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Protocol Number: 20090406
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Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Evaluate the Efficacy, Safety and Effect on Radiographic Progression of Brodalumab in Subjects With Psoriatic Arthritis: AMVISION-1

AMG 827 / Brodalumab

Amgen Protocol Number 20090406
EudraCT Number 2013-003554-25

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Date: 10 September 2013

Amendment 1 **26 March 2014**

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Investigator's Agreement

I have read the attached protocol entitled "A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Evaluate the Efficacy, Safety and Effect on Radiographic Progression of Brodalumab in Subjects With Psoriatic Arthritis", dated **26 March 2014**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

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Name of Investigator

Date (DD Month YYYY)

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Protocol Synopsis

Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Evaluate the Efficacy, Safety and Effect on Radiographic Progression of Brodalumab in Subjects With Psoriatic Arthritis

Study Phase: 3

Indication: Psoriatic Arthritis

Primary Objective: To evaluate the efficacy of brodalumab (210 mg every 2 weeks [Q2W]; and 140 mg Q2W) compared to placebo, in subjects with psoriatic arthritis, as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at week 16.

Secondary Objective(s): To evaluate the efficacy of brodalumab compared to placebo on the following: Psoriasis Area and Severity Index (PASI) 75 at week 16, and Van der Heijde modified Total Sharp score (mTSS) at week 24.

Safety Objective: To evaluate the safety profile of brodalumab.

Hypotheses:

Primary: Brodalumab at 210 mg Q2W and 140 mg Q2W is more efficacious than placebo, as measured by the proportion of subjects who achieve an ACR20 response at week 16.

Secondary: Brodalumab at 210 mg Q2W and 140 mg Q2W is more efficacious than placebo, as measured by:

- the proportion of subjects with PASI 75 response at week 16
- the mean change from baseline in mTSS at week 24

Primary Endpoint: ACR20 response at week 16

Secondary Endpoint(s): PASI 75 at week 16, and mTSS change from baseline at week 24

Study Design: The study begins with a 24-week, randomized, double-blind, placebo-controlled phase with the primary endpoint at week 16. Subjects will be randomly assigned to treatment, with even allocation (1:1:1), to subcutaneous doses of brodalumab 140 mg, brodalumab 210 mg or placebo Q2W with 1 additional dose at week 1. Randomization will be stratified based on baseline body weight, prior use of a biologic and geographic region.

Starting at their week 24 visit, all subjects receiving placebo will be transitioned, in a blinded fashion, to treatment with 210 mg brodalumab for the remainder of the study.

Original treatment assignments will remain blinded until all subjects reach the week 52 or early termination visit, whichever comes first. After treatment assignments are unblinded, all subjects will receive open label brodalumab at their current dose Q2W.

The entire study will be 166 weeks (approximately 3 years) in duration.

Subjects on the following permitted concomitant medications (methotrexate, sulfasalazine, leflunomide, corticosteroids and nonsteroidal anti-inflammatory drugs [NSAIDs]) are expected to remain on a stable dose through week 16. Starting at week 16, initiation and/or adjustment of the concomitant medications will be allowed for subjects with an inadequate response to investigational product. In addition, subjects receiving placebo who have an inadequate response will initiate treatment with 210 mg brodalumab. Starting at week 28, IP will be discontinued in subjects who are nonresponders, who will then become eligible for any available treatment including biologic disease-modifying antirheumatic drugs (DMARDs) ([Section 6.2.1.3.3](#)).

For approximately 15% of subjects (80 to 110 subjects), samples at additional timepoints for pharmacokinetic analysis will be collected as an optional substudy (according to the schedule in [Section 7.3.12.2](#)).

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

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

Sample Size: 630

Summary of Subject Eligibility Criteria: Subjects must be ≥ 18 years old and have a diagnosis of psoriatic arthritis (by the Classification of Psoriatic Arthritis criteria (CASPAR), with ≥ 3 tender and ≥ 3 swollen joints (excluding the distal interphalangeal joints)). Subjects must have at least 1 psoriatic skin lesion (plaque ≥ 2 cm diameter) as well as either ≥ 1 erosion on a centrally read radiograph or CRP ≥ 1.0 mg/dL. For subjects using methotrexate or sulfasalazine or leflunomide, they must have been treated for ≥ 3 months, with a stable dose (not to exceed 25 mg/wk methotrexate, 3 g/day sulfasalazine, or 20 mg/day leflunomide) for ≥ 4 weeks prior to initiation of investigational product and must be expected to remain stable for the next 16 weeks. For subjects using corticosteroids (not to exceed the equivalent of 10 mg/day of prednisone) or NSAIDs they must have been on a stable dose for ≥ 4 weeks prior to initiation of investigational product and must be expected to remain stable for the next 16 weeks. All subjects must have a negative tuberculosis test (or prophylaxis).

For a full list of eligibility criteria, please refer to [Section 4.1.1](#) through [Section 4.1.2](#).

Investigational Product

Amgen Investigational Product (IP) Dosage and Administration:

The IP will be brodalumab (and placebo for brodalumab). Subjects will receive brodalumab 140 mg, 210 mg or placebo at baseline, week 1, week 2 and then Q2W thereafter up to week 22. At week 24, all subjects receiving placebo will be switched to 210 mg brodalumab Q2W with an additional dose at week 25. Subjects who were on brodalumab will continue with the same dose with an additional dose (placebo) at week 25 to maintain the blind. After all subjects have reached week 52 and the primary analysis has occurred, treatment will be unblinded and subjects will receive open label brodalumab at their current dose Q2W. For additional detail on dosage and administration, see [Section 6.2.1](#).

IP will be administered subcutaneously, according to the guidance in [Section 6.2.1](#). Doses should be withheld for absolute neutrophil count abnormalities, hepatotoxicity, or infections according to the rules in [Section 6.2.1.3](#). IP should be permanently discontinued for certain adverse events (including significant or persistent absolute neutrophil count abnormalities) and for nonresponse ([Section 6.2.1.3](#), [Section 8.1](#)).

Procedures:

At the screening visit, subjects will be dispensed an electronic hand-held diary device (eDiary) and instructions on its use to capture daily psoriasis symptoms using the Psoriasis Symptom Inventory. Subjects will complete the Psoriasis Symptom Inventory daily during the entire screening period and during the study up to week 24, then week 48 to 52, according to the schedule in [Table 1](#).

Physical examination, medication and medical history, adverse event and concomitant medication assessment, vital signs measurement, electrocardiograms, tuberculosis test, urinalysis, and blood draw for serum chemistry and hematology analytes, C-reactive protein, ESR, fasting lipids, pharmacokinetics, and anti-brodalumab antibody assay will be performed according to [Table 1](#). Regular urine pregnancy tests will be performed in women of child-bearing potential. Tender and swollen joint assessments, patient and physician global assessments, patient assessment of pain), dactylitis and enthesitis assessments, psoriasis area and severity index (PASI), involved body surface area assessment, Dermatology Life Quality Index, SF-36v2, Bath Ankylosing Spondylitis Disease Activity Index, HAQ-DI, **Columbia Suicide Severity Rating Scale and Patient Health Questionnaire (PHQ-8) depression scale** will be assessed periodically throughout the study according to [Table 1](#).

Optional substudies/procedures that may require additional consent include:

- Post-dose pharmacokinetic samples at additional timepoints for brodalumab pharmacokinetic analysis

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- Biomarker blood collection
- Pharmacogenetic analysis

For a full list of study procedures, including the timing of each procedure, please refer to [Section 7](#) and the Schedule of Assessments ([Table 1](#)).

Statistical Considerations:

The primary and key secondary endpoints will be tested using a sequential testing procedure to control the family-wise 2-sided type one error rate at the significance level of 0.05.

The primary endpoint, ACR20 response at week 16, will be tested using a stratified Cochran-Mantel-Haenszel method between the brodalumab and placebo groups (stratified by baseline body weight, prior biologic use and geographic region). A similar analysis method (including baseline grouping as an additional stratification variable) will be used for the key secondary endpoint PASI 75 response at week 16.

Mean change from baseline mTSS will be assessed at week 24 using analysis of covariance model on the Van der Waerden normal scores with rank baseline mTSS, and stratification factors in the model.

For other continuous endpoints that exhibit normal distribution, a linear mixed effect model will be used. The model will include treatment group, visit, interaction of treatment group by visit, and stratification variables as fixed effects, baseline value and baseline value by treatment group as covariates, within subject variance will be estimated by an unstructured covariance matrix. However, for continuous endpoints that deviate from normality, data will be transformed by Van der Waerden method before using linear mixed effect model. The stratified Cochran-Mantel-Haenszel method will be used to analyze binary endpoints.

Primary analyses will be performed using non-responder imputation for binary endpoints; no imputation will be used for continuous endpoints.

All summary statistics of continuous variables will include: n, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence interval (except for safety laboratory assessment). For categorical variables, frequency and percentage will be reported.

No formal testing will be performed on safety data.

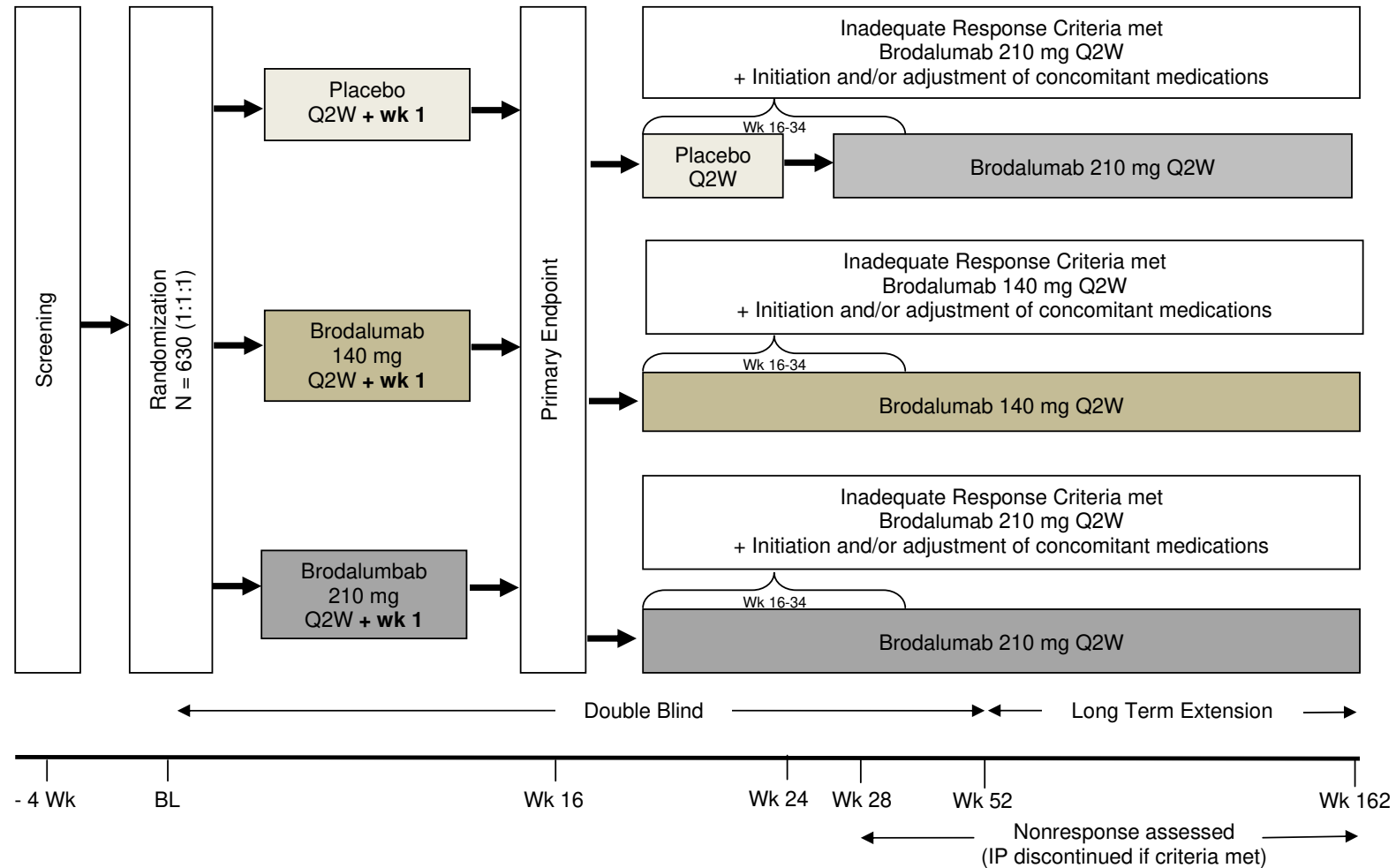
For a full description of statistical analysis methods, please refer to [Section 10](#).

Sponsor: Amgen Inc.

Data Element Standards DES 3, 31 January 13
Version(s)/Date(s):

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Study Design and Treatment Schema



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Study Glossary

Abbreviation or Term	Definition/Explanation
ACR	American College of Rheumatology
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BSA	Body surface area
CASPAR	Classification of Psoriatic Arthritis
CBC	Complete Blood Count
CDAI	Clinical Disease Activity Index
CRP	C-reactive protein
CTCAE	Common Terminology Criteria of Adverse Events
DAS 28	Disease Activity Score with a 28 joint count
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DIP	Distal interphalangeal joint
DMC	Data Monitoring Committee
DMARD	Disease modifying anti-rheumatic drug
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic self-rated version, Columbia Suicide Severity Rating Scale
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
Exposure-Response Analysis	mechanism-based modeling and simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the analysis at week 52.
End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject

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Abbreviation or Term	Definition/Explanation
ESR	Erythrocyte sedimentation rate
HAQ-DI	Health Assessment Questionnaire – Disability Index
IB	Investigator’s Brochure
IPIM	Investigational Product Instruction Manual
IWR	Interactive Web Response. Web based technology that is linked to a central computer in real time as an interface to collect and process information.
IL	Interleukin
IP	Investigational product
NSAID	Nonsteroidal anti-inflammatory drug
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PHQ-8	Patient Health Questionnaire–8 depression scale
PK	Pharmacokinetics
PPD	Purified protein derivative
PRN	Pro re nata: “as needed”
PRO	Patient reported outcome
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
Q2W	Every other week
WBC	White blood cell
w/v	Weight per volume
SF-36v2	Medical Outcomes Health Survey Short Form 36 items version 2
SC	Subcutaneous
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TBL	Total bilirubin
TNF	Tumor necrosis factor

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1. OBJECTIVES

1.1 Primary

To evaluate the efficacy of brodalumab, (210 mg every 2 weeks (Q2W); and 140 mg Q2W) compared to placebo, in subjects with psoriatic arthritis, as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at week 16.

1.2 Key Secondary

To evaluate the efficacy of brodalumab compared to placebo on the following:

- Psoriasis Area and Severity Index (PASI) 75 at week 16
- Van der Heijde modified Total Sharp score (mTSS) at week 24

1.3 Other Secondary

To evaluate the effect of brodalumab on mTSS at weeks 52 and 100.

To evaluate the effect of brodalumab compared to placebo, at other measured timepoints, on the following:

- ACR20
- PASI 75

To evaluate the effect of brodalumab compared to placebo on the following at all measured timepoints:

- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- ACR50
- ACR70
- Disease Activity Score with a 28 joint count and C-reactive protein (DAS 28)
- Components of ACR
- Dactylitis
- Enthesitis
- PASI 90 and 100
- Involved Body Surface Area (BSA)
- Clinical Disease Activity Index (CDAI) score
- Psoriasis Symptom Inventory responder definition
- Psoriatic Arthritis Response Criteria (PsARC)
- Psoriatic Arthritis Disease Activity Score (PASDAS)
- Dermatology Life Quality Index (DLQI)
- Medical Outcomes Health Survey Short Form 36 items version 2 (SF-36v2)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

To characterize the pharmacokinetics (PK) of brodalumab

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To explore brodalumab exposure/response relationship

1.4 Exploratory

To explore the effect of treatment with brodalumab on laboratory parameters of interest (ie, inflammatory markers).

To evaluate self-administration of brodalumab.

To collect blood 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 psoriatic arthritis and/or subject response to brodalumab (this part of the study is optional).

1.5 Safety

To evaluate the safety profile of brodalumab in subjects with psoriatic arthritis.

2. BACKGROUND AND RATIONALE

2.1 Psoriatic Arthritis

Psoriatic arthritis is a heterogeneous chronic inflammatory disorder involving joints, tendon sheaths, entheses, and the axial skeleton as well as skin and nails. It is classified as a sero-negative spondyloarthropathy and presents with several clinical phenotypes varying from oligoarticular disease to severely destructive arthritis mutilans.

Psoriatic arthritis can develop at any age but most commonly appears between the ages of 30 and 50. It may be associated with significant disability and joint damage (Olivieri et al, 2010). According to the National Psoriasis Foundation, between 10 and 30% of patients with chronic psoriasis suffer from psoriatic arthritis (www.psoriasis.org). On average it tends to appear about 10 years after the first signs of psoriasis, however, in about 1 in 7 cases the joint involvement precedes the skin manifestation.

2.2 Amgen Investigational Product Background (brodalumab)

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

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

For the most up-to-date information regarding brodalumab, including the efficacy and safety profile demonstrated in the phase 2 psoriatic arthritis study (Study 20101227), please consult the current version of the [brodalumab Investigator's Brochure](#) (IB).

Refer to Section 4 of the IB for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Rationale

2.3.1 Clinical

Genetic risk factors implicate the IL-23 pathway and the induction and regulation of type 17 T-helper (Th17) cells in the pathogenesis of both psoriasis and psoriatic arthritis. Upregulation of cytokines such as IL-22 and IL-17 could not only lead to hyperproliferation of keratinocytes, but potentially synoviocytes resulting in cellular proliferation and inflammation in both the skin and joints ([Nograles et al, 2009](#)). Th17 cells have been found to be 10 fold higher in the synovial fluid and psoriatic plaques of psoriatic arthritis patients than osteoarthritis controls ([Raychaudhuri et al, 2012](#)). Circulating Th17 cells have been found to be more numerous in patients with spondyloarthropathies (psoriatic arthritis and ankylosing spondylitis) than in rheumatoid arthritis patients ([Jandus et al, 2008](#)). These data suggest a potential role for IL-17 in the pathogenesis and ongoing inflammation of psoriatic disease, with similarity in inflammatory pathways for both skin and joint inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids are considered first-line therapy and are useful to relieve pain and stiffness. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs), alone or in combination, are recommended and have been successfully employed in the treatment of psoriatic arthritis ([Gossec et al, 2012](#); [Ritchlin et al, 2009](#)). Non-biologic DMARDs such as methotrexate, sulfasalazine and leflunomide not only impact the signs and symptoms of psoriatic arthritis but have shown some efficacy in psoriatic skin disease ([Gupta et al, 1990](#); [Heydendael et al, 2003](#); [Kaltwasser et al, 2004](#)). Although the efficacy of these drugs on structural damage has been questioned, it should be noted that optimally dosed, sized and designed studies have not been conducted with these agents ([Ash et al, 2012](#)). On the other hand, anti-tumor necrosis factor (TNF) therapies

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have been adequately evaluated and are highly effective for both the joint and skin manifestations of psoriatic arthritis. However, there remains a significant unmet need for drugs with novel mechanisms of action targeting the growing pool of patients who do not respond to, lose their response to, or do not tolerate TNF inhibitors.

The study participants will be similar to those who were enrolled in the phase 2 study and will consist of subjects who have had active psoriatic arthritis for at least 6 months and currently meet the Classification of Psoriatic Arthritis [CASPAR] criteria. Only subjects who have had an inadequate response to or are intolerant of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or non-biologic DMARDs will be enrolled. The study population will include subjects who are naïve to biologic therapies as well as subjects who have previously used biologic therapies, primarily TNF- α inhibitors. Based on experience from the phase 2 psoriatic arthritis study, it is predicted that approximately 60% of prior biologics users will be primary and secondary TNF- α inhibitor failures due to lack of efficacy while the rest would be subjects who discontinued drug due to intolerance or other non-specified reasons. Finally, to enrich the population for subjects with active disease with radiographic involvement, study participants would be required to have at least 1 erosion of the hands or feet or high CRP (≥ 1.0 mg/dL).

2.3.2 Phase 2 Results

The 12 week double-blind period of the phase 2 study (20101227) in subjects with psoriatic arthritis has ended, and brodalumab was shown to be more efficacious than placebo at both doses evaluated (140 and 280 mg Q2W) as demonstrated by the primary endpoint (ACR20 response) and several secondary endpoints (eg, ACR 50, DAS28, CDAI) at week 12. There was also evidence of additional improvement from weeks 12 to 24 (the open label phase of the study), suggesting that optimal efficacy would require more than 12 weeks of treatment. Furthermore, the 2 doses of brodalumab (140 and 280 mg Q2W) exhibited an acceptable safety profile. For more details, see the [brodalumab IB](#).

2.3.3 Dose Rationale

The 2 doses of brodalumab evaluated in phase 2 (140 and 280 mg) were shown to be more efficacious than placebo. Although the phase 2 study was not adequately powered to formally differentiate between the 2 tested doses, numerical trends favoring the 280 mg dose for a number of endpoints (ACR components, CDAI, BASDAI, Psoriasis Symptom Inventory) were observed. Thus, despite the meaningful efficacy demonstrated with the 140 mg dose in the first 12 weeks of the study, it will be

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necessary to include a higher dose in the larger phase 3 program to ensure the identification of the optimal dosing regimen for brodalumab in the treatment of subjects with psoriatic arthritis.

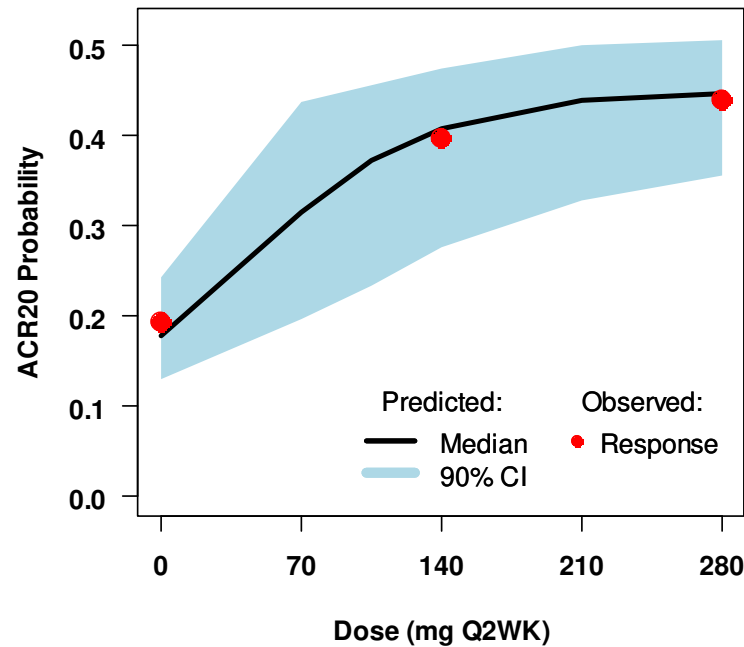
Brodalumab exhibits non-linear pharmacokinetic behavior typical for monoclonal antibodies that undergo target-mediated drug disposition. Brodalumab exposure, as assessed by pharmacokinetic parameters of C_{max} and AUC_{0-t} , indicated nonlinear pharmacokinetics across dose levels between 140 and 280 mg subcutaneous brodalumab. Using combined results from phase 2 pharmacokinetic sub-studies in subjects with psoriasis, asthma, and psoriatic arthritis, C_{max} and AUC_{0-t} increased approximately 2.2- and 2.5-fold, respectively, for 210 vs 140 mg and increased approximately 3- and 3.7-fold, respectively, for 280 vs 140 mg. Although 210 mg was not tested in subjects with psoriatic arthritis, exposures to 210 mg are expected to be similar to those for subjects in other indications including psoriasis.

To support phase 3 dose selection for the psoriatic arthritis studies, a semi-mechanistic pharmacokinetic (PK)/pharmacodynamic (PD) model was developed to characterize the time-course of ACR response. Monte Carlo simulation based on the model was used to simulate the ACR20 response time-course for a range of doses. From this simulation, brodalumab week 12 ACR20 dose-response was then plotted (Figure 1). The shaded region represents the 90% confidence interval of the model prediction. The semi-mechanistic model predicted that administration of 140 mg would provide near maximal week 12 ACR20 response, whereas the 210 mg dose was predicted to be on the response plateau with similar efficacy to the 280 mg dose.

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Figure 1. Observed and Semi-mechanistic PK/PD Model Predicted Week 12 ACR20 Response (and 90% Confidence Interval) in Brodalumab Phase 2 Study in Psoriatic Arthritis

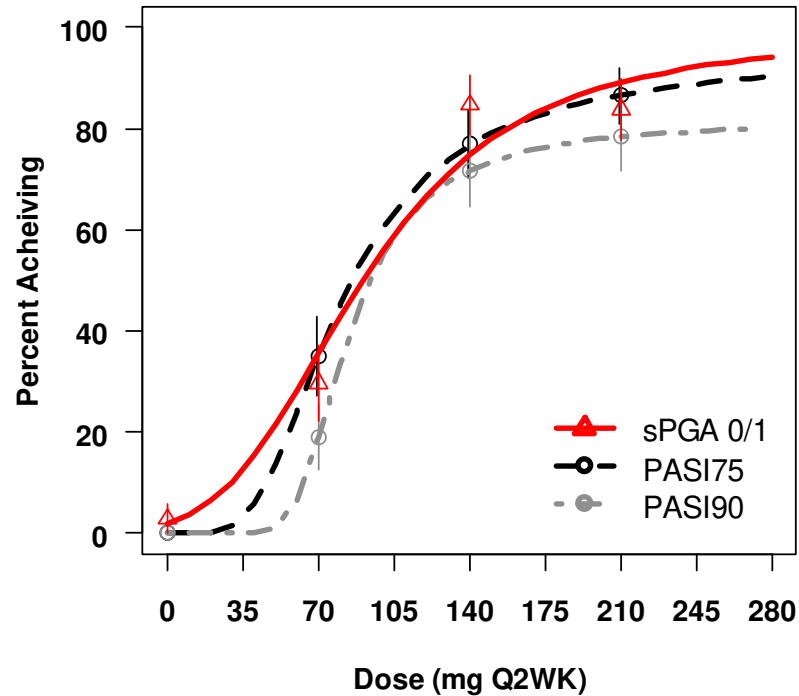


While not studied in the phase 2 psoriatic arthritis study, the predicted response at doses below 140 mg are expected to be sub-optimal, consistent with the observed dose-response of PASI score from the phase 2 psoriasis study (Figure 2). In that study, the 70 mg Q2W dose was shown to have sub-optimal efficacy, the 140 mg Q2W dose was shown to be sub-maximally efficacious, whereas the 210 mg Q2W dose (observed) and the 280 mg Q2W dose (predicted) were required to provide maximal PASI improvement.

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Figure 2. Observed and EMAX Model Predicted Week 12 Dose Response in Brodalumab Phase 2 Study in Psoriasis



Thus, 210 and 140 mg are the doses selected for evaluation in the phase 3 psoriatic arthritis program.

2.4 Clinical Hypotheses

The primary hypothesis of this study is that brodalumab (140 mg Q2W and 210 mg Q2W) will demonstrate greater efficacy than placebo, as measured by the proportion of subjects who achieve an ACR20 response at week 16.

The secondary hypotheses of this study are that brodalumab (210 mg Q2W and 140 mg Q2W) will demonstrate greater efficacy than placebo, as measured by:

- the proportion of subjects with PASI 75 response at week 16
- the mean change from baseline in mTSS at week 24

3. EXPERIMENTAL PLAN

3.1 Study Design

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

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This is a randomized, double-blind, placebo-controlled study with a long term extension for subjects with psoriatic arthritis.

Subjects will be randomized in a 1:1:1 ratio to receive brodalumab (140 mg or 210 mg) or placebo. Randomization will be stratified by baseline body weight, prior use of a biologic, and geographic region ([Section 5.1](#)). Starting at the week 24 visit, subjects in the placebo group will receive 210 mg brodalumab for the duration of the study.

To minimize risk to study participants, subjects will be evaluated for inadequate response starting at week 14 (see [Section 6.2.1.1](#)) and evaluated for nonresponse starting at week 28 (see [Section 6.2.1.3.3](#)). Inadequate responders will be eligible for initiation and/or dose adjustment of methotrexate, sulfasalazine or leflunomide, non-biologic DMARDs that have demonstrated efficacy, are part of the standard of care in the treatment of psoriatic arthritis, and can be used in combination with brodalumab without requiring a washout period. For nonresponders, investigational product (IP; brodalumab) will be discontinued and any available treatment, including the use of biologic DMARDs after an appropriate washout period, will be allowed.

Treatment assignments will remain blinded until after all subjects have reached week 52 or early termination visit and all data up to week 52 has been collected. This is to ensure the blind is protected for the primary endpoint at week 16 and the secondary endpoints at measured timepoints up to week 52. After treatment assignments have been unblinded, subjects will continue to receive open label brodalumab at their current dose Q2W.

The entire study will be up to 166 weeks (approximately 3 years) in duration.

The safety of study participants will be evaluated on an ongoing basis by the Amgen global safety team. In addition, during the blinded portion of the study, there will be regular review of unblinded safety data by an independent Data Monitoring Committee (DMC). Membership, meeting frequency, and other details will be defined in the DMC charter.

The study endpoints are defined in [Section 10.1.1](#).

3.2 Number of Sites

The study will be conducted at approximately 130 centers in the United States, Canada, Europe and Latin America. Other regions may be added as needed. Sites that do not enroll subjects within 2 months of site initiation may be closed.

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3.3 Number of Subjects

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

Approximately 630 subjects will be enrolled into the study. Rationale for the sample size is provided in [Section 10.2](#).

For approximately 15% of the subjects (80-110 subjects), samples at 5 additional timepoints for pharmacokinetic analysis will be collected as a optional substudy (according to the schedule in [Section 7.3.13.2.2](#)).

An additional pharmacogenetic substudy will be conducted in all subjects willing to participate, ie, this will be an optional component of the overall study.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

After signing the informed consent, subjects should be randomised within 30 days. Subjects will participate in the study for up to approximately 166 weeks (includes up to 30 days for screening) or until the investigator’s recommendation of discontinuation, Amgen’s recommendation of discontinuation, the subject’s decision to discontinue for any reason, or an administrative decision to close the study is made for any reason, including, but not limited to, no proven or insufficient efficacy demonstrated on the primary analysis.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the analysis at week 52.

End of Trial: the time when the last subject is assessed.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Web Response (IWR) system.

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

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4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

- 101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures.
- 102 Subject is ≥ 18 years of age at time of screening
- 103 Subject has had a diagnosis of psoriatic arthritis for at least 6 months and currently meets the CASPAR criteria
- 104 Subject has ≥ 3 tender and ≥ 3 swollen joints (excluding the distal interphalangeal joints as part of a 66/68 joint count) at screening and at baseline
- 105 Subject has at least one erosion of the hands or feet (centrally read) or CRP ≥ 1.0 mg/dL
- 106 Subject has an active psoriatic skin lesion (at least one psoriatic plaque approximately 2 cm or more in diameter)
- 107 Subject has a history of intolerance or inadequate response to NSAIDs and/or DMARDs for psoriatic arthritis
- 108 For subjects receiving NSAIDs (including as needed use [PRN]): the subject must be on a stable dose for ≥ 4 weeks prior to initiation of investigational product
- 109 For subjects receiving methotrexate, sulfasalazine or leflunomide: subject has received treatment for ≥ 3 months, with a stable dose (not to exceed 25 mg methotrexate per week, 3 g sulfasalazine per day or 20 mg leflunomide per day) for ≥ 4 weeks prior to initiation of investigational product
- 110 For subjects receiving oral corticosteroids: the subject must be on a stable dose (not to exceed the equivalent of 10 mg of prednisone per day) for ≥ 4 weeks prior to initiation of investigational product

4.1.2 Exclusion Criteria

Other Medical Conditions

- 201 Subject has known history of active tuberculosis
- 202 Subject has a positive test for tuberculosis during screening defined as either:
- positive purified protein derivative (PPD) (≥ 5 mm of induration at 48 to 72 hours after test is placed)
- OR
- positive Quantiferon test.
 - Subjects with a positive PPD and a history of Bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test.
 - Subjects with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have ALL of the following:
 - no symptoms per tuberculosis worksheet provided by Amgen
 - documented history of a completed course of adequate prophylaxis (completed treatment for latent TB) per local standard of care prior to the start of investigational product

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- no known exposure to a case of active tuberculosis after most recent prophylaxis
 - no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product
- 203 Subject has a planned surgical intervention between baseline and the week 52 evaluation
- 204 Subject has an active infection or history of infections as follows:
- any active infection for which systemic anti-infectives were used within 28 days prior to first investigational product dose
 - a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first investigational product dose
 - recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject
- 205 Subject has any systemic disease (eg, renal failure, heart failure, hypertension, liver disease, diabetes, anemia) considered by the investigator to be clinically significant and uncontrolled.
- 206 Subject has known history of human immunodeficiency virus
- 207 Subject has positive hepatitis B surface antigen, hepatitis B core antibody or hepatitis C virus antibody serology
- 208 Subject had myocardial infarction, unstable angina pectoris or stroke within the past 12 months prior to the first investigational product dose
- 209 Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
- 210 Subject has history of malignancy within the last 5 years EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, in situ cervical cancer or in situ breast ductal carcinoma
- 211 Subject has any concurrent medical condition or electrocardiogram (ECG) abnormality that, in the opinion of the investigator, could cause this study to be detrimental to the subject.
- 212 Subject has active Crohn's disease or a history of Crohn's disease

Laboratory Abnormalities

- 213 Subject has any of the following laboratory abnormalities at screening:
- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal (ULN)
 - serum direct bilirubin ≥ 1.5 mg/dL (25.7 $\mu\text{mol/L}$)
 - white blood cell (WBC) count < $3.00 \times 10^3/\mu\text{L}$
 - absolute neutrophil count (ANC) < $2.00 \times 10^3/\mu\text{L}$
 - Subject has any other laboratory abnormality, which, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results

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Washouts or Other Treatments

- 214 Subject has used any of the following within 28 days of investigational product initiation:
- hydroxychloroquine
 - cyclosporine
 - systemically administered calcineurin inhibitors
 - azathioprine
 - parenteral corticosteroids including intramuscular or intraarticular administration
 - live vaccines
- 215 Subject has used a narcotic analgesic within 24 hours prior to the baseline visit
- 216 Subject has used topical therapy as follows:
- super-potent or potent topical steroids or topical anthralin/dithranol within 28 days before first dose of investigational product
 - any other formulation or potency of topical therapy within 14 days before first dose of investigational product (exception: upper mid-strength or lower potency topical steroids permitted on the face, axillae, and groin; bland emollients [without urea or alpha or beta hydroxy acids]; shampoo without steroids.
- 217 Subject has used the following within 28 days of first dose of investigational product: ultraviolet A light therapy (with or without psoralen); ultraviolet B light therapy; excimer laser; oral retinoids; thioguanine; hydroxyurea; fumarates for psoriasis; other non-biologic systemic therapy for psoriasis.
- 218 Subject has used commercially available or investigational biologic therapies for psoriasis and/or psoriatic arthritis as follows:
- anti-tumor necrosis factor (TNF) therapy within 2 months prior to investigational product initiation
 - other experimental or commercially available biologic therapies for psoriasis and/or psoriatic arthritis within 3 months prior to investigational product initiation
 - anti-IL17 or anti-IL12/IL23 biologic therapy, including brodalumab, secukinumab, ixekizumab, ustekinumab, briakinumab at any time
 - rituximab at any time

General

- 219 Subject is currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s) prior to screening.
- 220 Other investigational procedures while participating in this study are excluded.
- 221 Subject has known sensitivity to any of the products or components to be administered during dosing.
- 222 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures through week 24

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(eg, Patient Reported Outcomes [PROs]) to the best of the subject and investigator's knowledge.

- 230 Subject has a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia Suicide Severity Rating Scale (eC-SSRS) at screening or at baseline**
- 231 Subject has a history or evidence of a **psychiatric disorder** or substance abuse that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- 232 Subject has severe depression based on a total score of ≥ 15 on the Patient Health Questionnaire-8 (PHQ-8) at screening or baseline. (note: subjects with a total score of 10-14 on the PHQ-8 should be referred to a mental health professional)**
- 224 Subject has a history or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- 225 Subject previously has entered this study.
- 226 Women who are pregnant or planning to become pregnant while on study through 8 weeks after the last dose of Amgen study drug.
- 227 Women with a positive pregnancy test (assessed by a serum pregnancy test during screening and a urine pregnancy test at baseline) women who have had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or are at least 2 years postmenopausal, with postmenopausal status confirmed by follicle-stimulating hormone [FSH] in the postmenopausal range are not required to have pregnancy tests.
- 228 Women of reproductive potential who are not willing to use an acceptable form of birth control during the study and for an additional 8 weeks after the last dose of study drug.
- 229 Women who are lactating/breastfeeding or planning to breastfeed during the study and for an additional 8 weeks after the last dose of Amgen study drug.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see [Section 11.2](#)). All subjects must personally sign and date the IEC/IRB and Amgen approved informed consent form before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

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Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned using interactive web response (IWR) system. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not be the same as the randomization number assigned for the study. The subject identification number will be assigned in sequential order in the format 406XXXXX### where "XXXXX" refers to the site number and "###" refers to the sequential subject ordering (eg, 40666001001, 40666001002).

5.1 Randomization/Treatment Assignment

Subjects will be randomly assigned (randomized) to receive brodalumab 210 mg, brodalumab 140 mg or placebo in a 1:1:1 ratio via IWR system at baseline. The randomization will be stratified by baseline body weight (≤ 100 kg, > 100 kg), prior biologic use and geographic region (North America, Central and Eastern Europe, Western Europe, and Latin America). The randomization lists will be generated by Amgen using a permuted block design within each stratum. Subjects with prior use of biologics will be capped at no more than 60% of the global study population. Subjects naïve to biologics will also be capped at no more than 60% of the global study population. Each randomized subject will receive a single, unique randomization number.

The randomization date is to be documented in the subject's medical record and on the enrollment eCRF.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should be unblinded only when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding is via IWR system with appropriate access level. Unblinding at the study site for any other reason will be considered a protocol deviation.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, will provide guidance on how to unblind via IWR system. Once a subject's treatment assignment is unblinded via IWR system, the subject will not be allowed to

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receive any further investigational product. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, **provided that this does not compromise subject safety**, but must do so within 1 working day after the event and must document the unblinding in the subject's eCRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product and/or placebo in this study will be brodalumab and placebo for brodalumab.

The IPIM, contains detailed information regarding the storage, preparation, and administration of brodalumab.

The medical device(s) used in this study include: prefilled syringes, alcohol swaps and sharps containers.

6.2 Amgen Investigational Product [brodalumab]

Brodalumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Brodalumab will be presented as 140 mg/mL brodalumab, 10 mM L-glutamate, 3% (weight per volume, w/v) L-proline, 0.01% (w/v) polysorbate 20, pH 4.8 in a prefilled syringe (0.5 or 1.0 mL fill). Brodalumab will be packaged in dispensing packs containing 2 prefilled syringes. **During the open-label phase 140 mg dose will be packaged in dispensing packs containing 1 pre-filled syringe.**

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

6.2.1 Dosage, Administration, and Schedule

All subjects will receive 2 subcutaneous injections of IP (one 1.0 mL and one 0.5 mL) on day 1 and weeks 1, 2, 4, and then every 2 weeks through week 22. These injections will be brodalumab and/or placebo, depending upon randomized arm.

Starting at week 24, subjects who were originally randomized to placebo and have not already met criteria for inadequate response ([Section 6.2.1.1](#)) will receive 210 mg Q2W with an additional dose at week 25. Subjects who were originally randomized to either of the brodalumab treatment arms will remain on the same dose Q2W with an additional dose of IP (placebo) at week 25 to maintain the blind.

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After treatment assignments are unblinded, all subjects will receive open label brodalumab at their current dose Q2W.

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

6.2.1.1 Inadequate Response

Starting at week 14 (through week 34), subjects will be assessed for inadequate response to IP (defined by the failure to achieve $\geq 10\%$ improvement from baseline in their tender and swollen joint counts at 2 consecutive scheduled visits [eg, weeks 14 and 16] where joint counts are assessed). The inadequate response criteria will be administered through the IWR system using the joint counts that are entered via IWR system.

If the criteria for inadequate response are met, initiation and/or dose adjustments of the following non-biologic DMARDs will be allowed: methotrexate, not to exceed 25 mg/week; sulfasalazine, not to exceed 3 g/day; or leflunomide, not to exceed 20 mg/day. For subjects currently receiving treatment with one or more of these medications, the dose can be titrated upwards per local standard of care. Methotrexate and leflunomide cannot be used concurrently.

Additionally, initiation and/or dose adjustments of oral corticosteroids (not to exceed the equivalent of 10 mg of prednisone per day) and NSAIDs can be used to supplement treatment with non-biologic DMARDs in these subjects.

Furthermore, the subjects with inadequate response who are receiving placebo will begin treatment with 210 mg brodalumab Q2W. Subjects receiving 140 and 210 mg brodalumab Q2W will continue to receive the same dose of brodalumab. To maintain the blind, all subjects who meet the criteria for inadequate response will receive an additional dose of IP one week after the criteria has been met: brodalumab for subjects previously on placebo and placebo for subjects previously on brodalumab.

Inadequate response may only be assessed at a scheduled visit per [Section 7.1](#).

6.2.1.2 Administration

Through the week 34 visit, doses of IP must be given within ± 3 days from the scheduled dose date. Starting at week 36, doses of IP must be administered ± 7 days from the scheduled dose date; however, any 2 consecutive doses must be at least 7 days apart (other than the doses at week 1 and week 25, or the dose that is administered 1 week after a change in IP due to meeting the criteria for inadequate response). If that window

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is missed, that dose will not be administered. The next dose will be administered at the next scheduled dosing date. When an injection is to be administered on the same day as a study visit, it should not be administered until all other study visit procedures have been completed.

IP will be administered via subcutaneous injections to the abdomen, thigh, or upper arm. Subsequent injections may be administered to the same body region.

Through week 34, IP will be administered by a qualified staff member after all other study visit procedures have been completed, according to [Table 1](#).

Starting at week 36 and through the end of the study, subjects may self-administer IP every other week by subcutaneous injection (“self-administration” includes administration by a trained designated person). Before a subject may begin self-administration, it is the responsibility of the study staff to ensure that the subject or the subject’s designated person is trained to prepare and administer the injection. All subjects or their designated person will receive training and study tools designed to educate the subject on the proper storage and self-administration of IP. The completion of training on self-administration (or training of a designated person) will be recorded in the source documentation.

The first self-administered dose must be administered in the office by the subject or the trained designated person. After the first self-administered dose, doses will be administered by the subject or trained designated person (in-office dosing is not required). Subjects will be supplied with a diary in which to record the date, time, and injection site of each study dose, whether the full dose was injected, and any potential adverse events and changes to concomitant medications. Study site staff will review the diary with the subject at each clinic visit and transcribe all pertinent information onto the eCRF. The diaries will be retained at the study site as part of the source documentation once a subject has completed his/her study participation.

The date, time, administered volume of IP and reason for dose change will be recorded on the individual subject’s eCRF.

Starting at week 36, supplies of brodalumab will be dispensed according to [Table 1](#) to subjects for self-administration. The site will ensure that each subject is supplied with all necessary materials required for self-administration.

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6.2.1.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Subjects who discontinue investigational product should be requested to continue to return for all other study procedures and measurements through the end of the study. At a minimum, the subjects should return at the key timepoints of weeks 16, 24, 52, and 100 for study procedures and measurements including radiographs of the hands and feet. Discontinuation from investigational product is addressed in [Section 8](#), separately from withdrawal from study to avoid missing information.

6.2.1.3.1 Absolute Neutrophil Count Abnormalities

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

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

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

- During the first 36 weeks of the study, other visit procedures (including CBC) should be completed as scheduled but dosing should be held.
- After week 36, the subject should be contacted and instructed to hold the dose(s) and to return to the clinic as soon as possible for a repeat CBC.

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

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

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

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

6.2.1.3.2 Infections

The scheduled dose should not be administered if the subject has an infection for which systemic anti-infectives are indicated. In addition, the dose should not be administered if the subject has signs and/or symptoms of an infection that, in the opinion of the investigator, warrant holding the dose. The dose should be delayed or withheld until the infection has resolved in the opinion of the investigator (regardless of completion of

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antibiotics). If the dosing window is missed because of persistent infection, that dose should not be administered. The next dose should be administered at the next scheduled dosing date (unless the infection is still unresolved).

6.2.1.3.3 Nonresponse

Nonresponse may only be assessed at a scheduled visit, through week 52 ([Section 7.1](#)). After week 52, nonresponse may also be assessed at unscheduled visits. From week 28 through week 34, subjects who do not achieve $\geq 10\%$ improvement from baseline in their tender and swollen joint counts at any visit despite ≥ 12 weeks of continuous IP after meeting the criteria for inadequate response (outlined in [Section 6.2.1.1](#)) will be considered nonresponders. Investigational product will be discontinued in these subjects and they will be allowed any treatment deemed suitable by the investigator, including biologic DMARDs.

At or after week 36 (through the end of study), subjects who do not achieve $\geq 20\%$ improvement from baseline in their tender and swollen joints at any visit despite ≥ 12 weeks of continuous IP with or without initiation and/or dose adjustments of concomitant medications will be considered nonresponders. Investigational product will be discontinued in these subjects and they will be allowed any treatment deemed suitable by the investigator including biologic DMARDs.

Biologic DMARDs can only be used to treat nonresponders 8 weeks after the last dose of investigational product.

6.2.1.3.4 Suicidal Ideation or Behavior

Suicidal ideation and behavior will be assessed using the eC-SSRS. IP should be permanently discontinued according to the following rules:

- **subject reports suicidal ideation after randomization, with severity of 4 or 5**
- or
- **subject reports any suicidal behavior after randomization.**

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

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6.2.1.3.5 Depression

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

6.3 Hepatotoxicity Stopping and Rechallenge Rules

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

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the [FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009](#)).

6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Brodalumab should be discontinued permanently and the subject should be followed according to the recommendations in [Appendix A](#) (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

TBL > 2x upper limit of normal (ULN) or INR > 1.5

AND increased AST or ALT from the relevant baseline value as specified below:

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

AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

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- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational product outlined in [Section 6.3.1](#) and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

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

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

OR: TBL > 3x ULN at any time

OR: ALP > 8x ULN at any time

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Brodalumab should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in [Appendix A](#) for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline ([Section 6.3.3](#)).

Subjects who experience an increase in ALT or AST to > 3X ULN, even with a normal serum bilirubin, should undergo a period of special observation as outlined in [Appendix A](#).

6.3.3 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then brodalumab should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Section 6.3.1](#)) should never be rechallenged.

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.7](#).

Concomitant therapies are to be collected in the eCRF from informed consent through the end of study. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

Below is guidance regarding use of analgesics, NSAIDs, corticosteroids and DMARDs:

6.4.1 Analgesics

Acetaminophen may be used by the subject as needed (PRN) except within 12 hours before a scheduled study efficacy evaluation. Narcotic analgesics will only be allowed at or after week 16 for subjects who meet the criteria for inadequate response ([Section 6.2.1.1](#)) or at or after week 28 for subjects who meet the criteria for nonresponse ([Section 6.2.1.3.3](#)) but must be withheld for 24 hours prior to a scheduled visit.

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6.4.2 NSAIDs

If the subject enters the study taking an NSAID, the dose of NSAIDs can be reduced or discontinued during the study if necessary for safety reasons or standard of care. In cases of flare, the dose of NSAIDs can be temporarily increased as needed. However, the subject must return to the maintenance dose (the NSAID dose at baseline) as soon as the flare resolves. In subjects not taking an NSAID, one may be added temporarily to treat a flare in psoriatic arthritis. It should be tapered and discontinued with resolution of flare.

If the subject meets the criteria for inadequate response at or after week 16 ([Section 6.2.1.1](#)) NSAIDs may be initiated or adjusted.

6.4.3 Corticosteroids

Subjects taking oral corticosteroids (not to exceed the equivalent of 10 mg of prednisone per day) must remain on a stable dose.

If the subject meets the criteria for inadequate response at or after week 16 ([Section 6.2.1.1](#)) corticosteroids may be initiated or adjusted.

6.4.4 Non-biologic DMARDs

Subjects taking either methotrexate (not to exceed 25 mg/week), sulfasalazine (not to exceed 3 g/day) or leflunomide (not to exceed 20 mg/day) must remain on a stable dose. Subjects may not use a combination of methotrexate and leflunomide.

If the subject meets the criteria for inadequate response at or after week 16 ([Section 6.2.1.1](#)) non-biologic DMARDs may be initiated or adjusted.

6.5 Medical Devices

Pre-filled syringes will be used in this study and provided by Amgen. They will be used to administer IP. Additional details will be provided in the IPIM.

Medical devices (eg, syringes, sterile needles) that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices. Once subjects begin self-administration of investigational product, Amgen will provide puncture resistant containers, alcohol swabs, and a tote bag.

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6.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen is to be reported according to the instructions provided in the IPIM.

6.7 Excluded Treatments and/or Procedures During Study Period

6.7.1 Primary Treatment Period (baseline through week 52)

The following medications are proscribed during this treatment period except for the treatment of nonresponders ([Section 6.2.1.3.3](#)):

- narcotic analgesics (eg, hydrocodone, oxycodone, codeine, tramadol, and/or propoxyphene) are only allowed for subjects who meet the criteria for inadequate response at or after week 16.
- intraarticular injections of corticosteroids
- gold
- hydroxychloroquine
- intraarticular hyaluronic acid injections
- TNF antagonists (eg, etanercept, infliximab, adalimumab) or any other biologics, approved for the treatment of psoriatic arthritis (can be used only after an 8-week washout of brodalumab)

The following medications are proscribed during this treatment period:

- any investigational agent other than brodalumab
- abatacept
- anakinra
- Azathioprine
- chronic minocycline or tetracycline (except use for ≤ 10 days to treat infection, or for non-psoriatic arthritis indications, eg, acne)
- cyclosporine
- systemically administered calcineurin inhibitors
- cytotoxic agents including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- live vaccines
- mycophenolate mofetil
- Prosurba Column
- rituximab

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- efalizumab
- tacrolimus
- tocilizumab
- other immuno-modulating biologic agents with the exception of those approved for the treatment of psoriatic arthritis, which can be used to treat non responders starting at week 28
- ultraviolet A light therapy (with or without psoralen)
- ultraviolet B light therapy
- thioguanine
- oral retinoids
- hydroxyurea
- fumarates for psoriasis or psoriatic arthritis
- topical therapy
 - 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

6.7.2 Long Term Extension Treatment Period (week 52 through week 162)

Proscribed medications during this treatment period include the following:

- any investigational agent other than brodalumab
- abatacept
- anakinra
- azathioprine
- cytotoxic agents including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- live vaccines
 - 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 should not be reinitiated for at least 28 days.
- rituximab
- efalizumab
- TNF antagonists (eg, etanercept, infliximab, adalimumab) except for the treatment of nonresponders (after an 8-week washout of brodalumab)
- tocilizumab

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- other immuno-modulating biologic agents with the exception of those approved for the treatment of psoriatic arthritis, which can be used to treat nonresponders (after an 8-week washout of brodalumab).

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and [Table 1](#) can only be performed after obtaining informed consent. This includes any modifications of the subject's medication for the purpose of participation in this study.

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

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

7.1 Schedule of Assessments

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**Table 1. Schedule of Assessments
 Screening Through Week 52**

Study Visit-Week	Scr	BL	1	2	4	6	8	10	12	14	16	18	20	22	24	25	26	28	30	32	34	36	40	44	48	52/ET ^b	
Informed consent	X																										
Randomization via IWR		X																									
Patient Reported Outcomes																											
Patient Global Assessment		X		X	X		X		X		X		X		X			X				X				X	
HAQ-DI		X		X	X		X		X		X		X		X			X				X				X	
BASDAI		X							X		X				X											X	
DLQI		X		X	X		X		X		X		X		X			X				X				X	
SF-36v2		X							X		X				X							X				X	
eDiary dispense / retrieve	X														X										X	X	
Psoriasis Symptom Inventory																										Daily	
General and safety assessments																											
Medical / Medication History	X																										
Demography	X																										
Physical examination	X	X							X						X							X				X	
Height	X																										
Weight	X	X							X						X							X				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	←-----→																										
Adverse Events	←-----→																										
Concomitant Medications	←-----→																										
Electrocardiogram	X														X											X	
Chest X-ray	X ^c																										
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease assessments																											
Joint Count Assessment	X	X		X	X		X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment		X		X	X		X		X		X		X		X			X				X				X	
Dactylitis / Enthesitis		X		X					X		X				X							X				X	
PASI / Involved Body Surface Area		X		X	X		X		X		X		X		X			X				X				X	
Radiographs of hands and feet ^a	X														X											X	

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Scr = screening; BL = baseline; eDiary = electronic handheld device; PASI = Psoriasis Area and Severity Index;

^a Any subject who satisfies the inadequate response criteria between weeks 16 and 18 or satisfies the nonresponse criteria between weeks 28 and 36 must obtain additional radiographs of hands and feet within 14 days.

^b Any subject who discontinues prior to week 52 should complete the week 52 assessments, any subject who discontinues after week 52 should complete the week 160 assessments.

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

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**Table 1. Schedule of Assessments
 Screening Through Week 52 (cont'd)**

Study Visit-Week	Scr	BL	1	2	4	6	8	10	12	14	16	18	20	22	24	25	26	28	30	32	34	36	40	44	48	52/ET ^b	
Laboratory assessments																											
PPD or Quantiferon	X																										
Serum pregnancy test ^d	X																										
Follicle-stimulating hormone ^d	X																										
Urine pregnancy test ^d		X			X		X		X		X		X		X			X		X		X	X	X	X	X	
Hepatitis serology	X																										
Rheumatoid factor		X																									
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X			X		X		X		X		X		X			X		X		X				X	
Urinalysis		X							X						X							X				X	
Fasting lipids		X									X				X											X	
C-reactive protein	X	X		X	X		X		X		X		X		X			X				X				X	
ESR		X		X	X		X		X		X		X		X			X				X				X	
Anti-brodalumab antibodies		X									X														X		
Pharmacokinetic sample		X	X	X	X		X		X	X	X		X												X		
Biomarker blood sample ^{e, f}		X	X								X				X											X	
Investigational Product																											
Investigational product admin ^h		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^g				
Investigational product dispense																						X ^g	X	X	X	X	
Review and collect investigational product self-administration diary																							X	X	X	X	

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

^d If applicable

^e For consenting subjects only.

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

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

^h All subjects who meet the criteria for inadequate response will receive an additional dose of IP one week after the criteria has been met. This will require an extra dosing visit sometime between week 17 and 25 depending on when the criteria are met.

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Table 1. Schedule of Assessments – Week 53 Through End of Study

Study Visit-Week	64	76	88	100	112	124	136	148	160 / early termination ^b	162 ⁿ / End of follow Up
Patient Reported Outcomes										
Patient Global Assessment		X		X					X	
HAQ-DI		X		X					X	
BASDAI		X		X					X	
DLQI		X		X					X	
General and safety assessments										
Physical examination				X					X	
Weight				X					X	
Vital signs	X	X	X	X	X	X	X	X	X	
Serious Adverse Events		←-----→								
Adverse Events		←-----→								
Concomitant Medications		←-----→								
Electrocardiogram				X					X	
eC-SSRS		Every 4 weeks (56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160/ET)								
PHQ-8		Every 4 weeks (56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160/ET)								
Disease assessments										
Joint Counts	X	X	X	X	X	X	X	X	X	
Physician Global Assessment		X		X					X	
Dactylitis / Enthesitis				X					X	
PASI / involved BSA				X					X	
Radiographs of hands & feet ⁱ				X					X ⁱ	
Laboratory assessments										
Urine pregnancy test ^l		←----- at every visit -----→								
Hematology / Chemistry	X	X	X	X	X	X	X	X	X	
Urinalysis				X					X	
Fasting lipids				X					X	
C-reactive protein / ESR		X		X					X	
Anti-brodalumab antibodies				X					X	
Pharmacokinetic sample				X					X	
Investigational Product										
Investigational product dispense	X	X	X	X	X	X	X	X	X	
Review and collect investigational product self-administration diary	X	X	X	X	X	X	X	X	X	

PASI = Psoriasis Area and Severity Index; BSA = body surface area;

^b Any subject who discontinues prior to week 52 should complete the week 52 assessments, any subject who discontinues after week 52 should complete the week 160 assessments.

^h May be by telephone contact

ⁱ any subject who terminates the study prior to week 100 must obtain radiographs of hands and feet as part of the ET visit. Subjects who complete the week 160 visit or terminate the study after week 100 do not need any further radiographs of the hands or feet

^l If applicable

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7.2 General Study Procedures

7.2.1 Screening

Informed consent must be obtained before completing any other screening procedure. After informed consent has been signed, subjects will be screened in order to assess eligibility for study participation. The screening window is 30 days starting from date of signing consent. If a subject has not met all eligibility criteria at the end of the 30-day window the subject will be registered in IWR system as a screen failure. Subjects who screen fail may be eligible to re-screen per [Section 7.2.2](#). Laboratory assessments used to determine subject eligibility may be repeated for confirmation during the screening period before the subject is considered a screen failure.

The following procedures are to be completed during the screening period:

- Confirmation that the informed consent form has been signed
- medical / medication history
- Demographic data including sex, date of birth or age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact of biomarker variability and pharmacokinetics of the protocol-required therapies.
- physical examination
- height and weight
- vital signs
- serious adverse events
- electrocardiogram
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - joint counts
 - radiographs of hands and feet
 - distribution of electronic hand-held device (eDiary) and instructions on its use for collection of daily Psoriasis Symptom Inventory
 - Psoriasis Symptom Inventory will be completed daily during screening.
- laboratory assessments
 - PPD or Quantiferon
 - chest x-ray / TB worksheet (only for subjects with a positive tuberculosis test)
 - serum pregnancy test, if applicable
 - follicle-stimulating hormone, if applicable

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- determination of Hepatitis B and C status
 - o If Hepatitis B status and/or Hepatitis C status is known to be positive by serology, no additional laboratory testing procedures are required
 - o If Hepatitis B and/or Hepatitis C status is not known to be positive by serology, the following laboratory testing is required:
 - Hepatitis B Surface Antigen (HepBsAg) and total Hepatitis B Core Antibody (HepBcAb)
 - If results are HepBcAb positive or HepBsAg positive, no additional testing is necessary
 - Hepatitis C virus antibody
 - If results are Hepatitis C virus antibody positive, no additional testing is necessary
- hematology
- chemistry
- C-reactive protein

7.2.2 Re-screening

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to re-screen twice for a total of 3 screenings. Re-screen subjects must first be registered as screen failures in IWR system and subsequently registered as re-screens. Subjects will retain the same subject identification number assigned at the original screening. Subjects will continue to complete the Psoriasis Symptom Inventory daily during re-screening. A subject must be in re-screening for at least 7 days before being randomized.

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

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

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7.2.3 Baseline

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

- Patient Reported Outcomes
 - Patient Global Assessment
 - HAQ-DI
 - BASDAI
 - DLQI
 - SF-36v2
 - Psoriasis Symptom Inventory (completed daily)
- physical examination
- weight
- vital signs
- serious adverse events
- adverse events
- concomitant medications
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - Joint Counts
 - Physician Global Assessment
 - Dactylitis / Enthesitis
 - PASI
 - Involved Body Surface Area (BSA)
- laboratory assessments
 - urine pregnancy test, if applicable
 - rheumatoid factor
 - hematology
 - chemistry
 - urinalysis
 - fasting lipids
 - C-reactive protein
 - erythrocyte sedimentation rate (ESR)
 - anti-brodalumab antibodies
 - pharmacokinetic sample
 - biomarker blood sample (for consenting subjects only)

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- randomization via IWR
- investigational product administration

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

7.2.4 Week 1 to Week 24

Visits will occur per the Schedule of Assessments ([Table 1](#)). On-study visits may be completed within ± 3 days of the target visit date. Subjects who discontinue investigational product should be requested to continue to return for all other study procedures and measurements. At a minimum, the subjects should return for the weeks 16 and 24 visits and complete all assessments including radiographs of the hands and feet. Subjects ending the study prior to week 24 will be asked to complete an early termination visit per [Section 7.2.7.1](#) and an end of follow-up visit per [Section 7.2.8](#).

The following procedures will be completed as specified in the Schedule of Assessments in [Table 1](#):

- Patient Reported Outcomes
 - Patient Global Assessment
 - HAQ-DI
 - BASDAI
 - DLQI
 - SF-36v2
 - Psoriasis Symptom Inventory
- physical examination
- weight
- vital signs
- serious adverse events
- adverse events
- concomitant medications
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - Joint Counts
 - Physician Global Assessment
 - Dactylitis / Enthesitis
 - PASI / Involved BSA
 - Radiographs of hands and feet

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- laboratory assessments
 - urine pregnancy test, if applicable
 - hematology
 - chemistry
 - urinalysis
 - fasting lipids
 - C-reactive protein
 - ESR
 - anti-brodalumab antibodies
 - pharmacokinetic sample
 - biomarker blood sample, for consenting subjects only
- investigational product administration
- retrieval of eDiary at week 24

7.2.5 Week 25 to Week 52

Visits will occur per the Schedule of Assessments ([Table 1](#)). On-study visits may be completed within **± 3 days through week 36 and then ± 7 days** of the target visit date. Subjects who discontinue investigational product should be requested to continue to return for all other study procedures and measurements. At a minimum, the subjects should return for the week 52 visit and complete all assessments including radiographs of the hands and feet. Subjects ending the study prior to week 52 will be asked to complete an early termination visit per [Section 7.2.7.1](#) and an end of follow-up visit per [Section 7.2.8](#).

The following procedures will be completed as specified in the Schedule of Assessments in [Table 1](#):

- Patient Reported Outcomes
 - Patient Global Assessment
 - HAQ-DI
 - BASDAI
 - DLQI
 - SF-36v2
 - Psoriasis Symptom Inventory
- physical examination
- weight
- vital signs
- serious adverse events
- adverse events

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- concomitant medications
- electrocardiogram
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - Joint Counts
 - Physician Global Assessment
 - Dactylitis / Enthesitis
 - PASI / Involved BSA
 - Radiographs of hands and feet
- laboratory assessments
 - urine pregnancy test, if applicable
 - hematology
 - chemistry
 - urinalysis
 - fasting lipids
 - C-reactive protein
 - ESR
 - anti-brodalumab antibodies
 - pharmacokinetic sample
 - biomarker blood sample, for consenting subjects only
- investigational product administration
- investigational product dispense
- review/collect subject diary of investigational product administration
- distribution of eDiary at week 48
- retrieval of eDiary at week 52

7.2.6 Week 53 to Week 160

Visits will occur per the Schedule of Assessments ([Table 1](#)). On-study visits may be completed within ± 7 days of the target visit date. Subjects who discontinue investigational product should be requested to continue to return for all other study procedures and measurements. At a minimum, the subjects should return for the week 100 and week 160 visits and complete all assessments including radiographs of the hands and feet. Subjects ending the study prior to week 160 will be asked to complete an early termination visit per [Section 7.2.7.2](#) and an end of follow-up visit per [Section 7.2.8](#).

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The following procedures will be completed as specified in the Schedule of Assessments in [Table 1](#):

- Patient Reported Outcomes
 - Patient Global Assessment
 - HAQ-DI
 - BASDAI
 - DLQI
- physical examination
- weight
- vital signs
- serious adverse events
- adverse events
- concomitant medications
- electrocardiogram
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - Joint Counts
 - Physician Global Assessment
 - Dactylitis / Entesitis
 - PASI / Involved BSA
 - Radiographs of hands and feet
- laboratory assessments
 - urine pregnancy test, if applicable
 - hematology
 - chemistry
 - urinalysis
 - fasting lipids
 - C-reactive protein / ESR
 - anti-brodalumab antibodies
 - pharmacokinetic sample
- investigational product dispense
- review/collect subject diary of investigational product administration

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7.2.7 Early Termination

Subjects who early terminate should return to the site for an early termination visit and should also have a End of Follow up visit 4 weeks after last dose of investigational product.

7.2.7.1 Early Termination Baseline to Week 52

Subjects who early terminate between baseline and week 52 should have the following assessments . The following procedures will be completed per the Schedule of Assessments ([Table 1](#)):

- Patient Reported Outcomes
 - Patient Global Assessment
 - HAQ-DI
 - BASDAI
 - DLQI
 - SF-36v2
 - Psoriasis Symptom Inventory
- physical examination
- weight
- vital signs
- serious adverse events
- adverse events
- concomitant medications
- electrocardiogram
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - Joint Counts
 - Physician Global Assessment
 - Dactylitis / Enthesitis
 - PASI
 - Involved BSA
 - Radiographs of hands and feet
- laboratory assessments
 - urine pregnancy test, if applicable
 - hematology
 - chemistry
 - urinalysis

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- fasting lipids
- C-reactive protein
- ESR
- anti-brodalumab antibodies
- pharmacokinetic sample
- biomarker blood sample, for consenting subjects only
- review/collect subject diary of investigational product administration
- retrieval of eDiary

7.2.7.2 Early Termination Week 53 to Week 160

Subjects who early terminate between week 53 and week 160 should have the following assessments . The following procedures will be completed per the Schedule of Assessments ([Table 1](#)):

- Patient Reported Outcomes
 - Patient Global Assessment
 - HAQ-DI, if applicable
 - BASDAI
 - DLQI
- physical examination
- weight
- vital signs
- serious adverse events
- adverse events
- concomitant medications
- electrocardiogram
- **eC-SSRS**
- **PHQ-8**
- disease assessments
 - Joint Counts
 - Physician Global Assessment
 - Dactylitis / Enthesitis
 - PASI
 - Involved BSA
 - Radiographs of hands and feet (only subjects who early terminate before week 100)
- laboratory assessments
 - urine pregnancy test, if applicable
 - hematology

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- chemistry
- urinalysis
- fasting lipids
- C-reactive protein / ESR
- anti-brodalumab antibodies
- pharmacokinetic sample

7.2.8 Week 162 / End of Follow up

Subjects will complete follow up at week 162. If subjects early terminate, an end of follow up visit should occur 4 weeks after last dose of investigational product. The week 162/End of Follow Up visit may be conducted by telephone. The following procedures will be completed per the Schedule of Assessments ([Table 1](#)):

- serious adverse events
- adverse events
- concomitant medications

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in [Section 7.2](#).

7.3.1 Informed Consent

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

Depending on site and IEC/IRB requirements, subjects may have a separate informed consent for the PK, biomarker, and pharmacogenetic substudies. These are considered optional components to the main 20090406 protocol.

7.3.2 Medical History

The subject's complete medical and surgical history, including alcohol and tobacco use history will be obtained prior to enrollment and recorded on the eCRF. Diagnosis dates for psoriatic arthritis and psoriasis will also be collected. Reasonable steps should be made to obtain medical records for subjects that are referred to the site.

7.3.3 Medication History

The subject's history of medications taken within the 3 months prior to screening (signing informed consent) will be recorded on the eCRF. In addition, the subject's psoriatic arthritis and psoriasis-specific medication history for the past 6 months and any prior use of a DMARD (both non-biologic and biologic) for these indications should be recorded on the eCRF. For prior therapies, collect therapy name, indication, dose, unit, frequency,

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route, start date and stop date. Collect reason for discontinuation of both biologic and non-biologic DMARDs.

7.3.4 Physical Examination

The screening physical examination will be a complete physical examination. Breast, genital, and rectal examinations are not required at any study visit unless specific evaluation is warranted. Physical examination findings at screening should be recorded on the medical and surgical history eCRF. The physical examination at subsequent study visits should be used to monitor for any changes from the screening physical examination.

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

7.3.5 Physical Measurements

Height and weight should be recorded without shoes.

7.3.6 Vital Signs

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

The temperature location selected for a subject should remain the same throughout the study and documented on the vital signs eCRF.

7.3.7 Electrocardiogram

A standard 12-lead ECG will be obtained after the subject has been supine for at least 3 minutes and prior to blood samples being drawn. A standardized procedure for obtaining ECGs will be used by all sites and equipment will be provided. This procedure and instructions in sending ECGs will be provided in a separate manual provided by the central imaging vendor.

Subject must be in supine position in a rested and calm state for at least **3** minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible.

The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals.

The investigator or designated physician will review all ECGs. Once signed, the original

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ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.3.8 Chest Radiographs

Chest radiograph will include anterior/posterior and lateral views. Historical films obtained in the 3 months prior to screening are acceptable.

7.3.9 Psoriatic Arthritis Disease Assessments

7.3.9.1 Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria

The CASPAR criteria consist of established inflammatory articular disease with at least 3 points from the following features: current psoriasis (assigned a score of 2; all other features assigned a score of 1); a history of psoriasis (unless current psoriasis was present); a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis); dactylitis; juxta-articular new bone formation; rheumatoid factor negativity; and nail dystrophy.

7.3.9.2 Joint Assessments

Tender Joint Count Assessments – A total of 68 joints will be scored for presence or absence of tenderness.

Swollen Joint Count Assessments - A total of 66 joints will be scored for presence or absence of swelling.

All joint assessments will be performed by an experienced, independent and blinded joint evaluator who has been certified as trained by Amgen. The evaluator cannot be the treating physician and cannot interact with the subject on the study beyond the assessment of joints. The evaluator should not discuss the subject's clinical status nor should the evaluator have access to subject medical records or eCRFs including prior joint assessments.

If possible, each subject should have their assessments done by the same assessor throughout the study. Extra care should be taken to ensure that the same assessor performs the baseline, week 16 and week 24 assessments. If necessary, study visits may be rescheduled within the specified window to accommodate when the specific assessor will be available. An instruction manual will be provided.

Joints that have been replaced are considered not evaluable.

For the screening and baseline joint counts, the distal interphalanges should be evaluated, but will not be used to determine eligibility.

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Joint count assessment results will be entered in the IWR system system.

7.3.9.3 Dactylitis Count

Dactylitis will be assessed as present yes or no on 20 digits (fingers and toes).

Assessment will be performed by the same independent assessor as the joint counts (Section 7.3.9.2). On-line training and instruction manual will be provided; data are entered in the eCRF.

7.3.9.4 Entesitis Count

Entesitis will be assessed as present yes or no on 6 entheses. Assessment will be performed by the same independent assessor as the joint counts (Section 7.3.8.2).

On-line training and an instruction manual will be provided; data are entered in the eCRF.

7.3.9.5 Physician Global Assessment of Disease Activity

The blinded independent certified joint assessor may not complete the global disease assessment. The physician assessing the subject's global disease will have access to the joint assessments. The subject and physician must complete the global assessments independently from each other.

7.3.9.5.1 Physician Global Assessment of Arthritis Activity

The physician global assessment of arthritis disease activity will be assessed by completion of a visual analog scale. The physician will be asked to draw a vertical line through a horizontal line to indicate how the subject is doing based on the subjects current arthritis activity. The horizontal line is 100 mm in length with '0' and 'Very Well' on the left end of the line and '100' and 'Very Poorly' on the right end of the line. This questionnaire should take approximately 1 minute to complete.

7.3.9.5.2 Physician Global Assessment of Psoriasis and Arthritis Activity

The physician global assessment of arthritis and skin disease will be assessed by completion of a visual analog scale. The physician will be asked to draw a vertical line through a horizontal line to indicate how the subject is doing based on the subjects current arthritis and psoriasis activity. The horizontal line is 100 mm in length with '0' and 'Very Well' on the left end of the line and '100' and 'Very Poorly' on the right end of the line. This questionnaire should take approximately 1 minute to complete.

7.3.10 Psoriasis Disease Assessments

The following psoriasis disease assessments will be performed by a healthcare provider (any site staff in the investigator's team) who has been certified as trained by Amgen. If

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possible, each subject should have his/her assessments done by the same assessor throughout the study. Extra care should be taken to ensure that the same assessor performs the baseline, week 16 and week 24 assessments. If necessary, study visits may be rescheduled within the specified window to accommodate when the specific assessor will be available.

7.3.10.1 Psoriasis Area and Severity Index (PASI)

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

7.3.10.2 Involved Body Surface Area (BSA)

The involved BSA numerical score (0% to 100%) will be used to measure the investigator's assessment of the proportion of the subject's total BSA involved with psoriasis.

7.3.11 Hands and Feet Radiographs

Radiographic assessment will include an evaluation of hand/wrist and feet radiographs. A standardized procedure for obtaining radiographs will be used by all sites. This procedure and instructions on sending radiographs will be provided in a separate manual provided by the central imaging center. All original radiographs will be sent to the central image processing facility for analysis.

Screening radiographs will be used to determine the presence of erosions for eligibility and must be obtained during the screening period. Eligibility radiographs will be read centrally, by the image processing vendor. If the screening radiographs are obtained (both hands/wrists and feet) within 30 days of the baseline/study day 1, and satisfies the radiographic manual specification, the screening radiograph is acceptable for the baseline assessment.

If the subject rescreens for any reason, a new set of radiographs must be obtained if ≥ 30 days have transpired since the first radiographs were acquired.

7.3.12 Patient Reported Outcomes

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

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7.3.12.1 Patient Global Assessment

7.3.12.1.1 Patient Assessment of Joint Pain

The severity of the subject's joint pain will be assessed by completion of a visual analog scale. The subject will be asked to draw a vertical line through a horizontal line to indicate how much pain they are experiencing 'today'. The horizontal line is 100 mm in length with '0' and 'No Pain At All' on the left end of the line and '100' and 'Worst Pain Imaginable' on the right end of the line. This questionnaire should take approximately 1 minute to complete.

7.3.12.1.2 Patient Global Assessment of Arthritis Activity

The subject's global assessment of his or her arthritis disease activity will be assessed by completion of a visual analog scale. The subject will be asked to draw a vertical line through a horizontal line to indicate how they are doing based on all the ways their arthritis affects them at the time of completion. The horizontal line is 100 mm in length with '0' and 'Very Well' on the left end of the line and '100' and 'Very Poorly' on the right end of the line. The subject and physician must complete the global assessments independently from each other. This questionnaire should take approximately 1 minute to complete.

7.3.12.1.3 Patient Global Assessment of Psoriasis and Arthritis Activity

The subject's global assessment of his or her arthritis and skin disease by completion of a visual analog scale. The subject will be asked to draw a vertical line through a horizontal line to indicate how they are doing based on all the ways their psoriasis and arthritis affects them at the time of completion. The horizontal line is 100 mm in length with '0' and 'Very Well' on the left end of the line and '100' and 'Very Poorly' on the right end of the line. The subject and physician must complete the global assessments independently from each other. This questionnaire should take approximately 1 minute to complete.

7.3.12.2 Disability Index of the Health Assessment Questionnaire (HAQ-DI)

The Disability Index of the Health Assessment Questionnaire (HAQ-DI) will be utilized to assess the subject's physical function or disability according to the subject. The HAQ DI asks about the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores). Responses in each functional area are scored from 0 indicating no difficulty to 3 indicating inability to perform a task in that area. The study staff should not clarify any

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of the questions for the subject. This questionnaire should take approximately 5 minutes to complete.

7.3.12.3 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

This validated instrument is a self-administered questionnaire composed of six items using an 11-point numerical rating scale labeled from “0 = none” to “10 = very severe” for the first five items, and “0 = 0 hrs” to “10 = 2 or more hrs” for the sixth item that asks about the duration of morning stiffness. The BASDAI assesses the severity of fatigue, spinal and peripheral joint pain, localized tenderness, and morning stiffness. This questionnaire should take approximately 5 minutes to complete.

7.3.12.4 Dermatology Life Quality Index (DLQI)

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

7.3.12.5 SF-36v2 Health Survey

The SF-36v2 Health Survey ([Ware et al, 2000](#)) contains 36 items and is a revised version of the SF-36 Health Survey. The SF-36v2 is a generic measure of health-related quality of life. This survey yields assessments of 8 domains of health-related quality of life: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The scores from the 8 domains can further be aggregated into 2 summary component norm-based measures of physical and mental health. The SF-36v2 has either a 7 day recall (acute) or 4 week recall (standard), and the 4 week recall will be used in this study. This survey takes approximately 5 to 10 minutes to complete.

7.3.12.6 Psoriasis Symptom Inventory

The severity of the subject's psoriasis symptoms will be assessed by the subject using the Psoriasis Symptom Inventory, a psoriasis-specific patient-reported outcomes measurement that has been developed on the basis of literature review, in-depth physician interviews, and psoriasis patient focus groups and cognitive interviews. The Psoriasis Symptom Inventory consists of 8 psoriasis specific items eliciting scores ranging from “0 = not at all” to “4 = very severe”. Total Psoriasis Symptom Inventory scores for a given subject can range from 0 to 32 with higher scores indicating worse symptoms. The Psoriasis Symptom Inventory has a 24 hour recall and is completed as a daily diary taking approximately 3 minutes to complete.

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

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

7.3.12.8 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). PHQ-8 takes approximately 3 minutes to complete.

7.3.13 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of urine pregnancy, erythrocyte sedimentation rate (ESR), PPD, and Quantiferon (may be done by central or local laboratory). Additionally, laboratory assessments required per Section 0 may be done by central or local laboratory. The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, urinalysis, C reactive protein, and any other laboratory tests required. ESR, urine pregnancy and PPD testing, if applicable, will be performed locally with kits provided by the central laboratory (except PPD). The results of this testing will be maintained in the source documents at the site. Amgen or designee will be responsible for brodalumab pharmacokinetics, anti-brodalumab antibody, biomarker development and pharmacogenetic assessments, and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment).

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

Specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples are listed below (Table 2).

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Table 2. Analytes

Chemistry	Urinalysis	Hematology and Differential	Other Labs
Sodium	Specific gravity	RBC	Quantiferon ^a
Potassium	pH	RBC Morphology	Serum beta hCG ^a
Chloride	Blood	Hemoglobin	FSH
Bicarbonate	Protein	Hematocrit	Hepatitis B surface Ag
Total protein	Glucose	Platelets	Hepatitis B core Ab
Albumin	Bilirubin	WBC	Hepatitis C virus Ab
Calcium	Leukocyte esterase	Differential	Rheumatoid factor
Adjusted calcium	Ketones	• Bands/stabs	Fasting Lipids
Magnesium	Microscopic (Reflex testing if abnormal)	• Eosinophils	• Cholesterol
Phosphorus		• Basophils	• HDL
Glucose		• Lymphocytes	• LDL
BUN		• Monocytes	• Triglycerides
Creatinine ^b		• Neutrophils	C-reactive protein (high sensitivity)
Uric acid		ANC	ESR
Total bilirubin			Anti-brodalumab antibody
Direct bilirubin			Brodalumab PK
Alk phos			Biomarkers
AST			
ALT			

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell.; Ag = antigen; Ab = antibody; HDL = High-density lipoprotein; LDL = Low-density lipoprotein ; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone

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

^a If applicable

^b Estimated creatinine clearance will be calculated based on the Modification of Diet in Renal Disease formula

ESR will be analyzed on site, by blinded study personnel, using a Westergren method and kits will be supplied by the central lab. ESR and CRP values (except for at screening and baseline) will be kept blinded from subjects and study personnel. Missed visits, test(s) that are not done, and examinations that are not conducted must be reported as such on the eCRFs if applicable.

7.3.13.1 Antibody Testing Procedures

All subjects who receive brodalumab will have samples assayed for binding, and if positive, neutralizing antibodies.

Blood samples for antibody testing are to be collected as indicated in the Schedule of Assessments, [Table 1](#) for the measurement of anti-brodalumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing

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antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-brodalumab antibodies during the study.

Subjects who test positive for neutralizing antibodies to brodalumab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (\pm 4 weeks) after administration of brodalumab. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive brodalumab.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-brodalumab antibody response may also be asked to return for additional follow-up testing.

7.3.13.2 Brodalumab Pharmacokinetics

Samples will be collected, processed, frozen, and shipped per the central laboratory manual. The site is expected to complete a shipping log or requisition that will include subject identification information and the time and date of collection for each sample shipped. Missing samples must be clearly documented on the shipping log or requisition.

7.3.13.2.1 Main Pharmacokinetic Study (all subjects)

Blood samples for pharmacokinetic analysis will be collected from all subjects prior to dosing as shown in the Schedule of Assessments

7.3.13.2.2 Brodalumab PK Substudy (optional; additional consent required)

The pharmacokinetic substudy has a target enrollment of approximately 15% (80-110 subjects). These subjects will be required to visit the study site for additional blood draws at the post-dose timepoints shown in the brodalumab Pharmacokinetic Substudy Schedule of Assessments. Obtain confirmation that the sub-study informed consent form has been signed prior to performing substudy procedures.

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Table 3. Pharmacokinetic Substudy Schedule of Assessments

	Week 2 + 3 days (± 1 day)	Week 14 + 3 days (± 1 day)	Week 14 + 7 days (± 1 day)	Week 14 + 10 days (± 1 day)
Pharmacokinetic substudy sample	X	X	X	X

7.3.13.3 Urine Pregnancy

Urine pregnancy tests for women who have not had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or are not at least 2 years postmenopausal (confirmed by FSH) will be performed locally with centrally provided kits. On visits where required, urine pregnancy tests must be performed prior to dosing with IP. If a urine pregnancy test is positive, IP must be held; if pregnancy is confirmed, then IP must be discontinued.

7.3.13.4 Purified Protein Derivative (PPD)

The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. The test will be read per exclusion criterion 202. PPD test kits will not be provided by the sponsor and must be procured locally.

7.3.13.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. These investigations may be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease progression.

In addition to testing the safety and effectiveness of brodalumab in this study, Amgen may attempt to develop blood and/or tissue test(s) designed to identify subjects most likely to respond positively or negatively to brodalumab. Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods or ribonucleic acid transcript profiling.

Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

For subjects consenting to participate (participation is optional), blood samples will be collected for biomarker development at the time points defined in the Schedule of Assessments (Table 1). A cell pellet from the blood plasma tube may be utilized to assess the impact of brodalumab on circulating immune cells via deoxyribonucleic acid (DNA) methylation analysis, a pharmacodynamic assessment of methylation patterns of

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relevant genes. The DNA extracted will not be used for optional pharmacogenetic analyses unless the subject signs the additional consent.

7.3.13.6 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic analyses, DNA analyses may be performed. These optional pharmacogenetic analyses focus on genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of inflammatory disease and/or to identify subjects who may have a positive or negative response to brodalumab. No additional samples will be collected for this part of the study; however, for those subjects who consent to this study, DNA will be extracted from biomarker samples already collected (ie, must have consent for biomarker sample to be collected).

7.3.13.7 Sample Storage and Destruction

Any blood sample collected for biomarker development according to the Schedule of Assessments ([Table 1](#)) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the inflammatory conditions, the dose response and/or prediction of response to brodalumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be

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made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See [Section 11.3](#) for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments ([Table 1](#)) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments ([Table 1](#)) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with [Section 12.1](#).

8.3 Reasons for Removal From Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, malignancy (except basal cell or squamous cell carcinoma of the skin and cervical intraepithelial neoplasia), tuberculosis, serious opportunistic infection, ANC values as detailed in [Section 6.2.1.3](#), pregnancy, Crohn's disease)
- **suicidal ideation (severity of 4 or 5) or any suicidal behavior after randomization based on an assessment with the eC-SSRS**
- **severe depression after randomization, defined as a total score of ≥ 15 based on an assessment with the PHQ-8**
- decision by Sponsor (other than subject request, safety concern)
- death
- lost to follow-up
- disease flare requiring treatment not allowed in the protocol
- nonresponse status as assessed per protocol ([Section 6.2.1.3.3](#)) at or after week 28

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Subjects who discontinue investigational product are strongly encouraged to continue participation in the study and return for study visits at key timepoints ([sections 7.2.4](#), [7.2.5](#) and [7.2.6](#)) in order to facilitate the intent to treat analysis.

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

The worsening of psoriatic arthritis, the disease under study, should only be reported as an adverse event if it is clinically significant worsening. For situations when an adverse event or serious adverse event is due to worsening psoriatic arthritis report all known signs and symptoms. Note: The term "disease progression" should not be used to describe the adverse event.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

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The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to [Section 8.1](#) for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

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

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

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

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

The criteria for grade 4 in the Common Terminology Criteria for Adverse Events (CTCAE) grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2 Reporting of Adverse Events

9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization or first dose of investigational product through the end of study (including long term extension phase)

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and occurring within 4 weeks of the last dose of IP are reported using the applicable CRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

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

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event Summary CRF.

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

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

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

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 4 weeks after the last dose of investigational product or end of study,

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whichever is the later, are recorded in the subject's medical record and are submitted to Amgen.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

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

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?".

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

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

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If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

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

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies or if a male subject's partner is pregnant at the time of enrollment, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 8 weeks after the last dose of study drug.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet ([Appendix C](#)). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 8 weeks after the last dose of study drug.

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

9.4 Major Adverse Cardiovascular Events

If a suspected major adverse cardiovascular event (defined as stroke, myocardial infarction, or cardiovascular death) occurs in a subject, the principal investigator may be requested to provide additional information (eg, onset and duration of symptoms) to the Cardiovascular Events Committee for adjudication. As this reporting only occurs in cases where additional information is needed, it is not included in the Schedule of Assessments ([Table 1](#)).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary

- ACR20 response at week 16

10.1.1.2 Key Secondary

- PASI 75 at week 16
- mTSS change from baseline at week 24

10.1.1.3 Other Secondary

- mTSS change from baseline at week 52 and week 100

The following endpoints at other measured timepoints

- ACR20
- PASI 75

The following endpoints at all measured timepoints

- ACR50
- ACR70
- HAQ-DI change from baseline
- Components of ACR change from baseline
- DAS 28 CRP change from baseline
- Dactylitis / Enthesitis change from baseline
- CDAI change from baseline
- PsARC
- PASI 90
- PASI 100
- PASI percent change from baseline
- Involved BSA

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- Psoriasis Symptom Inventory responder definition (total score ≤ 8 , with no item score > 1)
- DLQI change from baseline
- SF-36v2 physical component score change from baseline
- SF-36v2 mental component score change from baseline
- SF-36v2 change from baseline in domain scores
- PK endpoints
- BASDAI change from baseline
- PASDAS

10.1.1.4 Exploratory Endpoints

- Biomarkers
- Pharmacogenetics parameters
- Self administration dosing data

10.1.1.5 Safety Endpoints

- Adverse events
- Events of interest
- Laboratory parameters (hematology, chemistry, urinalysis)
- Antibodies to brodalumab

10.1.2 Composite Endpoints

10.1.2.1 ACR

The ACR score is comprised of the following endpoints:

Tender joint count, swollen joint count, physician global assessment, patient global assessment, patient assessment of joint pain, HAQ-DI, CRP and ESR.

The details of how the ACR will be calculated is described in the SAP.

10.1.2.2 DAS28 CRP

The DAS28 CRP is comprised of the following endpoints:

Tender joint count, swollen joint count, patient global assessment and CRP.

The details of how the DAS28 CRP will be calculated is described in the SAP.

10.1.2.3 CDAI

The CDAI score is comprised of the following endpoints:

Tender joint count, swollen joint count, physician global assessment, patient global assessment.

The details of how the CDAI will be calculated is described in the SAP.

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10.1.2.4 PASDAS

The PASDAS score is comprised of the following endpoints:

Tender joint count, swollen joint count, physician global assessment of arthritis and skin, patient global assessment of arthritis and skin, CRP, enthesitis, dactylitis, SF-36 PCS.

The details of how the PASDAS will be calculated is described in the SAP.

10.1.2.5 PsARC

The PsARC score is comprised of the following endpoints:

Tender joint count, swollen joint count, physician global assessment and patient global assessment.

The details of how the PsARC will be calculated is described in the SAP.

10.1.3 Analysis Sets

10.1.3.1 Full Analysis Set

The full analysis set will consist of all randomized subjects. Subjects will be analyzed according to their randomized treatment group. Analyses of demographics, baseline characteristics, and efficacy endpoints (except psoriasis efficacy) will utilize this analysis set.

10.1.3.2 Psoriasis Efficacy Analysis Set

The psoriasis efficacy analysis set will consist of all randomized subjects with baseline psoriasis BSA $\geq 3\%$. Analyses of psoriasis efficacy endpoints (eg, PASI 75/90/100, Psoriasis Symptom Inventory responder definition) will utilize this analysis set.

10.1.3.3 Safety Analysis Set

The safety analysis set will consist of all randomized subjects who receive at least 1 dose of IP. Analysis for safety endpoints will utilize this analysis set. Subjects will be analyzed according to their randomized treatment group.

10.1.3.4 Per Protocol Analysis Set

The per protocol analysis set will include randomized subjects who complete the 16 week treatment period and who did not significantly deviate from the protocol through week 16. The per protocol analysis set will be used to perform the sensitivity analysis on both the primary endpoint and HAQ-DI change from baseline at week 16.

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10.1.3.5 Per Protocol Radiographic Endpoints Analysis Set

The per protocol radiographic endpoints analysis set will include randomized subjects who complete the 24 week treatment period, and who did not significantly deviate from the protocol through double-blind placebo controlled phase of the study.

10.1.3.6 Per Protocol Psoriasis Efficacy Analysis Set

The per protocol psoriasis efficacy analysis set will include randomized subjects with baseline psoriasis BSA $\geq 3\%$, who complete the 16 week treatment period and who did not significantly deviate from the protocol through week 16. The per protocol psoriasis efficacy analysis will be used to perform the sensitivity analysis on selected psoriasis efficacy endpoints.

10.1.3.7 Evaluable Subset for Long-term Extension Phase

The subset will include all subjects who had at least one dose of treatment at or after week 52. Subjects will be analyzed according to their randomized treatment groups.

10.1.3.8 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include all subjects in the safety subset who have at least 1 evaluable PK concentration measurement.

10.1.3.9 Antibody Analysis Set

The antibody analysis set will include all subjects in the safety analysis set who have at least one evaluable antibody test.

10.1.3.10 Biomarker Analysis Set

The biomarker analysis set will contain all subjects who were randomized, received at least 1 dose of IP and have both pre- and post-dose measurements of biomarker data.

10.1.4 Covariates and Subgroups

The primary endpoint and selected secondary endpoints will have a covariate analysis run to assess which covariates are associated with the endpoints. The covariates may include the following:

- Previous biologic use (Yes / No)
- Prior use of anti-tumor necrosis factor biologic (Yes / No)
- Number of prior biologic therapy failure
- Weight at baseline (> 100 kg / ≤ 100 kg)
- Baseline CRP value (≥ 10 mg/L / < 10 mg/L)
- Geographic Regions (North America, central and eastern Europe, western Europe and Latin America)
- Methotrexate use at baseline (Yes / No)

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- Steroid use at baseline (Yes / No)
- Disease duration (\geq median, $<$ median)
- Subject global assessment of joint pain
- Subject global assessment of disease activity
- Physician's global assessment of disease activity
- Sex (male / female)
- Age
- Race/ethnicity (white / non-white)
- Baseline BSA involvement
- Concomitant topical steroid use (Yes, No)
- Concomitant topical therapy use (Yes, No)
- Baseline body mass index

Selected efficacy and safety endpoints may also be explored using the following subgroups as deemed appropriate:

- Previous biologic use (Yes / No)
- Weight at baseline (> 100 kg / ≤ 100 kg)
- Geographic Regions (North America, central and eastern Europe, western Europe and Latin America)
- Age (< 65 years, ≥ 65 years)
- Gender
- Race/ethnicity
- Anti-brodalumab antibody status
- Topical steroid use
- Methotrexate/leflunomide/sulfasalazine use at baseline
- Corticosteroid use at baseline

10.2 Sample Size Considerations

To preserve the family-wise 2-sided type one error rate at 0.05 for the multiple comparisons of the two brodalumab doses with placebo, a sequential testing procedure will be used to determine statistical significance for the primary and key secondary endpoints. The adjusted powers are calculated based on the testing sequence specified in the following schema (Figure 3), where the significance of an endpoint is contingent on the significance of all endpoints that precede it in the hierarchy.

A total of 630 subjects will be enrolled in the study and randomized in a 1:1:1 ratio to placebo, brodalumab 140 mg Q2W and brodalumab 210 mg Q2W. This sample size has been selected to adequately evaluate brodalumab's efficacy in preventing structural damage to the joints (the key secondary endpoint-mTSS change from baseline at week 24). With this sample size, the adjusted power is $> 90\%$ (at 2-sided 5%

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significance level) to detect the treatment difference in the change from baseline of mTSS at week 24 between the placebo and brodalumab 210 mg Q2W, and > 80% between the placebo and brodalumab 140 mg Q2W. We assumed the changes in mTSS for the placebo and brodalumab arms would be 0.35 and 0, respectively, with common standard deviation of 1. The placebo and brodalumab rates were based on published etanercept (Mease et al, 2004) radiographic data, and account for the placebo subjects who may change treatments due to an inadequate response, starting from week 16. The assumed dropout rate at week 24 is 10%.

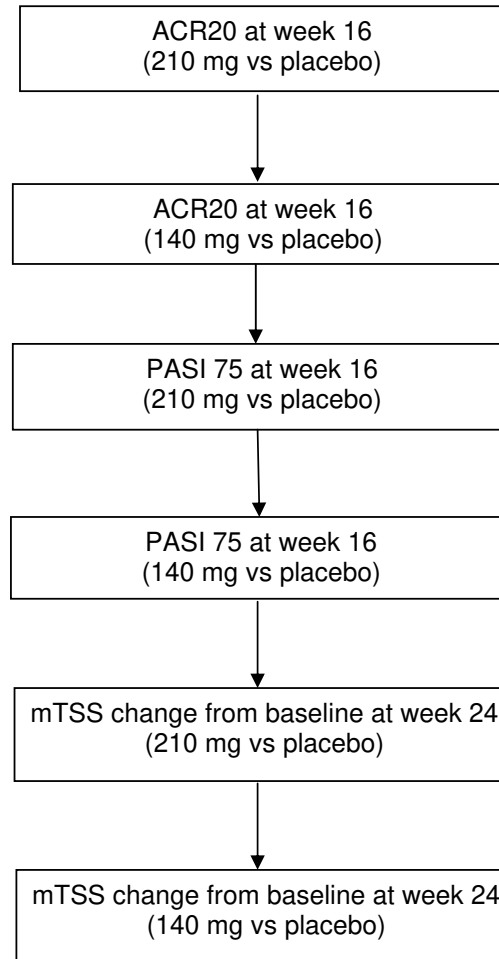
For ACR20 response, we assume that the placebo and the 2 treatment groups will have 18%, 45%, and 45% ACR20 response rates at week 16, respectively. The placebo response rate is based on the phase 2 brodalumab psoriatic arthritis study week 12 data from the placebo-controlled phase, and treatment group response rate is based on week 16 data from the long term extension phase. With the given sample size, the adjusted powers are > 90% (at 2-sided 5% significance level) to detect the treatment difference in ACR20 at week 16 between placebo and the 2 brodalumab groups.

Based on the phase 2 study, approximately 60% of the study population will have \geq 3% involved BSA. For PASI 75 response at week 24, it is assumed the placebo rate will be 10% and the 2 brodalumab groups will be at least 50%, respectively. With the given sample size, the adjusted powers are > 90% (at 2-sided 5% significance level) to detect the treatment difference in PASI 75 at week 16 between placebo and the 2 brodalumab groups.

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Figure 3. Sequential Testing Procedure



10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (week 52 primary analysis) except as specified (eg, [Section 5.2](#) and [Section 9.2.2](#)).

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

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Staff associated with tracking and assaying and analyzing brodalumab pharmacokinetic, anti-brodalumab antibody and biomarker samples may have access to the pharmacokinetic-related and biomarker-related information only.

10.4 Planned Analyses

10.4.1 Interim Analyses

No interim analyses are planned prior to the primary analysis.

10.4.2 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be convened to monitor the brodalumab phase 3 PsA program; membership, meeting frequency and other details will be defined in the DMC charter. The DMC is an independent, multidisciplinary group consisting of medical and statistical representatives; the membership is external to Amgen. The DMC will review all unblinded data throughout the double-blind portion of study.

Additionally, safety monitoring (review of blinded safety data) by the Amgen global safety team will occur in an ongoing fashion.

10.4.3 Cardiovascular Events Committee

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

10.4.4 Primary Analysis

Study will be unblinded and primary analysis will occur after last subject completes the week 52 visit or early termination from the study.

For ACR and PsARC response related endpoints, the stratified Cochran-Mantel-Haenszel test will be used to compare treatment groups with placebo adjusted for baseline weight, prior biologic use and geographic region. For binary endpoint that was dichotomized from continuous outcome, the stratification will also include a grouping of the baseline measure ($>$ median / \leq median). Missing data will be imputed by non-responder imputation for week 16 primary analysis.

For radiographic endpoints, data will be transformed by the Van der Waerden method, the analysis of covariance model with stratification variables and rank of baseline value as covariates will be used to compare treatment groups with placebo. Data will be analyzed as observed for primary analysis.

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For other continuous endpoints that exhibit normal distribution, a linear mixed effect model will be used. The model will include treatment group, visit, interaction of treatment group by visit, and stratification variables as fixed effects, baseline value, and baseline value by treatment group as covariates, within subject variance will be estimated by an unstructured covariance matrix. For continuous endpoints that are not normally distributed, data will be transformed by the Van der Waerden method before applying the linear mixed effect model. No imputation will be done for primary analysis.

For efficacy endpoints, analyses will be based on the full analysis set or psoriasis efficacy analysis set as appropriate, and data will be analyzed by the randomized treatment group.

For the primary analysis, regions may be pooled if the number of randomized subjects in a particular region is not adequate to assess treatment effects within each stratum.

10.4.5 Post-primary Analyses

One post-primary interim analysis is planned at the time when all subjects who are still continuing the study have reached week 100. Efficacy and safety analyses will be performed.

10.4.6 Final Analysis

The final analysis will be performed after the last subject either terminates the study or completes the week 162 safety followup; the final analysis will include a summary of the long term efficacy and safety endpoints.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Baseline demographics and disease characteristics will be summarized descriptively. Summary descriptive statistics by treatment group will be provided. For categorical endpoints, the descriptive statistics will contain the frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, and maximum.

All statistical tests will be 2-sided.

Details of all statistical methods (including scoring of patient reported outcome instruments and missing data handling) will be provided in the statistical analysis plan.

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10.5.2 Primary Efficacy Endpoint

The primary analysis of the primary endpoint, ACR20 response at week 16 will be based on the full analysis set. Stratified Cochran-Mantel-Haenszel test stratified by baseline weight, prior biologic use and geographic region will be used to compare brodalumab groups and placebo. Nonresponder imputation will be used for missing data for primary analysis.

Several sensitivity analyses will be considered:

- The primary analysis will be repeated for the per protocol analysis set.
- Last observation carried forward imputation approach and as observed approach will also be used to analyze the primary endpoint.

To control the family-wise 2-sided type one error rate at 0.05 for the multiple comparisons of the 2 brodalumab dose groups with placebo across the primary and key secondary endpoints, the hypotheses will be tested in a sequential fashion. Statistical significance can be claimed for a given endpoint only if the prior family of endpoints in the sequence meets the requirement for significance ([Section 10.2](#)).

10.5.3 Secondary Efficacy Endpoints

Key Secondary Endpoints

PASI 75 at week 16

The primary analyses of the key secondary endpoints, PASI 75 response at week 16 will be based on psoriasis efficacy analysis set. The stratified Cochran-Mantel-Haenszel (stratified by baseline body weight, prior biologic use, geographic region and baseline PASI score: \leq median, $>$ median) will be used to compare brodalumab groups and placebo. Sensitivity analyses will be similar to those applied for the ACR20 response except that the analyses will be based on psoriasis efficacy analysis set and per protocol psoriasis efficacy analysis set.

mTSS change from baseline at week 24

The primary analysis of mTSS change from baseline at week 24 will be based on the full analysis set; this endpoint will be assessed using analysis of covariance model on the Van der Waerden normal scores with rank baseline mTSS, and stratification factors in the model. Missing data will be limited primarily to lost to follow-up, withdrawal of consent, and death. As per the intent to treat principle, for rest of the subjects, their observed mTSS value at week 24 will be used in the primary analysis as randomized,

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irrespective of the actual treatments they are on at week 24 or before. Thus, for those subjects who had an inadequate response prior to week 24, the observed mTSS value at week 24 will be used in the primary analysis.

The following sensitivity analyses of mTSS change from baseline at week 24 will be considered:

- The primary analysis will be repeated for week 24 radiographic endpoints per protocol set.
- Subjects who are missing week 24 radiographs, impute their mTSS at week 24 using last observation carried forward method based on their most recent postbaseline radiographs.
- Subjects who are missing week 24 radiographs, impute their mTSS at week 24 by linear extrapolation based on their most recent postbaseline radiographs..
- Subjects who meet the criteria for inadequate response or who withdraw for any reason, impute their mTSS at week 24 by linear extrapolation based on radiographs at the time of inadequate response or withdrawal.
- Using Cochran-Mantel-Haenszel test to analyze the proportion of subjects with change in mTSS ≤ 0 .
- Using Cochran-Mantel-Haenszel test to analyze the proportion of subjects with change in mTSS ≤ 0.5 .

Other Secondary Endpoints

The analyses of other secondary endpoints (except PK endpoints) at different assessment points are:

- From baseline to week 24, the analyses will be based on appropriate efficacy analysis set depending on types of endpoints (eg, full analysis set, psoriasis efficacy analysis set); the primary analyses specified in [Section 10.4.4](#) will be applied to compare treatment groups and placebo.
 - For Psoriasis Symptom Inventory, an additional analysis will be performed based on Psoriasis Symptom Inventory total score of 0 (best possible score) and mean change in total score from baseline to week 16. Cumulative distribution curves for Psoriasis Symptom Inventory total score improvement from baseline at week 16 will be generated by treatment group.
 - For DLQI, additional analyses will include the proportion of subjects with at least 5-point improvement in total score, a total score of 0, and a total score of 0 or 1.

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- After week 24 to week 52, the analyses will be based on full analysis set, or psoriasis efficacy analysis set as appropriate. Data will be summarized as observed by randomized treatment group. Sensitivity analysis will also be performed by whether subjects met the criteria for inadequate response during the first 24 weeks.
- After week 52, data will be summarized as observed based on the efficacy evaluable subset in the the long term extension phase.

10.5.4 Safety Endpoints

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

The Medical Dictionary for Regulatory Activities will be used to code all adverse events to a system organ class and a preferred term. During the first 52 weeks of the study, safety data will be summarized using subject incidence based on safety analysis set by treatment phase and randomized group. After week 52, safety data will be summarized by brodalumab exposure adjusted event rates for each treatment group based on safety evaluable subset for the long term extension phase.

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

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

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

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serious treatment-related adverse events will be provided by preferred term in descending order of frequency.

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

Shift tables of the worst on-study laboratory toxicity based on CTCAE relative to baseline will be tabulated by treatment group. Subject listings of grade 2 and above laboratory toxicities will be provided.

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

The incidence and percentage of subjects who develop antibrodalumab antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

The ECG measurements from this clinical study were 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; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

Any other events of interest (eg, neutropenia, suicidal ideation, and suicidal behavior) will also be evaluated.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the

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aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

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11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subjects are to be identified by a unique subject identification number.

Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For Serious Adverse Events reported to Amgen, subjects are to be identified by unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

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12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IEC/IRB must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IEC/IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

In this study, the IWR system captures the following data points and these are considered source data: subject identification number and randomization numbers. ePRO entries will be considered source data. In this study, Psoriasis Symptom Inventory, Patient Global Assessment, HAQ-DI, BASDAI, DLQI and SF-36v2 are collected by ePRO. Additionally, Physician Global Assessment will be completed on an electronic tablet and will be considered source data.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

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- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IEC/IRB and Amgen
- Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

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

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

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

All source documentation supporting entries into the CRFs must be maintained and readily available.

Updates to CRFs will be automatically documented through the software's "audit trail".

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To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.

The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit) and clarifying “other, specify” if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments ([Table 1](#)), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

eCRFs must be completed in English. TRADENAMES[®] (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

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12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Subjects will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent. Subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

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14. APPENDICES

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Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events Version 4 (CTCAE V4) is available at the following location:

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

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in [Section 6.3.1](#) require the following:

The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in [Section 9.2.2](#).

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST or ALT elevations $>3 \times \text{ULN}$ are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

Additional Clinical Assessments and Observation that are required:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
 1. In cases of TBL $> 2 \times \text{ULN}$ or INR > 1.5 , retesting of liver tests, BIL (total and direct), and is to be performed every 24 hours until laboratory abnormalities improve
 2. In cases of ALT or AST $> 3 \times \text{ULN}$ and when TBL is normal, repeat liver enzyme and serum bilirubin tests two or three times weekly.
- Testing frequency may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

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- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies

If liver tests (ALT or AST) are elevated for greater than 48 hours without a clear etiology, the following tests should be performed as appropriate to determine the etiology of the elevation in the liver tests.

- Obtain complete blood count (CBC) with differential to assess for eosinophilia
- Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
- Obtain serum acetaminophen (paracetamol) levels
- Obtain a more detailed history of:
 1. symptoms and prior or concurrent diseases.
 - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting and fever
 2. Exposure to environmental and/or industrial chemical agents
 3. Prior and/or concurrent use of alcohol, recreational drugs and special diets
 4. Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies to rule out acute or chronic hepatitis including viral hepatitis types A, B, C, D, and E; EBV, and CMV
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

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Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20090406 brodalumab	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use
--	--

Complete either Section A or Section B and follow the instructions provided:

Section A

EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):

An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)
 Screening event (as defined by the protocol) **OR** On-study event (as defined by the protocol)

- Complete ONLY Sections 1, 2 and 3 (page 1)
 - Sign and date the signature section following Section 3
 - Fax completed page of the form to the number noted in the header above Section 1

Section B

Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):

Screening event (as defined by the protocol)
 This is a new event report
 This is follow-up information for a previously reported event

Event after access to the EDC system (eg, Rave) has ended (provide subject's End of Study date in Section 2)
 This is a new event report
 This is follow-up information for a previously reported event

- Complete ALL sections of the form (all 3 pages)
 - Sign and date the signature section at the end of the form
 - Fax completed form (all 3 pages) to the number noted in the header above Section 1

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country
Reporter	Phone Number ()	Fax Number ()

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth	Sex	Race	If applicable, provide End of Study date
	Day Month Year	<input type="checkbox"/> F <input type="checkbox"/> M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day ____ Month ____ Year ____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day ____ Month ____ Year ____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event	Date Started	Date Ended	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship		Relationship		Outcome of Event	Check only if event is related to study procedure eg, biopsy
					Is there a reasonable possibility that the event may have been caused by IP?	Is there a reasonable possibility that the event may have been caused by an Amgen device?	Resolved	Not resolved		
	Day Month Year	Day Month Year			Nov	Yes	Nov	Yes		

Serious Criteria: 01 Fatal 02 Immediately life-threatening 03 Required/prolonged hospitalization 04 Persistent or significant disability/incapacity 05 Congenital anomaly / birth defect 06 Other medically important serious event

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

Signature of Investigator or Designee - _____	Title	Date
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I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.

FORM-056006


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Appendix C. Pregnancy and Lactation Notification Worksheets



Pregnancy Notification Worksheet
 Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: brodalumab / 20090406

Study Design: **Interventional** **Observational** (If Observational: **Prospective** **Retrospective**)

2. Contact Information

Investigator Name _____ Site # _____
 Phone (____) _____ Fax (____) _____ Email _____
 Institution _____
 Address _____

3. Subject Information

Subject ID # _____ Subject Gender: Female Male Subject DOB: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? Yes No
 If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____

Did the subject withdraw from the study? Yes No

5. Pregnancy Information

Pregnant female's LMP mm ____ / dd ____ / yyyy ____ Unknown
 Estimated date of delivery mm ____ / dd ____ / yyyy ____ Unknown N/A
 If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____

Has the pregnant female already delivered? Yes No Unknown N/A
 If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____

Was the infant healthy? Yes No Unknown N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____
 Signature: _____ Date: _____


Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

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Appendix C. Pregnancy and Lactation Notification Worksheets (cont'd)

Print Form

 **Lactation Notification Worksheet**

Fax Completed Form to the Country-respective Safety Fax Line
 SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number:

Study Design: Interventional Observational (If Observational: Prospective Retrospective)

2. Contact Information

Investigator Name Site #

Phone () Fax () Email

Institution

Address

3. Subject Information

Subject ID # Subject Date of Birth: mm / dd / yyyy

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	mm <input type="text"/> / dd <input type="text"/> / yyyy <input type="text"/>

Was the Amgen product (or study drug) discontinued? Yes No

If yes, provide product (or study drug) stop date: mm / dd / yyyy

Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? Yes No

If No, provide stop date: mm / dd / yyyy

Infant date of birth: mm / dd / yyyy

Infant gender: Female Male

Is the infant healthy? Yes No Unknown N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:

Form Completed by:

Print Name: Title:

Signature: Date:

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

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Amendment 1

Protocol Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Evaluate the Efficacy, Safety and Effect on Radiographic Progression of Brodalumab in Subjects With Psoriatic Arthritis: AMVISION-1

Amgen Protocol Number Brodalumab (AMG 827) 20090406

Amendment Date: 26 March 2014

Rationale:

Based on identification of suicidal behavior and suicidal ideation as a potential risk and after discussion with regulatory agencies, the Columbia Suicide Severity Rating Scale and the Patient Health Questionnaire depression scale have been added as instruments to assess eligibility and monitor subject safety (ie, stopping rules).

Other minor editorial corrections and clarifications have been made.

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Description of Changes:[Section: Global](#)

Change date to 26 March 2014

[Section: Synopsis Procedures](#)

Add: Columbia Suicide Severity Rating Scale and Patient Health Questionnaire (PHQ-8) depression scale

[Section: Study Design and Treatment Schema](#)

Add: + wk 1 to each of the treatment arms

[Section: Study Glossary](#)

Add: eC-SSRS Electronic Self Rated Version, Columbia Suicide Severity Rating Scale

Add: PHQ-8 Patient Health Questionnaire - 8 depression scale

[Section: 4.1.2 Exclusion Criteria](#)

Add:

230 Subject has a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia Suicide Severity Rating Scale (eC-SSRS) at screening or at baseline

Replace:

223 Subject has a history of substance abuse that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

With:

231 Subject has a history or evidence of a **psychiatric disorder** or substance abuse that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

Add:

232 Subject has severe depression based on a total score of ≥ 15 on the Patient Health Questionnaire-8 (PHQ-8) at screening or baseline. (note: subjects with a total score of 10-14 on the PHQ-8 should referred to a mental health professional)

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Section 5.2: Site Personnel Access to Individual Treatment Assignments

Replace:

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, will provide guidance on how to unblind via IWR system. Once a subject's treatment assignment is unblinded via IWR system, the subject will not be allowed to receive any further investigational product. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's eCRF.

With:

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, will provide guidance on how to unblind via IWR system. Once a subject's treatment assignment is unblinded via IWR system, the subject will not be allowed to receive any further investigational product. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, **provided that this does not compromise subject safety**, but must do so within 1 working day after the event and must document the unblinding in the subject's eCRF.

Section 6.2 Amgen Investigational Product [brodalumab]

Add:

During the open-label phase 140 mg dose will be packaged in dispensing packs containing 1 prefilled syringe.

Section 6.2.1.3: Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Add:

6.2.1.3.4 Suicidal Ideation or Behavior

Suicidal ideation and behavior will be assessed using the eC-SSRS. IP should be permanently discontinued according to the following rules:

- **subject reports suicidal ideation after randomization, with severity of 4 or 5**
- or
- **subject reports any suicidal behavior after randomization.**

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

6.2.1.3.5 Depression

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

[Section: Table 1. Schedule of Assessments](#)

Add: eC-SSRS at every visit from screening through week 52

Add: EC-SSRS every 4 weeks (56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160/ET)

Add: PHQ-8 at every visit from screening through week 52

Add: PHQ-8 every 4 weeks (56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160/ET)

Add: Vital signs at wk 76, 88, 112, 124, 136 and 148

Add: urine pregnancy “at every visit” from wk 64 and 160

[Section 7.2 General Study Procedures](#)

Add: eC-SSRS to every visit

Add: PHQ-8 to every visit

[Section 7.2.2 Re-Screening](#)

Replace:

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

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With:

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

[Section 7.2.5 Week 25 to Week 52](#)

Replace:

Visits will occur per the Schedule of Assessments (Table 1). On-study visits may be completed within ± 7 days of the target visit date.

With:

Visits will occur per the Schedule of Assessments (Table 1). On-study visits may be completed within **± 3 days through week 36 and then ± 7 days** of the target visit date.

[Section 7.2.6 Week 53 to 160](#)

Replace:

Urine pregnancy test, if applicable monthly home urine pregnancy test between visits

With:

Urine pregnancy test, if applicable

[Section 7.3.7 Electrocardiogram](#)

Replace:

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible.

With:

Subject must be in supine position in a rested and calm state for at least **3** minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible.

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Section 7.3.12 Patient Reported Outcomes

Add:

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

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

7.3.12.8 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). PHQ-8 takes approximately 3 minutes to complete.

Section 7.3.13.2.2 Brodalumab PK Substudy (optional; additional consent required)

Replace

Table 3. Pharmacokinetic Substudy Schedule of Assessments

	Week 2 + 3 days (± 1 day)	Week 14 + 1 days (± 1 day)	Week 14 + 3 days (± 1 day)	Week 14 + 7 days (± 1 day)	Week 14 + 10 days (± 1 day)
Pharmacokinetic substudy sample	X	X	X	X	X

With

Table 3. Pharmacokinetic Substudy Schedule of Assessments

	Week 2 + 3 days (± 1 day)	Week 14 + 3 days (± 1 day)	Week 14 + 7 days (± 1 day)	Week 14 + 10 days (± 1 day)
Pharmacokinetic substudy sample	X	X	X	X

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Section 8.3.1: Reasons for Removal From Treatment

Add:

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

Section 9.1.2 Definition of Serious Adverse Events

Add:

Suicidal behavior and suicidal ideation (severity 4 or 5) should be reported as serious adverse events.

Section 10.5.4 Safety Endpoints

Delete: (sentence appears twice)

The incidence and percentage of subjects who develop anti-brodalumab antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

Add:

Any other events of interest (eg, neutropenia, suicidal ideation and suicidal behavior) will also be evaluated.

Section: References

Add:

Kroenke K and Spitzer RL. The PHQ-9: a new depression and diagnostic severity measure. *Psychiatric Ann.* 2002;32: 509–521.

Kroenke K, Strine TW, Spitzer RL, Williams JB, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord.* 2009; 114(1-3):163-173.

Mundt, JC, Geist JH, Gelenberg AJ et al, 2010b, Feasibility and Validation of a ComputerAutomated Columbia-Suicide Severity Rating Scale Using Interactive Voice Response Technology, *J Psychiatric Res*, 44(16); 1224-1228.

Posner, K, Brown GK, Stanley B et al., 2011, The Columbia-Suicide Severity Rating Scale (eC-SSRS): Internal Validity and Internal Consistency Findings From Three Multi-Site Studies With Adolescents and Adults, *Am J Psychiatry*, 168:1266-1277.