analysis. The dropout rates were assumed to

be in the range of 0 (no missing) to 80% (extremely high) annual dropout. We defined various dropout reasons under each scenario to allow for differential dropout rates between treatment arms (ie, lack of efficacy and all other random dropouts). The analysis methods considered in the simulation were last observation carried forward (LOCF), multiple imputation, and a mixed effects model. We completed 1000 replicated simulation runs under each scenario. The performance of methods was evaluated by the Type-1 error rate and effect size estimate bias.

The simulation results showed that under the scenario where the dropout rates and reasons for dropout between the 140 mg Q2WK brodalumab and placebo arms were similar, the 3 methods performed similarly. However, as the imbalance in the dropout rates and reasons increased, LOCF performed the worst, compared with multiple imputation and the mixed effects model. As a conclusion, we plan to use multiple imputation as the primary analysis method for handling missing continuous data in the phase 3 studies **during induction phase**. Last observation carried forward will be provided as a sensitivity analysis.

In the multiple imputation method, all post-baseline missing values **during induction phase** for continuous efficacy endpoints will be imputed **separately** by the Markov Chain Monte Carlo (MCMC) method, resulting in 3 complete datasets **for each endpoint**. The imputations will be conducted **based on all visits, simultaneously**. The missing percent improvement of PASI score and BSA, **and** missing improvement of NAPSI score and Psoriasis Symptom Inventory total score **will be derived accordingly**. **The imputation model is stratified by induction treatment group.**

Other imputation methods are described below.

- The non-responder imputation (NRI) method will impute missing dichotomous endpoints to a value which represents non-response. For example, for sPGA clear or almost clear response (Yes, No), the NRI method will impute the missing data to “No”.
- For the last observation carried forward (LOCF) method, baseline values will not be carried forward. Only post-baseline values will be carried forward as imputed values for missing post-baseline data. As a result, there may be cases that a imputed value is still missing using the LOCF method, for example, if all the post-baseline visits prior to the current visit are missing, the value for the current visit will be left as missing.

Induction Phase:

For all analyses through week 12, missing categorical variables will be imputed as non-responders for dichotomous endpoints, and missing continuous variables will be imputed by a multiple imputation technique. Various sensitivity analyses will be performed, including as-observed analysis and LOCF.

Maintenance and Rescue Phases:

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 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 and continuous variables will be imputed using LOCF. Sensitivity analyses will be performed using as-observed analysis. **LOCF will also be used as a sensitivity analysis on key dichotomous variables.**
- For testing the maintenance phase endpoint (sPGA success at week 52), subjects who have an inadequate response through 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 through 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 **through** week 52), or subjects who were randomized to ustekinumab and qualified for rescue after week 16 (and **through** 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.
- As a sensitivity analysis, to summarize all other **key** endpoints: Subjects who had an inadequate response at or after week 16 (and **through** 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.

For analyses requiring imputation after qualifying for rescue, and imputation after qualifying for rescue with treatment change, all subsequent maintenance visits (through week 52) will be set to missing and imputed as described in the table.

Maintenance	Rescue	Primary Analysis for Maintenance Endpoint (sPGA success at week 52)	Sensitivity Analysis for Maintenance Endpoint (sPGA success at week 52)	Main Analysis for Other Endpoints during the Maintenance Phase	Sensitivity Analysis for Selected Key Endpoints during the Maintenance Phase
210 mg Q2W	210 mg Q2W	NRI Imputation at inadequate response	No imputation at inadequate response	No imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response
140 mg Q2W	210 mg Q2W	NRI Imputation at inadequate response	NRI Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response
140 mg Q4W	210 mg Q2W	NRI Imputation at inadequate response	NRI Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response
Maintenance	Rescue	Primary Analysis for Maintenance Endpoint (sPGA success at week 52)	Sensitivity Analysis for Maintenance Endpoint (sPGA success at week 52)	Main Analysis for Other Endpoints during the Maintenance Phase	Sensitivity Analysis for Selected Key Endpoints during the Maintenance Phase

Maintenance	Rescue	Primary Analysis for Maintenance Endpoint (sPGA success at week 52)	Sensitivity Analysis for Maintenance Endpoint (sPGA success at week 52)	Main Analysis for Other Endpoints during the Maintenance Phase	Sensitivity Analysis for Selected Key Endpoints during the Maintenance Phase
140 mg Q8W	210 mg Q2W	NRI Imputation at inadequate response	NRI Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response
ustekinumab	210 mg Q2W	NRI Imputation at inadequate response	NRI Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response
ustekinumab	ustekinumab	NRI Imputation at inadequate response	No imputation at inadequate response	No imputation at inadequate response	Dichotomous: NRI Imputation at inadequate response Continuous: LOCF Imputation at inadequate response

For the induction phase, multiple imputation will be performed on all continuous endpoints (except DLQI total score, which will be calculated based on DLQI subscale scores, and WLQ Productivity Loss Score, which will be calculated based on WLQ subscales) non-responder imputation will be performed on all binary endpoints and as observed will be done for all endpoints. The following summarizes the imputations that are planned for each endpoint:

Endpoint	Type of Endpoint	Imputation Method Besides as Observed and NRI
PASI (Total)	Continuous	MI, LOCF
PSI (Total Score)	Continuous	MI, LOCF (derived based on item scores)
PSI (Responder)	Binary	LOCF (derived based on item and total score)
DLQI (Subscales)	Continuous	MI (derive total score), LOCF (derive total score)
DLQI (Total Score)	Continuous	MI (derived based on subscale), LOCF (derived based on subscale)
BSA	Continuous	MI
NAPSI	Continuous	MI
WLQ (Subscales)	Continuous	MI (derive WLQ Productivity Loss Score)
WLQ (Productivity Loss Score)	Continuous	MI (derived based on subscale scores)
WLQ4Q (Percentage of Productivity Lost Due to Work Absences)	Continuous	MI
WLQ4Q (Total Days of Work-Time Missed)	Continuous	MI
WLQ4Q (Total Hours of Work-Time Missed)	Continuous	MI

After week 52, all data will be analyzed as observed. Post-week 52 analyses are summarized in [Section 10.5](#).

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.

Laboratory values beyond the detectable limits of the lab test will be imputed as follows:

Analyte	Detectable Limit	Imputed value
C-Reactive Protein	< 0.2	0.2
Total Bilirubin	< 3.42	3.42
Direct Bilirubin	< 1.71	1.71
Urine Red Blood Cell	> 150	150
Urine White Blood Cell	> 150	150
Potassium	> 7.3	7.3

Missing post-baseline safety endpoints will not be imputed.

9.3.4 Missing Components of Composite Endpoints

For multiple imputation-based and LOCF-based analyses, missing PASI components will not be imputed. Instead, the missing values of PASI total score will be imputed.

Missing PRO components will be handled according to the scoring algorithm (See [Appendix F](#)).

9.3.5 Missing Biomarkers

Missing data (either baseline or post-baseline values) will not be imputed.

9.4 Detection of Bias

This study has been designed to minimize potential bias by selecting subjects, allocating treatment groups, assessing endpoints, and handling withdrawals without knowledge of the treatment. Other factors that may bias the results of the study include:

- major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- blind breaking before database lock and formal unblinding
- investigational product dosing non-compliance
- the timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors will be assessed. Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be listed and/or tabulated in the clinical study report (CSR). If necessary, the incidence of other factors will be tabulated (if applicable, reason (eg, reason for withdrawal) will be included).

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed. Data from subjects whose treatment assignments are unblinded prior to formal unblinding will be listed. The timing and reason for unblinding will be included in these listings.

Tabulation of important protocol deviations regarding IP dosing non-compliance by treatment group will be provided.

The timing of and reasons for early withdrawal from treatment and from study will be listed.

Evaluation of suicidal ideation, behavior and symptoms of depression, as measured by the eC-SSRS and PHQ-8 may be limited due to the delayed implementation of these questionnaires to only post-baseline assessments.

This limits the ability to identify onset of new symptoms or to align potential events with treatment data. In addition, the lack of baseline data for these two questionnaires requires classification of prior history to be based on a retrospective assessment so will be considered exploratory and used for descriptive purposes.

9.5 Outliers

Outliers in the continuous variables used in the analyses will be identified by utilizing histograms. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before interim data snapshots and final database lock. The validity of any questionable values or outliers will be confirmed. No valid measurement will be purposely excluded from descriptive or inferential analyses. However, sensitivity analyses may be conducted to evaluate the influence of extreme values in the data. These analyses will be documented in the CSR.

9.6 Distributional Characteristics

Sensitivity analyses may be performed to check the robustness of the analysis.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System and S-plus.

10. Statistical Methods of Analysis

10.1 General Principles

Summary descriptive statistics by treatment group will be provided. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, maximum, and 95% confidence interval. For dichotomous endpoints, the descriptive statistics will contain the frequency and percentage.

All statistical tests will be 2-sided. For comparisons in the placebo family and ustekinumab family, the significance level will be 0.01 and 0.04, respectively.

Following rerandomization at week 12, the maintenance phase endpoint (sPGA success at week 52) will be tested at full alpha = 0.05.

10.2 Subject Accountability

The disposition for the 12-week double-blind induction phase will be summarized by the initial randomized treatment group. The summary will include the number of subjects who are randomized, who are dosed with investigational product, who complete the 12-week induction phase, who enter the maintenance phase, who are rerandomized at week 12 (if applicable), and who withdraw prematurely and their reasons for withdrawal.

The subject disposition for the maintenance phase will be summarized by the rerandomized treatment group at week 12 for the rerandomized subjects and the initial randomized treatment for subjects randomized to placebo or ustekinumab during the induction phase. The summary will include the number of subjects who enter the maintenance phase, who are rerandomized (if applicable), who have an inadequate response and begin receiving rescue treatment, and who withdraw prematurely and their reasons for withdrawal.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study, **and IPDs will be summarized in tables and listings.**

10.4 Demographic and Baseline Characteristics

For the induction phase, baseline demographics **and** disease characteristics will be summarized descriptively for the full analysis set by initial randomized treatment group.

For the maintenance phase, demographics and disease characteristics will be summarized descriptively for **all subjects entering the maintenance phase for the maintenance phase efficacy analysis** set by rerandomized treatment group for **all rerandomized subjects** and by a combination of induction and maintenance phase treatment group for **non-rerandomized subjects**. **For all rerandomized subjects**, demographics and disease characteristics will be summarized descriptively by a combination of induction phase and rerandomized treatment group.

Demographic and disease characteristics may be re-evaluated for the safety analysis set if it is materially different from the full analysis set or the maintenance phase efficacy analysis set.

10.5 Efficacy Analyses

The full analysis set, as defined earlier, will include all subjects randomized to IP at the initial randomization. Subjects will be analyzed according to their **initial randomized treatment group** regardless of the actual treatment received during the study. All the primary and secondary efficacy endpoints up to week 12 will be evaluated on the full analysis set. For subjects rerandomized at week 12, the efficacy endpoints after week 12 rerandomization will be evaluated on the maintenance phase (rerandomized subjects) efficacy analysis set. For subjects who were not rerandomized at week 12 (originally on placebo or ustekinumab), the efficacy endpoints after week 12 will be evaluated based on the **maintenance phase (non-rerandomized subjects) efficacy analysis set**.

For the induction phase, stratification factors at the initial randomization including baseline total body weight at baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), and geographic region, will be used in the analyses. Geographic region was defined at the initial randomization by country, with US split into **US-West**, **US-Midwest**, **US-Northeast**, **US-South**. States were assigned to regions within the US as follows:

Region	States
West	Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming
Midwest	Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin
Northeast	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Pennsylvania
South	Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington DC, West Virginia, Delaware

In order to ensure geographic regions have complete randomization across all strata, regions from the initial randomization will be collapsed as follows:

- Canada
- Eastern Europe
 - Hungary

- Latvia
- Poland
- Russia
- Western Europe
 - Australia
 - Belgium
 - France
 - Greece
 - Italy
- United States – Midwest
- United States – Northeast
- United States – South
- United States – West

During the course of the study, if a subject transfers sites to a geographic region different from where the initial randomization took place, all analyses by geographic region will be performed by the region at the initial randomization.

For the maintenance phase, stratification factors at the rerandomization including induction phase treatment group, week 12 total body weight group (≤ 100 kg, > 100 kg), and week 12 sPGA response (0, ≥ 1), will be used in the analyses.

Analyses of endpoints through week 12:

The comparisons of dichotomous efficacy and PRO endpoints between treatment arms, including the proportion of subjects achieving success on the sPGA, PASI 75, and PASI 100, and the proportion of subjects achieving the responder definition of Psoriasis Symptom Inventory, will be performed using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline total body weight group (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and the dichotomized baseline value of the outcome measure (\leq median, $>$ median for continuous variables), except sPGA-related dichotomous endpoints. For sPGA-related dichotomous endpoints, baseline sPGA score(3, 4, or 5) will be adjusted as a categorical variable. For key dichotomous endpoints, a logistic regression model may be used as an additional supportive analysis.

The comparisons of continuous efficacy and PRO endpoints between treatment arms, including % PASI improvement, will be performed using analysis of covariance (ANCOVA) models, adjusting for the baseline total body weight group (≤ 100 kg,

> 100 kg), prior biologic use (yes, no), and geographic region, with the continuous baseline value of the outcome measure as a covariate. For % PASI improvement, depending on the normality of the data, the stratified Wilcoxon Rank Sum Test may also be conducted as a sensitivity analysis, adjusting for the baseline stratification factors and baseline PASI group (\leq median, $>$ median).

Analyses of endpoints after week 12 through week 52:

The comparisons of dichotomous efficacy and PRO endpoints between treatment arms will be performed using the CMH test adjusting for treatment received in the 12-week induction phase, week 12 total body weight group (\leq 100 kg, $>$ 100 kg), and week 12 sPGA response (0, \geq 1). For key dichotomous endpoints, a logistic regression model may be used as an additional supportive analysis.

The comparisons of continuous efficacy and PRO endpoints between treatment arms, including % PASI improvement, will be performed using analysis of covariance (ANCOVA) models, adjusting for treatment received in the 12-week induction phase, week 12 total body weight group (\leq 100 kg, $>$ 100 kg), and week 12 sPGA response (0, \geq 1). For % PASI improvement, depending on the normality of the data, the stratified Wilcoxon Rank Sum Test may also be conducted as a sensitivity analysis, adjusting for stratification factors at the rerandomization.

The analysis methods and corresponding covariates included in the model are summarized below.

Type	Endpoint	Timing	Method	Covariate ^{ab}
Continuous	% PASI Improvement	Through Week 12	Primary: ANCOVA	Baseline PASI score
			Sensitivity: Stratified Wilcoxon Rank Sum Test	Baseline PASI group
		After Week 12	Primary: ANCOVA	--
		Through Week 52	Sensitivity: Stratified Wilcoxon Rank Sum Test	--
		Other	ANCOVA	Baseline value
	PASI Responses	Through Week 12	ANCOVA	--
		After Week 12		
		Through Week 52		
		Through Week 12	Primary: CMH	Baseline PASI group
			Additional: Logistic	Baseline PASI score
Binary	sPGA 0/1	After Week 12	Primary: CMH	--
		Through Week 52	Additional: Logistic	--
		Through Week 12	Primary: CMH	Baseline categorical sPGA = 3, 4, or 5
			Additional: Logistic	Baseline categorical sPGA = 3, 4, or 5
		After Week 12	Primary: CMH	--
		Through Week 52	Additional: Logistic	--
	Other	Through Week 12	CMH	Baseline group (\leq median, $>$ median)
		After Week 12	CMH	--
		Through Week 52		

^aIn addition to the covariates listed here, all analyses will include the stratification factors. For analyses after week 12 through week 52, analyses which include the ustekinumab group will not be adjusted for the induction phase treatment group.

^bAdditional covariates listed in Section 10.5.3 may be added to the logistic regression models as exploratory analysis

Analyses after week 52:

After week 52, all analyses will be as observed, and will be summarized by treatment group through the primary analysis cutoff date based on the phase the

subject is in at week 52. Data for subjects who rescue after week 52 will be analyzed separately from subjects who qualify for rescue treatment through week 52. Post week 52 analysis will be conducted for key endpoints and be summarized by phase beginning at week 12 through the last visit prior to the data cutoff date.

10.5.1 Analyses of Primary and Key Secondary Efficacy Endpoints

Primary Efficacy Endpoints

Within the placebo family, the co-primary endpoints for this study are PASI 75 (210 mg Q2W brodalumab vs placebo and 140 mg Q2W brodalumab vs placebo) and sPGA success (210 mg Q2W brodalumab vs placebo and 140 mg Q2W brodalumab vs placebo) at week 12. Within the ustekinumab family, the primary endpoint is PASI 100 (210 mg Q2W brodalumab vs ustekinumab and brodalumab [140 mg for subjects \leq 100 kg and 210 mg for subjects $>$ 100 kg] vs ustekinumab) at week 12. Since all of these endpoints are dichotomous variables, CMH tests adjusting for baseline total body weight group (\leq 100 kg, $>$ 100 kg), prior biologic use (yes, no), and geographic region will be performed to examine the treatment effect. **For PASI 75 and PASI 100 response, baseline PASI group (\leq median, $>$ median) will also be adjusted for in the model. For sPGA success, baseline sPGA (3, 4, or 5) will also be adjusted for in the model.**

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 (PASI 75 and sPGA success rates at week 12) by 10-kg increments (eg, 51 to \leq 60 kg, 61 to \leq 70 kg) may be conducted. This analysis will be performed in a pooled fashion for studies 20120102, 20120103, and 20120103 to examine a weight threshold, if any. The details of this pre-specified analysis will be provided in a supplemental statistical analysis plan.

Key Secondary Efficacy Endpoints

The key secondary endpoints for this study will be analyzed as follows.

Key Secondary Endpoints Family of Hypotheses Based on Comparisons with Placebo

- The proportion of subjects achieving PASI 100 at week 12 will be compared between the 210 mg Q2W brodalumab and placebo treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline PASI group (\leq median, $>$ median).
- The proportion of subjects achieving sPGA of 0 at week 12 will be compared between the 210 mg Q2W brodalumab and placebo treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline sPGA score (3, 4, or 5).
- The proportion of subjects achieving PASI 100 at week 12 will be compared between the 140 mg Q2W brodalumab and placebo treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline PASI group (\leq median, $>$ median).
- The proportion of subjects achieving sPGA of 0 at week 12 will be compared between the 140 mg Q2W brodalumab and placebo treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline sPGA score (3, 4, or 5).
- The proportion of subjects achieving Psoriasis Symptom Inventory total score responder definition (≤ 8 with no item scores > 1) at week 12 will be compared between the 210 mg Q2W brodalumab and placebo treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline Psoriasis Symptom Inventory total score group (\leq median, $>$ median).
- The proportion of subjects achieving Psoriasis Symptom Inventory total score responder definition (≤ 8 with no item scores > 1) at week 12 will be compared between the 140 mg Q2W brodalumab and placebo treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline Psoriasis Symptom Inventory total score group (\leq median, $>$ median).

Key Secondary Endpoints Family of Hypotheses Based on Comparisons with Ustekinumab

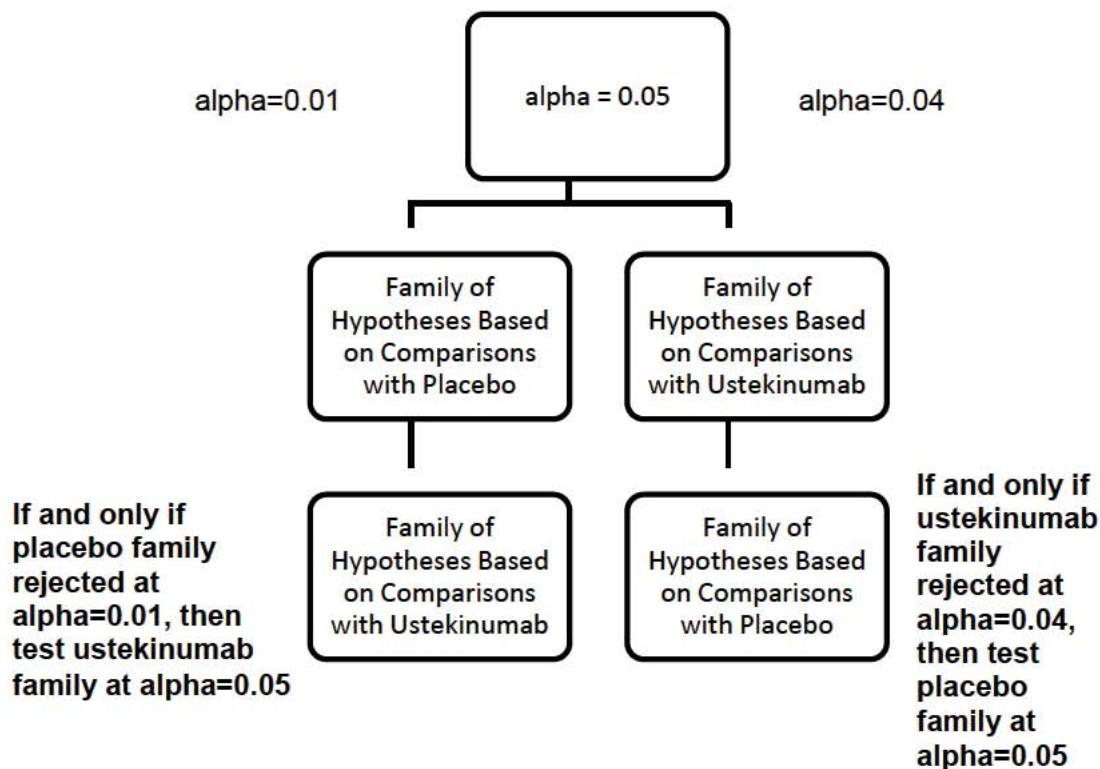
- The proportion of subjects achieving PASI 100 at week 12 will be compared between the 140 mg Q2W brodalumab and ustekinumab treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline PASI group (\leq median, $>$ median).
- The proportion of subjects achieving PASI 75 at week 12 will be compared between the 210 mg Q2W brodalumab and ustekinumab treatment arms using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline PASI group (\leq median, $>$ median).
- The proportion of subjects achieving PASI 75 at week 12 will be compared between brodalumab [140 mg for subjects ≤ 100 kg and 210 mg for subjects > 100 kg] and

ustekinumab using a CMH test, adjusting for baseline total body weight group, prior biologic use, geographic region, and baseline PASI group (\leq median, $>$ median).

Hypothesis Testing in the Placebo and Ustekinumab Families of Primary and Key Secondary Endpoints

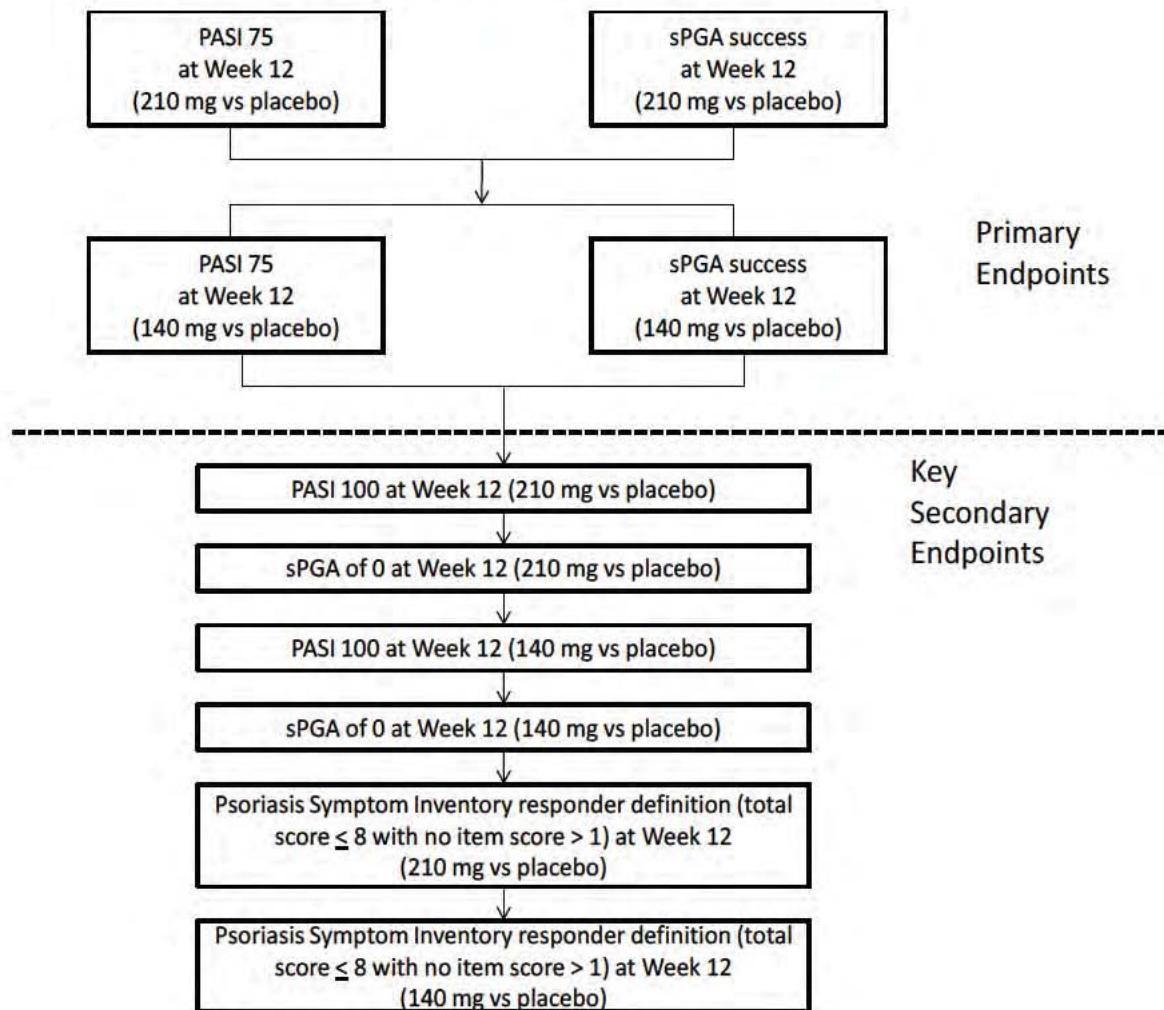
During the 12-week induction phase, in order to maintain the 2-sided family-wise type-1 error rate at 5%, a combination of parallel, sequential, and Bonferroni-based recycling testing will be followed for the week 12 primary and key secondary endpoints.

Initially, the week 12 primary and key secondary endpoints will be tested in the placebo family at alphas = 0.01 (2-sided) and in the ustekinumab family at alpha = 0.04 (2-sided). If and only if the null hypotheses for all the primary and key secondary endpoints within either the placebo (alpha=0.01) or ustekinumab (alpha=0.04) family are rejected, the fraction of the overall alpha (either 0.01 or 0.04) allocated to that family will be recycled to the testing of the hypotheses in the other family (Burman et al, 2009). For example, if all null hypotheses within the placebo family are rejected at alpha=0.01, this alpha of 0.01 will be recycled to the testing of the hypotheses within the ustekinumab family, which will be tested at the full alpha level of 0.05.

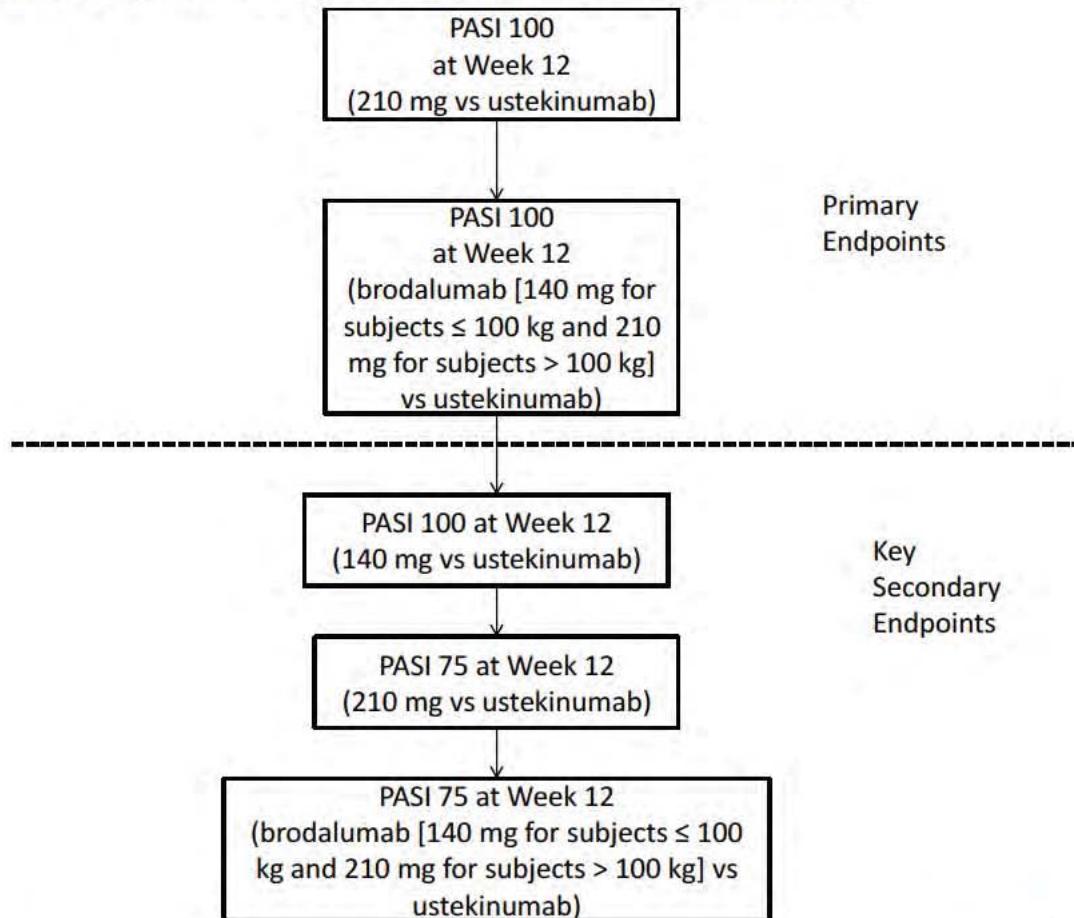


Within the placebo and ustekinumab families, the primary endpoints will be tested first. If the null hypothesis for any of the primary endpoints within a family is not rejected, all the subsequent hypotheses for the key secondary endpoints at week 12 within that family will not be tested. However, if 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. The sequential testing procedure is outlined below.

Family of Hypotheses Based on Comparisons with Placebo



Family of Hypotheses Based on Comparisons with Ustekinumab



The adjusted *p*-values, constructed according to the sequential testing procedure will be provided so that the statistical significance of a test can be obtained by comparing the adjusted *p*-value with a nominal significance level 0.05. The definitions of the adjusted *p*-values for primary, co-primary and key secondary endpoints are summarized in [Appendix A](#).

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

In order to utilize all data at different time points, as a sensitivity analysis, Generalized Estimating Equation (GEE) model will be used for primary endpoints with data as observed, assuming a logit link and AR(1) covariance matrix. The model will include the treatment group, week, treatment group by week interaction and baseline covariates. To avoid non-convergence, in order for the GEE model to be used, for the placebo family comparisons, at least one subject in the placebo treatment arm is required to achieve PASI 75 or sPGA success at week 12 and 3 or more additional visits in the induction phase. For ustekinumab family

comparisons, at least one subject in the ustekinumab, 140 mg Q2W brodalumab and 210 mg Q2W brodalumab treatment arm is required to achieve PASI 100 at week 12 and 3 or more additional visits in the induction phase.

In addition, analyses of covariates may be performed using the covariates listed in [Section 10.5.3](#)

Maintenance Phase Endpoint (sPGA Success at Week 52)

After rerandomization during the maintenance phase, the maintenance endpoint (sPGA success at week 52) will be compared between the rerandomized treatment arms (210 mg Q2W brodalumab, 140 mg Q2W brodalumab, 140 mg Q4W brodalumab, 140 mg Q8W brodalumab) using CMH tests, adjusting for week 12 total body weight group (≤ 100 kg, > 100 kg), week 12 sPGA response (0, ≥ 1), and treatment received in the 12-week induction phase.

Following rerandomization, we consider testing of the maintenance endpoint (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 endpoint sPGA success at week 52 will be sequentially tested at full alpha = 0.05 level (2-sided) between the rerandomized treatment groups, independent of prior testing results for the primary and key secondary endpoints 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 adjusted *p*-values, constructed according to the sequential testing procedure will be provided so that the statistical significance of a test can be obtained by comparing the adjusted *p*-value with a nominal significance level 0.05. The definitions of the adjusted *p*-values for the maintenance endpoints are summarized in [Appendix A](#).

10.5.2 Analyses of Other Secondary and Exploratory Endpoints

Time to sPGA success and PASI response (PASI 50, 75, 90 and 100) in the initial 12-week phase will be summarized by Kaplan-Meier estimates. These analyses will include comparisons of the brodalumab treatment arms with placebo and with ustekinumab. Subjects who discontinue study prior to study day 91 will be

censored at the date of the last assessment taken prior to or on the early termination visit. Continuing subjects who reach study day 91 without achieving response will be censored at the date of the last assessment taken prior to or on study day 91. If the last assessment is prior to study day 1, the subject will be censored at study day 1.

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](#)).

All patient-reported outcomes included as other secondary endpoints will have treatment difference compared between the brodalumab arms and placebo.

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. Furthermore, the Psoriasis Symptom Inventory total score improvement from baseline at week 12 will be analyzed based on ANCOVA models, adjusting for baseline Psoriasis Symptom Inventory total score and the relevant baseline stratification factors, to compare treatment arms. Finally, a mixed-effects model for repeated measures will be applied to compare mean post-baseline Psoriasis Symptom Inventory total scores between treatment arms through week 12. The mixed model will include treatment group, week, treatment-by-week interaction, baseline stratification factors and baseline Psoriasis Symptom Inventory total score as fixed effects, and within subject covariance will be estimated by an AR(1) covariance matrix.

For DLQI, the main analysis will be a mean improvement in total score from baseline at week 12, and additional analyses will include the proportion of subjects with at least a 5-point improvement in total score (the published minimal important difference for the DLQI), a total score of 0, and a total score of 0/1 at week 12. For WLQ, the main analysis will be a mean improvement from baseline at week 12 for each domain score.

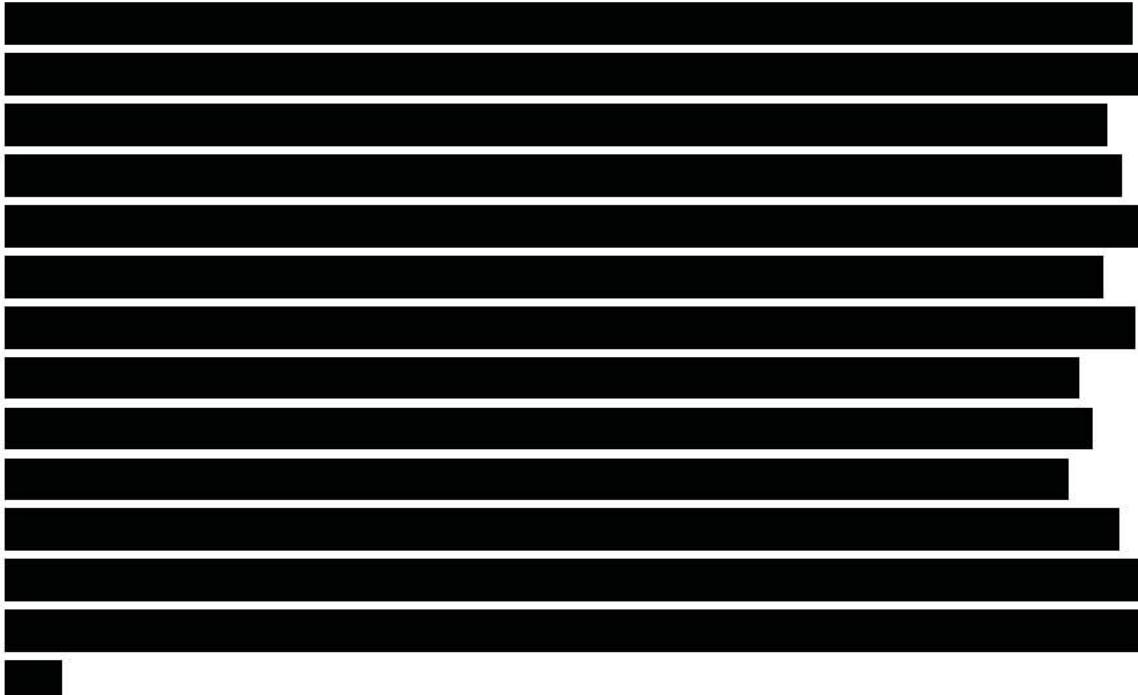
All other secondary and exploratory endpoints, including non-key secondary PRO endpoints, will be summarized descriptively. Summary statistics of continuous variables will include: n, mean, median, standard deviation, standard error, minimum, and

maximum, and 95% confidence interval (except for safety laboratory assessment). For comparisons of continuous endpoints, an ANCOVA model adjusting for baseline value (**week 12 endpoints only**) and stratification factors will be used. **For post baseline % PASI improvement, as a sensitivity analysis, a mixed-effects model for repeated measures will be applied to compare the treatment arms through week 12.** The mixed model will include treatment group, week, treatment-by-week interaction, baseline stratification factors, and baseline PASI score as fixed effects, and within subject covariance will be estimated by an AR(1) covariance matrix.

Summary statistics of dichotomous variables will be presented using frequencies and incidences, which include n, %, and N, where N is the total number of subjects with recorded values in the corresponding arm. For comparisons of dichotomous endpoints, a CMH test adjusting for stratification factors and the dichotomized **baseline** value of the measure (\leq median, $>$ median; **week 12 endpoints only**) will be used.

All statistical analysis performed for the biomarkers and pharmacogenetic data will be considered exploratory. Summary statistics and p-values will be provided as appropriate and the relationship between different parameters will be assessed. Descriptive and graphical summaries will be provided.

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



10.5.3 Covariate and Subgroup Analyses

The initial randomization stratification factors, baseline total body weight group (≤ 100 kg, > 100 kg), prior biologic use, and geographic region, will be adjusted for in all primary efficacy analyses. The following covariates at baseline may be used in the exploratory analyses based on logistic regression models (for dichotomous endpoints) and ANCOVA models (for continuous endpoints).

The efficacy endpoints may have a multiple regression analysis run to assess which covariates had influence on the endpoint. The covariates to be adjusted 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
- baseline BSA involvement
- geographic regions
- sex (male, female)
- age
- race/ethnicity
- baseline body mass index
- baseline total body weight
- disease duration

The 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, \geq 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)
- baseline body mass index (\leq 35 kg/m², $>$ 35 kg/m²)
- baseline total body weight
- **baseline disease severity (\leq median PASI, $>$ median PASI or sPGA 3, 4, 5)**
- disease duration (\leq median, $>$ median)
- concomitant topical steroid use (Yes, No)
- concomitant topical therapy use (Yes, No)
- anti-brodalumab antibody status (presence, absence)
- **prior failure of systemic agent or contraindication (Yes, No)**

All races with less than 5% of the total randomized subjects will be pooled together for summary purposes.

As a supportive secondary analysis, the effects of region by treatment interaction will be assessed for the primary endpoints using a logistic regression model. For the analysis of co-primary endpoints, sPGA success and PASI 75 at week 12 for the 210 mg Q2W and 140 mg Q2W brodalumab arms vs placebo, region will be as defined for the stratification at the initial randomization, ie, by country for non-US countries and by geographic region for within the United States (US-West, US-Midwest, US-Northeast, US-South). For the analysis of the primary endpoint, PASI 100 at week 12 for the 210 mg Q2W and weight-based (140 mg Q2W for subjects \leq 100 kg with 210 mg Q2W for subjects $>$ 100 kg) brodalumab groups vs ustekinumab, region will also be as defined for the initial randomization, ie, by

country for non-US countries and by geographic region for within the United States (US-West, US-Midwest, US-Northeast, US-South).

10.5.4 Pharmacokinetic Endpoints

[REDACTED]

10.5.5 Biomarker Endpoints

[REDACTED]

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) 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. **Exposure adjusted event rates will be provided through week 52 by planned treatment group defined in the table below, as constant 210 mg, constant 140 mg, 140/210 combination, mixed brodalumab, ustekinumab, and ustekinumab/210 mg mixed treatment groups.**

Planned Sequence of Treatments			
Treatment Group	Induction	Maintenance	Rescue
Placebo	Placebo	Missing	Missing
	Placebo	210 mg Q2W	Missing
210 mg Q2W	210 mg Q2W	Missing	Missing
	210 mg Q2W	210 mg Q2W	Missing
	210 mg Q2W	210 mg Q2W	210 mg Q2W
140 mg Q2W	140 mg Q2W	Missing	Missing
	140 mg Q2W	140 mg Q2W	Missing
	140 mg Q2W	140 mg Q2W	210 mg Q2W
	140 mg Q2W	210 mg Q2W	Missing
140 mg Q2W / 210 mg Q2W Combination	140 mg Q2W	210 mg Q2W	210 mg Q2W
	210 mg Q2W	140 mg Q2W	Missing
	210 mg Q2W	140 mg Q2W	210 mg Q2W
	Ustekinumab	Missing	Missing
Ustekinumab	Ustekinumab	Ustekinumab	Missing
	Ustekinumab	Ustekinumab	Ustekinumab
Ustekinumab/ 210 mg Q2W Mixed	Ustekinumab	Ustekinumab	210 mg Q2W
	140 mg Q2W	140 mg Q4W	Missing
	140 mg Q2W	140 mg Q4W	210 mg Q2W
	140 mg Q2W	140 mg Q8W	Missing
	140 mg Q2W	140 mg Q8W	210 mg Q2W
Mixed	210 mg Q2W	140 mg Q4W	Missing
	210 mg Q2W	140 mg Q4W	210 mg Q2W
	210 mg Q2W	140 mg Q8W	Missing
	210 mg Q2W	140 mg Q8W	210 mg Q2W

* Subjects who do not enter a phase are classified as missing a treatment assignment in that phase



The subject incidence and exposure-adjusted event rates of adverse events will be summarized for all treatment-emergent, CTCAE 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 (EOI) will also be summarized according to their categories. The EOI 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, **CTCAE** grade 2 and above, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, **those leading to study discontinuation**, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of serious adverse events and treatment-emergent adverse events occurring in at least 1% of the subjects in any treatment arm 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 10.5.3.

10.6.2 Suicidal Ideation and Behavior

Suicidal ideation and behavior will be evaluated using the electronic self rated version, Columbia-Suicide Severity Rating Scale (eC-SSRS). The C-SSRS will be summarized by treatment group and will also be summarized by the following subgroups of history of suicidal ideation and behavior: no prior history, with prior history, and unknown prior history based on a retrospective assessment of a subject's history of suicidal ideation or behavior. Additionally, subject listings will be provided, and patient profiles (including information on medical history, concomitant medications, adverse events, PASI, IP dosing, eC-SSRS, and PHQ-8) will be generated for subjects with reported suicide ideation/behavior adverse events and/or C-SSRS scores above a defined threshold. As this data was only collected at post-baseline visits with prior history defined based on a retrospectively version of the questionnaire, the analyses will be considered exploratory and descriptive.

10.6.3 Depression

Depression will be evaluated at post-baseline timepoints using the Patient Health Questionnaire depression scale (PHQ-8). The PHQ-8 will be summarized by treatment group. Additionally, subject listings will be provided, and patient profiles (including information on medical history, concomitant medications, adverse events, PASI, IP dosing, eC-SSRS, and PHQ-8) will be generated for subjects with PHQ-8 scores above a defined threshold. As this data was only collected at post-baseline visits and with no baseline data, the analyses will be considered exploratory and descriptive.

To derive the total score for the PHQ-8 at a time point, the sum of the eight items is taken. If more than one item is missing, the total score at the time point will be set to missing. If one item is missing, the average score of the seven observed items will replace the missing item in the calculation of the PHQ-8 score at that time point.

10.6.4 Laboratory Test Results

Laboratory shift tables based on version 4.0 of the Common Toxicology Criteria for Adverse Events (CTCAE) grade will be provided to compare baseline laboratory values with the most extreme post-baseline values. The percentages of subjects with laboratory toxicities by CTCAE grade will be summarized. Laboratory values and

change in laboratory values will also be descriptively summarized by study phase, scheduled visit, and treatment group for key laboratory assessments of interest.

Graphs showing the mean and standard deviation of the changes from baseline or actual values over time may be provided for notable laboratory parameters.

For the laboratory analytes of Uric Acid (Hyperuricemia) and Potassium (Hypokalemia), laboratory test results may be summarized based on standard normal ranges or by CTCAE grade utilizing investigator's input.

The specific analytes for the serum chemistry and hematology assessments, as well as other assessments to be conducted on blood and urine samples, are outlined in the protocol.

Additional laboratory assessments may be collected as part of follow-up to investigate the possibility of drug-induced liver injury as defined in the protocol. These additional laboratory results may be part of subject-level narratives for subjects who experience abnormal liver tests. These results will not be included in tables summarizing laboratory results based on planned visit laboratory collection, as defined in the scheduled of assessments, but may be included in laboratory shift tables or overall laboratory listings.

10.6.5 Vital Signs

Vital signs (ie, heart rate, systolic and diastolic blood pressures, respiration) will be summarized and reviewed. Summaries of vital signs data over time and/or changes from Day 1 over time may be provided.

Additional vital sign data may be collected as part of follow-up to investigate the possibility of drug-induced liver injury as defined in the protocol. These additional vital sign results may be part of subject-level narratives for subjects who experience abnormal liver tests. These results will not be included in tables or listings summarizing vital sign results based on planned visit vital sign collection, as defined in the scheduled of assessments.

10.6.6 Electrocardiogram (ECG)

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither

summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.6.7 Antibody Formation

The antibody testing strategy for this study will be to test all protocol-specified samples in a validated immunoassay.

10.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. The number and percentage of subjects with dose modifications and reason for modification will be summarized by **planned** treatment group.

Duration of IP Administration = last IP dose date – first IP dose date + 1

Duration of brodalumab exposure by phase:

Induction phase

= min(last active brodalumab IP dose date in induction phase + 14, end of induction phase date, maintenance phase start date - 1, EOS date) - first active brodalumab IP dose date +1

Maintenance phase

= min(last active brodalumab IP dose date in maintenance phase + 14, end of maintenance phase date, rescue phase start date - 1, long term extension phase start date - 1, primary analysis data cutoff, EOS date) - first active brodalumab IP dose date in maintenance phase +1, if randomized to brodalumab 210 mg Q2W or 140 mg Q2W

= min(last active brodalumab IP dose date in maintenance phase + 28, end of maintenance phase date, rescue phase start date – 1, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date in maintenance phase +1, if randomized to brodalumab 140mg Q4W

= min(last active brodalumab IP dose date in maintenance phase + 56, end of maintenance phase date, rescue phase start date – 1, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date in maintenance phase +1, if randomized to brodalumab 140mg Q8W

Rescue Treatment phase (through week 52)

= min(last active brodalumab IP dose date in rescue phase + 14, end of rescue phase date, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date in rescue phase +1

Duration of brodalumab exposure through week 52:

= min(last active brodalumab IP dose date prior to week 52 + 14, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date +1, if last planned dose of brodalumab prior to week 52 is 210 mg Q2W or 140 mg Q2W

= min(last active brodalumab IP dose date prior to week 52 + 28, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date +1, if last planned dose of brodalumab prior to week 52 is 140mg Q4W

= min(last active brodalumab IP dose date prior to week 52 + 56, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date +1, if last planned dose of brodalumab prior to week 52 is 140mg Q8W

Duration of brodalumab exposure through data cutoff:

= min(last active brodalumab IP dose date prior to data cutoff +14, primary analysis data cutoff, EOS) – first active brodalumab IP dose date + 1, if last planned dose of brodalumab prior to data cutoff is 210 mg Q2W or 140 mg Q2W

= min(last active brodalumab IP dose date prior to data cutoff +28, primary analysis data cutoff, EOS) – first active brodalumab IP dose date + 1, if last planned dose of brodalumab prior to data cutoff is 140 mg Q4W

= min(last active brodalumab IP dose date prior to data cutoff +56, primary analysis data cutoff, EOS) – first active brodalumab IP dose date + 1, if last planned dose of brodalumab prior to data cutoff is 140 mg Q8W

Duration of ustekinumab exposure by phase:

Induction phase

= min(last active ustekinumab IP dose date in induction + 84, end of induction phase date, maintenance phase start date – 1, EOS date) – first active ustekinumab IP dose date +1

Maintenance phase

= min(last active ustekinumab IP dose date in maintenance phase + 84, end of maintenance phase date, rescue phase start date – 1, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active ustekinumab IP dose date in maintenance phase +1 + min[end of maintenance phase date, active ustekinumab IP dose date at week 16 – 1, active brodalumab IP dose date at week 16 – 1, max(last active ustekinumab IP dose date in induction phase + 84, maintenance phase start date – 1)] – maintenance phase start date + 1

Rescue Treatment phase (through week 52)

= [min(last active ustekinumab IP dose date in rescue phase + 84, end of rescue phase date, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active brodalumab IP dose date in rescue phase +1] + min[end of rescue phase date, first active ustekinumab IP dose date in rescue phase - 1, max(last active ustekinumab IP dose date in maintenance phase + 84, rescue phase start date – 1)] – rescue phase start date + 1

Duration of ustekinumab exposure through week 52:

= min(last active ustekinumab IP dose date prior to week 52 + 84, long term extension phase start date – 1, first active brodalumab IP dose date – 1, primary analysis data cutoff, EOS date) – first active ustekinumab IP dose date + 1, for ustekinumab treatment group rescued to brodalumab 210 mg Q2W at week 16

= min(last active ustekinumab IP dose date prior to week 52 + 84, long term extension phase start date – 1, primary analysis data cutoff, EOS date) – first active ustekinumab IP dose date + 1, for all other subjects

10.6.9 Exposure to Concomitant Medication

The number and proportion of subjects who received concomitant topical corticosteroids will be summarized for each treatment group by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. The list of selected medications and their groupings will be finalized prior to the database unblinding.

11. Changes from Protocol-Specified Analyses

The SAP has the following changes from protocol-specified analyses:

- Updated analysis sets for the following:
 - Replaced Maintenance Phase (Subjects Initially Randomized to Placebo) and Maintenance Phase (Comparisons with Ustekinumab) analysis sets with Maintenance Phase (Non-Rerandomized Subjects) analysis set
- Additional analysis sets for the following:
 - Efficacy and safety analysis sets for rescue phase through week 52 for rerandomized subjects
 - Efficacy and safety analysis sets for the rescue phase after week 52
 - Safety analysis set for long term safety analyses for subjects exposed to active brodalumab
 - Week 12-52 per protocol analysis set
- Removal of adjustment for week 12 value of the endpoint from analyses of post week 12 endpoints
- Addition of details on recycling of alpha for placebo and ustekinumab family of comparisons if all null hypotheses in either family are rejected

12. Literature Citations / References

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13. Prioritization of Analyses

[REDACTED]

14. Data not Covered by this Plan

[REDACTED]

[REDACTED]

[REDACTED]

! [REDACTED]

[REDACTED]

15. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Definitions of Adjusted *p*-values

The definitions of the adjusted *p*-values are displayed below ([Dmitrienko et al, 2005](#)).

The adjusted *p*-values, constructed according to the sequential and recycling testing procedure are provided so that the statistical significance of a test can be obtained by comparing the adjusted *p*-value with a nominal significance level 0.05.

Testing algorithm (first round):

The null hypotheses in family 1 and family 2 will be tested according to the testing procedure in the tables below. In family 1, if the adjusted *p*-value for the *i*-th endpoint is < 0.05, then the corresponding null hypothesis is rejected. In family 2, if the adjusted *p*-value for the *i*-th endpoint is < 0.05, then the corresponding null hypothesis is rejected.

Testing algorithm (second round):

If the adjusted *p*-value for endpoint 10 is <0.05 in the first round of testing for family 1, then family 2 will be retested as follows: in the second round of testing in family 2, if the adjusted *p*-value for the *i*-th endpoint is < 0.05, then the corresponding null hypothesis is rejected.

If the adjusted *p*-value for endpoint 5 is <0.05 in the first round of testing for family 2, then family 1 will be retested as follows: in the second round of testing in family 1, if the adjusted *p*-value for the *i*-th endpoint is < 0.05, then the corresponding null hypothesis is rejected.

Family 1: Family of Hypotheses Based on Comparisons with Placebo (first round alpha = 0.01; second round alpha=0.05)

Test ID	Endpoint	Raw p-value	Adjusted p-value (APV) First Round	Adjusted p-value (APV) Second Round
Co-Primary Endpoints				
1	PASI 75 at week 12 (210 mg Q2W brodalumab vs placebo)	p_1	5X Max { p_1, p_2 }	Max { p_1, p_2 }
2	sPGA success at week 12 (210 mg Q2W brodalumab vs placebo)	p_2	5X Max { p_1, p_2 }	Max { p_1, p_2 }
3	PASI 75 at week 12 (140 mg Q2W brodalumab vs placebo)	p_3	5X Max { p_1, p_2, p_3, p_4 }	Max { p_1, p_2, p_3, p_4 }
4	sPGA success at week 12 (140 mg Q2W brodalumab vs placebo)	p_4	5X Max { p_1, p_2, p_3, p_4 }	Max { p_1, p_2, p_3, p_4 }
Key Secondary Endpoints				
5	PASI 100 at week 12 (210 mg Q2W brodalumab vs placebo)	p_5	5X Max { p_1, p_2, p_3, p_4, p_5 }	Max { p_1, p_2, p_3, p_4, p_5 }
6	sPGA of 0 at week 12 (210 mg Q2W brodalumab vs placebo)	p_6	5X Max{ $p_1, p_2, p_3, p_4, p_5, p_6$ }	Max{ $p_1, p_2, p_3, p_4, p_5, p_6$ }
7	PASI 100 at week 12 (140 mg Q2W brodalumab vs placebo)	p_7	5X Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7$ }	Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7$ }
8	sPGA of 0 at week 12 (140 mg Q2W brodalumab vs placebo)	p_8	5X Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8$ }	Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8$ }
9	Psoriasis Symptom Inventory responder definition at week 12 (210 mg Q2W brodalumab vs placebo)	p_9	5X Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9$ }	Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9$ }
10	Psoriasis Symptom Inventory responder definition at week 12 (140 mg Q2W brodalumab vs placebo)	p_{10}	5X Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, p_{10}$ }	Max{ $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, p_{10}$ }

Family 2: Family of Hypotheses Based on Comparisons with Ustekinumab (first round alpha = 0.04; second round alpha=0.05)

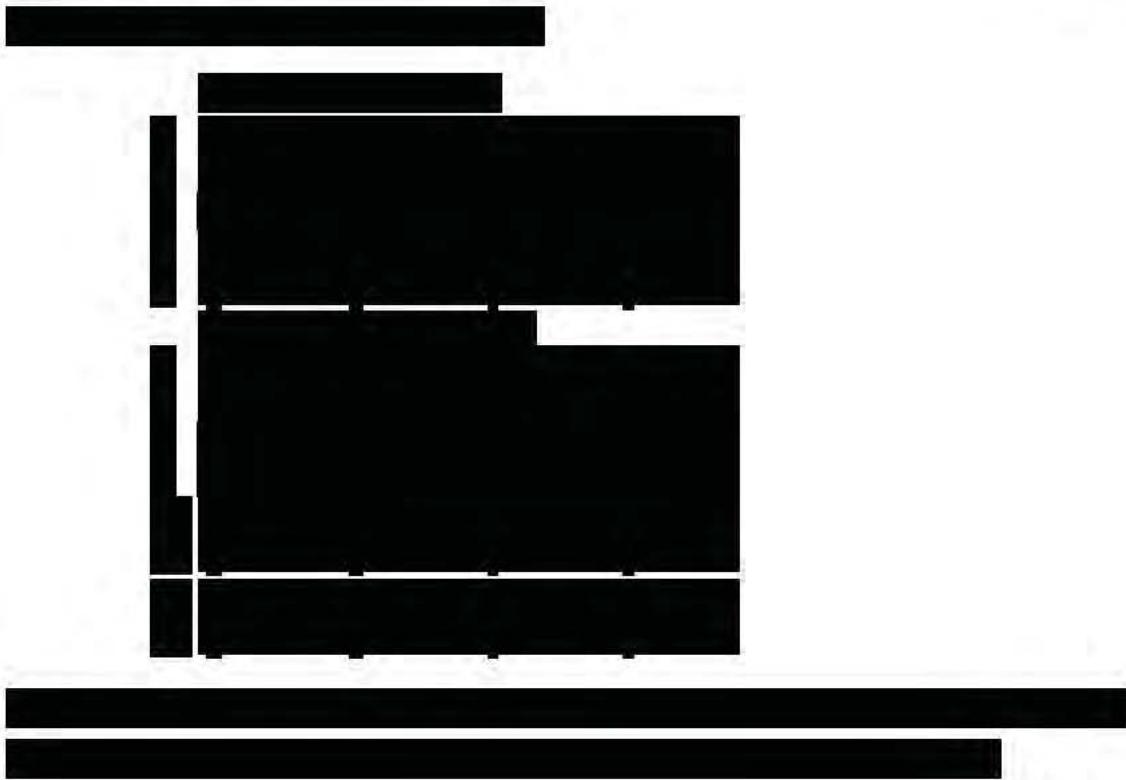
Test ID	Endpoint	Raw p-value	Adjusted p-value (APV) First Round	Adjusted p-value (APV) Second Round
Primary Endpoints				
1	PASI 100 at week 12 (210 mg Q2W brodalumab vs ustekinumab)	p'_1	1.25X p'_1	p'_1
2	PASI 100 at week 12 (brodalumab [140 mg Q2W for subjects \leq 100 kg and 210 mg Q2W for subjects > 100 kg] vs ustekinumab)	p'_2	1.25X Max { p'_1, p'_2 }	Max { p'_1, p'_2 }
Key Secondary Endpoints				
3	PASI 100 at week 12 (140 mg Q2W brodalumab vs ustekinumab)	p'_3	1.25X Max { p'_1, p'_2, p'_3 }	Max { p'_1, p'_2, p'_3 }
4	PASI 75 at week 12 (210 mg Q2W brodalumab vs ustekinumab)	p'_4	1.25X Max { p'_1, p'_2, p'_3, p'_4 }	Max { p'_1, p'_2, p'_3, p'_4 }
5	PASI 75 at week 12 (brodalumab [140 mg Q2W for subjects \leq 100 kg and 210 mg Q2W for subjects > 100 kg] vs ustekinumab)	p'_5	1.25X Max { $p'_1, p'_2, p'_3, p'_4, p'_5$ }	Max { $p'_1, p'_2, p'_3, p'_4, p'_5$ }

For the maintenance phase endpoint (sPGA success at week 52) the definition of the testing procedure is detailed below.

Maintenance Phase (alpha = 0.05)

Test ID	Endpoint	Raw p-value	Adjusted p-value (APV)
1	sPGA success at week 52 (210 mg Q2W brodalumab vs 140 mg Q8W brodalumab)	p^*_1	p^*_1
2	sPGA success at week 52 (140 mg Q2W brodalumab vs 140 mg Q8W brodalumab)	p^*_2	Max { p^*_1, p^*_2 }
3	sPGA success at week 52 (210 mg Q2W brodalumab vs 140 mg Q4W brodalumab)	p^*_3	Max { p^*_1, p^*_2, p^*_3 }
4	sPGA success at week 52 (140 mg Q2W brodalumab vs 140 mg Q4W brodalumab)	p^*_4	Max { $p^*_1, p^*_2, p^*_3, p^*_4$ }
5	sPGA success at week 52 (210 mg Q2W brodalumab vs 140 mg Q2W brodalumab)	p^*_5	Max { $p^*_1, p^*_2, p^*_3, p^*_4, p^*_5$ }





Appendix B. Code Fragments

This image shows a document page that has been heavily redacted. The majority of the page is covered by thick black horizontal bars. There are several vertical black bars on the left side, and a few small white rectangular areas where text might have been present but is now illegible. The overall appearance is that of a heavily censored or protected document.

[REDACTED]

[REDACTED]

Appendix C. Sensitivity Analyses

Sensitivity analysis may be performed to check the robustness of the analysis.

The per protocol analysis sets may be used to perform sensitivity analyses on both the primary and key secondary endpoints.

Through week 12, various sensitivity analyses will be performed for missing data, including as-observed analysis and last observation carried forward.

After week 12 through week 52, various sensitivity analyses will be performed for missing data, including as-observed analysis and last observation carried forward. After week 52, all data will be analyzed as observed.

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, which may utilize efficacy and safety data after partial consent withdrawal.

Sensitivity analyses may also be conducted to evaluate the influence of extreme values in the data and to check the robustness of distributional assumptions.

Appendix D. Reference Values/Toxicity Grades

CTCAE version 4 is available at the following link:

http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAEv4.pdf

Appendix E. Concomitant Medications

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:** the 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).

Appendix F. NAPSI and Patient-reported Outcome Forms/Instruments

The figure consists of four horizontal panels, each containing several black bars of varying lengths. The top panel has 10 bars. The second panel from the top has 7 bars. The third panel from the top has 5 bars. The bottom panel has 6 bars. The bars are positioned above a dashed vertical line.

2. Scoring Algorithm for Dermatology Life Quality Index (DLQI)



3. Psoriasis Symptom Inventory Item Scoring

The Psoriasis Symptom Inventory will be assessed daily and includes eight individual symptoms based on literature review, clinician interviews, and patient qualitative research. Each of the items measures a distinct symptom construct. The symptoms and their response options are listed below. Items 1 through 8 are assessed by means of a 5-point scale ranging from 0 ("not at all") to 4 ("very severe").

Psoriasis Symptom Inventory Item Response Options:

Symptom	Response options (<i>higher=worse</i>)
1. Itch from psoriasis	0-4 (severity)
2. Redness of skin lesions	0-4 (severity)
3. Scaling of skin lesions	0-4 (severity)
4. Burning of skin lesions	0-4 (severity)
5. Stinging of skin lesions	0-4 (severity)
6. Cracking of skin lesions	0-4 (severity)
7. Flaking of skin lesions	0-4 (severity)
8. Pain from skin lesions	0-4 (severity)

Total daily score (8-question version) is defined as the sum of Q1 to Q8.

The daily assessment of the Psoriasis Symptom Inventory will be analyzed as a weekly average. Completion of all 8 items is required to compute the daily score. In order to compute the average for a given week, at least 4 of the daily scores must be non-missing; otherwise the weekly average will be left as missing. The weekly average will be computed over the non-missing scores for the week (for example, if the subject has 4 non-missing daily scores, the average of the 4 daily scores will be the weekly average). As a supportive analysis, the weekly average may be analyzed for at least 5 non-missing daily scores.



Term	Percentage
GMOs	100%
Organic	2%
Natural	10%
Artificial	10%
Organic	100%
Natural	100%
Artificial	100%
Organic	100%
Natural	100%
Artificial	100%
Organic	100%
Natural	100%
Artificial	100%
Organic	100%
Natural	100%
Artificial	100%
Organic	100%
Natural	100%
Artificial	100%

**Table A3. Association Between Psoriasis Symptom Inventory (24 Hour Recall)
Responder Definition and DLQI Response at Week 12**

	Psoriasis Symptom Inventory (24 hour recall) ¹			Kappa (ASE)
	Responder, N(%)	Non-Responder, N(%)	Total, N	
DLQI 0²				
Responder, N(%)	61 (100.0)	0 (0.0)	61	
Non Responder, N(%)	53 (42.4)	72 (57.6)	125	
Total , N(%)	114 (61.3)	72 (38.7)	186	0.47 (0.052)
DLQI 0/1³				
Responder, N(%)	82 (94.3)	5 (5.7)	87	
Non Responder, N(%)	32 (32.3)	67 (67.7)	99	
Total , N(%)	114 (61.3)	72 (38.7)	186	0.61 (0.055)

¹ Responder: Psoriasis Symptom Inventory total score \leq 8 without a score of > 1 on any item;

Non-responder: Psoriasis Symptom Inventory total score total core > 8 or a score of > 1 on any item

² Responder: DLQI=0;

Non-responder: DLQI \geq 1

³ Responder: DLQI=0 or 1, defined as having no effect at all on a subject's life;

Non-responder: DLQI \geq 2

4. Scoring Algorithm for Work Limitations Questionnaire (WLQ)



5. Scoring Algorithm for Work Limitations Questionnaire (WLQ) Work Absence Module

Appendix G. Details of PK Methods for Modeling