Title Page

Protocol Title:	A Multicenter, Randomized, Double-blinded Study Evaluating the Pharmacokinetics, Efficacy and Safety of Multiple Switches Between Ustekinumab and ABP 654 Compared With Continued Use of Ustekinumab in Subjects with Moderate to Severe Plaque Psoriasis
Short Title:	A Study to Investigate Interchangeability of ABP 654 for the Treatment of Subjects with Moderate to Severe Plaque Psoriasis
Compound:	ABP 654
Indication:	Moderate to Severe Plaque Psoriasis
Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks CA 91320-1799, US
Protocol Number:	20200417
Study Phase:	Phase 3
Regulatory Agency Identifying Number:	IND: 139331 EudraCT: 2020-005205-42
Approval Date:	Final 2.0, 02 June 2021

NCT Number: NCT04761627
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

Protocol Signature Page - Sponsor Signatory:

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Amgen Inc. representative(s):

[redacted] [redacted]

Print Name Title

[redacted] [redacted]

Signature Date (DD MMM YYYY)

Protocol Signature Page – Contract Research Organization

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Contract research organization representative(s):

Print Name	Title
Signature	Date (DD MMM YYYY)

Protocol Signature Page – Investigator

I have read this protocol, which has been agreed to by Amgen Inc. and given approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee, and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by Amgen Inc. or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Amgen Inc. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the general guidelines indicated in the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), and applicable national or regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Amgen Inc. and inspection by the appropriate regulatory authorities.

I agree to make my subjects' study records available to Amgen Inc. personnel, their representatives and relevant regulatory authorities in order to verify data that I have entered into the case report forms. I will retain the study-related essential documents until Amgen Inc. indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Amgen Inc.

I agree to ensure that Financial Disclosure Statements will be completed by me (including, if applicable, my spouse [or legal partner] and dependent children) and my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I understand that Amgen Inc. may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Amgen Inc.

Investigator:

Print Name	Title

Institution

Signature	Date (DD MMM YYYY)

Protocol Amendment Summary of Changes

Document History		
Document	Version	Date
Substantial Amendment 1	Final 2.0	02 June 2021
Original Protocol	Final 1.0	19 November 2020

Substantial Amendment 1 (02 June 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment:

Section	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Study Schema 5 Study Population 9.3 Sample Size Determination	Change of sample size from 352 enrolled subjects to 480 enrolled subjects.	Adjustment of sample size to maintain sufficient power on primary objective to align with Food and Drug Administration recommended margin (0.8, 1.25).
1.1 Synopsis 2.1 Study Rationale 3 Objectives and Endpoints 4.2 Scientific Rationale for Study Design 9.2 Statistical Hypotheses	Update verbiage of bioequivalence and pharmacokinetic equivalence to similarity and pharmacokinetic similarity.	To provide clarity using the appropriate terminology for a proposed biosimilar product.
1.1 Synopsis 9.2 Statistical Hypotheses 9.3 Sample Size Determination	Update of bioequivalence margin from (0.77, 1.3) to (0.8, 1.25).	To follow Food and Drug Administration recommended bioequivalence margin.
1.1 Synopsis 9.5 Planned Analyses	Change in method for handling missing values for the Psoriasis Area and Severity Index endpoint from last observation carried forward method to multiple imputation method.	To follow Food and Drug Administration recommendation.
1.3 Schedule of Assessments	Include pharmacokinetic and antidrug antibody samples at week 4.	To follow Food and Drug Administration recommendation.
	Update to Table 1-2: Clarification of tolerance windows for pharmacokinetic sample collection times.	To provide better clarity on expected sample collection times.
1.3 Schedule of Assessments 5.2 Exclusion Criteria 8.2 Safety Assessments	Include human immunodeficiency virus serology at screening and electrocardiogram at baseline and weeks 16, 28, 40, and 52.	To follow Food and Drug Administration recommendation.
5.1 Inclusion Criteria	Update to inclusion criterion 3: removed additional mention of baseline Psoriasis Area and Severity Index.	Removal of duplicative wording.

Section	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Update of exclusion criterion 23: update to specify female subject should not get pregnant for at least 5 months after the last dose of investigational product.	To ensure consistency of contraception language and pregnancy criteria throughout the protocol.
9.5 Planned Analyses	Include electrocardiogram data analysis descriptive summary for the number of abnormal electrocardiograms.	To follow Food and Drug Administration recommendation.
	Clarify that the concomitant medication for Run-in Treated Set is for Run-in Period.	To align with language in the Statistical Analysis Plan.
Throughout protocol	Minor formatting and grammatical revisions.	To ensure correction of typographical errors and inconsistencies.

Table of Contents

Protocol Amendment Summary of Changes 6
Table of Contents 8
1 Protocol Summary 12
1.1 Synopsis 12
1.2 Schema 18
1.3 Schedule of Assessments 19
2 Introduction 21
2.1 Study Rationale 21
2.2 Background 22
2.3 Benefit/Risk Assessment 24
2.3.1 Overall Benefit: Risk Conclusion 24
3 Objectives and Endpoints 25
4 Study Design 26
4.1 Overall Design 26
4.2 Scientific Rationale for Study Design 26
4.2.1 Subject Input into Design 27
4.3 Justification for Dose 27
4.4 End of Study Definition 27
5 Study Population 27
5.1 Inclusion Criteria 28
5.2 Exclusion Criteria 29
5.3 Subject Enrollment 31
5.4 Lifestyle Considerations 32
5.4.1 Meals and Dietary Restrictions 32
5.4.2 Caffeine, Alcohol, and Tobacco 32
5.4.3 Activity 32
5.4.4 Coronavirus Disease 2019 Considerations 32
5.5 Screen Failures 33
6 Investigational Product 33
6.1 Investigational Product(s) Administered 34
6.1.1 ABP 654 Dosage Form 34

6.1.2 Ustekinumab Dosage Form....35
6.2 Preparation, Handling, Storage, and Accountability....35
6.3 Investigational Product Complaints....36
6.4 Measures to Minimize Bias: Blinding and Randomization....36
6.4.1 Blinding....36
6.4.2 Randomization....37
6.5 Investigational Product Compliance....38
6.6 Concomitant Therapy....38
6.6.1 Prohibited Treatments....38
6.6.2 Prior and Concomitant Therapy....38
6.7 Dose Modification....39
6.8 Intervention After the End of the Study....40
7 Discontinuation of Investigational Product and Subject Discontinuation....40
7.1 Discontinuation of Investigational Product....40
7.2 Subject Discontinuation/Withdrawal from the Study....41
7.3 Loss of Subjects to Follow-Up....42
8 Study Assessments and Procedures....43
8.1 Efficacy Assessments....44
8.1.1 Psoriasis Area and Severity Index....44
8.1.2 Static Physical Global Assessment....45
8.1.3 Affected Body Surface Area....45
8.2 Safety Assessments....45
8.2.1 Physical Examinations....45
8.2.2 Vital Signs....45
8.2.3 Twelve-lead Electrocardiogram....46
8.2.4 Tuberculosis Testing....46
8.2.5 Chest Radiography....46
8.2.6 Clinical Safety Laboratory Assessments....46
8.3 Adverse Events and Serious Adverse Events....48
8.3.1 Definitions....48
8.3.2 Assessments of Adverse Events....52
8.3.3 Causality....52
8.3.4 Documenting and Reporting of Adverse Events....53
8.3.5 Pregnancy....57

8.3.6 Events of Interest 57
8.4 Treatment of Overdose 58
8.5 Pharmacokinetics 58
8.6 Pharmacodynamics 58
8.7 Genetics 58
8.8 Biomarkers 58
8.9 Immunogenicity Assessments 58
9 Statistical Considerations 60
9.1 General Considerations 60
9.2 Statistical Hypotheses 60
9.3 Sample Size Determination 61
9.4 Populations for Analysis 61
9.5 Planned Analyses 62
9.5.1 Primary Endpoints 62
9.5.2 Secondary Endpoint(s) 62
9.5.3 Safety Endpoints 63
9.5.4 Other Analyses 64
9.5.5 Demographic and Baseline Characteristics 65
9.5.6 Exposure to Investigational Product 65
9.5.7 Exposure to Prior and Concomitant Medication 65
9.5.8 Subgroup Analyses and Covariates 66
9.6 Interim Analyses 66
10 Supporting Documentation and Operational Considerations 67
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 67
10.1.1 Regulatory and Ethical Considerations 67
10.1.2 Informed Consent Process 68
10.1.3 Data Monitoring Committee 70
10.1.4 Financing and Insurance 70
10.1.5 Data and Records Management 71
10.1.6 Publication Policy 75
10.1.7 Auditing and Monitoring 76
10.1.8 Data Protection 78
10.1.9 Protocol Approval and Amendment 78
10.1.10 Study and Site Start and Closure 78

10.2 Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information 79
10.3 Appendix 3: Static Physician's Global Assessment Scale 85
10.4 Appendix 4: Abbreviations and Trademarks 86
11 References 88

List of Figures

Figure 1–1. Study Schema 18

List of Tables

Table 1-1. Schedule of Assessments 19
Table 1-2. Tolerance Windows for Pharmacokinetic Endpoint Sample Collection 20
Table 3-1. Objectives and Endpoints 25
Table 4-1. Investigational Product Groups 26
Table 6-1. Investigational Product(s) Administered 34
Table 8-1. Protocol-required Safety Laboratory Assessments 48
Table 9-1. Populations for Analysis 61

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Multicenter, Randomized, Double-blinded Study Evaluating the Pharmacokinetics, Efficacy and Safety of Multiple Switches Between Ustekinumab and ABP 654 Compared With Continued Use of Ustekinumab in Subjects with Moderate to Severe Plaque Psoriasis

Sponsor Protocol No.: 20200417

Study Phase: Phase 3

Sponsor: Amgen Inc.

Rationale:

The current study is designed to investigate the pharmacokinetics similarity, efficacy, safety and immunogenicity of multiple switches between ustekinumab and ABP 654 compared with continued use of ustekinumab in subjects with moderate to severe plaque psoriasis.

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective: • To demonstrate similarity of pharmacokinetics in subjects with multiple switches between ustekinumab and ABP 654 compared to subjects receiving continued use of ustekinumab	Primary Endpoints: Pharmacokinetic parameters: • AUC_{tau} between week 52 and week 64 • C_{max} between week 52 and week 64
Secondary Objective: • To assess the efficacy, safety and immunogenicity in subjects with multiple switches between ABP 654 and ustekinumab compared with subjects receiving continued use of ustekinumab	Secondary Endpoints: Pharmacokinetic-related Endpoints: • t_{max} between week 52 and week 64 • $C_{trough,ss}$ between week 28 and week 52 Efficacy-related Endpoints: • PASI percent improvement from baseline (day 1) to week 64 • PASI 75 response at week 64 • PASI 100 response at week 64

Objectives	Endpoints
	Safety-related Endpoints: • Treatment-emergent adverse events and serious adverse events, post randomization • Events of interest, post randomization • Incidence of antidrug antibodies, post randomization

AUC_{tau}: area under the curve from time 0 over the dosing interval; C_{max}: maximum concentration; $C_{trough,ss}$: trough concentration at steady state; PASI: Psoriasis Area and Severity Index; t_{max}: time of maximum concentration

Overall Design:

This is a randomized, double-blinded, phase 3 study in adult subjects with moderate to severe plaque psoriasis.

The total duration of study participation for each subject will be 68 weeks, with up to 4 weeks for screening and 64 weeks after the first investigational product administration.

Subjects will receive an initial 3 doses of ustekinumab on day 1 (week 0), week 4 and week 16. From week 28, subjects in the continued-use group will stay on ustekinumab and subjects in the switching group will switch between ABP 654 and ustekinumab every 12 weeks.

At week 28, efficacy assessments will be conducted including evaluation of Psoriasis and Area Severity Index (PASI).

Subjects who do not achieve a PASI 50 response or better improvement at week 28 are considered as run-in failures and will not be randomized at week 28; these subjects will complete End of Study procedures at week 28. The run-in period will occur from day 1 until randomization at week 28. Those unable to complete the week 28 visit or did not have a PASI assessment completed at week 28 will be discontinued from the study. All enrolled subjects not randomized at week 28 will be considered run-in failures and the run-in failure reason will be documented.

Disclosure Statement: This is a parallel group, treatment study with 2 arms that are both subject and investigator blinded.

Number of Arms:

Continued-use group

Switching group

Number of Subjects:

Approximately 480 subjects will be enrolled to receive ustekinumab during the run-in period. Subjects with prior biologic use for psoriasis will be capped at 50% of the total enrolled subjects. This sample size will ensure approximately 310 randomized subjects at week 28 after the run-in period, considering 35% run-in failures. Randomization will be in a 1:1 ratio to the continued-use group or the switching group. The randomization will be stratified by prior biologic use for psoriasis (yes versus no) at baseline (week 0), geographic region, and body weight at baseline (week 0). The number of subjects enrolled may be adjusted during the study with the actual run-in failure rate seen to ensure approximately 310 randomized subjects at week 28. Subjects already enrolled will be allowed to be randomized at week 28. The sample size of 310 randomized subjects will provide 90% power to demonstrate similarity of the primary PK endpoints based on the Two One Sided Tests at a 0.05 significance level, assuming a between-subject variability (as measured by coefficient of variation) of 55% for ABP 654 and ustekinumab, a true geometric mean ratio (GMR) of 1 between ABP 654 and ustekinumab, a similarity margin of (0.8, 1.25), and 25% drop-outs after randomization through week 64 (including subjects who discontinue the study prior to week 52 and those reaching week 52 but do not have evaluable primary PK endpoints between weeks 52 and 64).

Intervention Groups and Duration:

The total duration of study participation for each subject will be 68 weeks, with up to 4 weeks for screening, and for 64 weeks after the first administration of ustekinumab.

Dose regimens: Continued use of ustekinumab (ustekinumab 45 mg or 90 mg, subcutaneous [SC] injection) and switching group (ustekinumab and ABP 654 45 mg or 90 mg, SC injection).

Reference Group **Continued-use Group**	Continued use of ustekinumab administered by subcutaneous injection using a blinded prefilled syringe at a dose of 45 mg (baseline body weight ≤ 100 kg) or 90 mg (baseline body weight > 100 kg) at day 1, week 4, and week 16. Subsequent dosing will be done at the same dose every 12 weeks at weeks 28, 40, and 52.
Test Group **Switching Group**	Switching group with ustekinumab administered by subcutaneous injection using a blinded prefilled syringe at a dose of 45 mg (baseline body weight ≤ 100 kg) or 90 mg (baseline body weight > 100 kg) at day 1, week 4 and week 16. Subject will then be switched to ABP 654 at week 28, back to ustekinumab at week 40, and again to ABP 654 at week 52.

Sites and Regions:

This study is planned to be conducted globally at sites including but not limited to North America and Europe.

Data Monitoring Committee: For details on the Data Monitoring Committee, refer to Section 10.1.3, Appendix 1.

Statistical Analysis:

The primary analysis of the primary PK endpoints, AUC_{tau} and C_{max}, between weeks 52 and 64 will be performed based on the PK Parameter Analysis Set (consisting of all subjects who are randomized and receive all 3 doses of the assigned investigational product between weeks 28 and 52 and who have an evaluable ABP 654 or ustekinumab serum concentration-time profile between weeks 52 and 64), according to the actual treatment groups (switching group versus continued-use group). The point estimates and 90% confidence intervals (CIs) for the GMRs between ABP 654 and ustekinumab for AUC_{tau} and C_{max} between weeks 52 and 64 will be estimated using an analysis of covariance (ANCOVA) model adjusting for stratification factors. Prior to statistical modeling, the PK parameters will be logarithmically-transformed (natural log). Point estimates and 90% CIs for the mean difference in logarithmic PK parameters will be estimated from the ANCOVA model, which will then be transformed back to the original scale to obtain the point estimates and 90% CIs for GMR. AUC_{tau} and C_{max} of ABP 654 and ustekinumab between weeks 52 and 64 will be listed by subject and summarized descriptively by treatment group. A sensitivity analysis of the primary PK endpoints will be conducted on the Per-protocol PK Parameter Analysis Set (consisting of all subjects from the PK Parameter Analysis Set who do not have an important protocol deviation that could affect the primary PK endpoints). To support a demonstration of interchangeability, the 90% CI of GMRs of ABP 654 versus ustekinumab for AUC_{tau} and C_{max} from the primary analysis should fall within the pre-specified similarity margin.

The analyses of the secondary PK endpoints of t_{max} between weeks 52 and 64 and $C_{trough,ss}$ between weeks 28 and 52 will be based on the PK Parameter Analysis Set according to the actual treatment groups (switching group versus continued-use group); t_{max} will be summarized descriptively by treatment group and $C_{trough,ss}$ between weeks 28 and 52 will be summarized descriptively by visit and treatment group. The point estimates and 90% CIs for GMR for $C_{trough,ss}$ between the two treatment groups will be estimated using an ANCOVA model adjusting for stratification factors.

The analysis of the secondary efficacy endpoints will be based on the Per-protocol Efficacy Analysis Set (consisting of all subjects who are randomized and receive all 3 doses of the assigned investigational product between weeks 28 and 52 and who have not experienced an important protocol deviation that may affect the evaluation of the efficacy endpoints) according to the actual treatment groups (switching group versus continued-use group). The point estimate and 90% CI of the mean difference in PASI percent improvement from day 1 at week 64 will be estimated from an ANCOVA model adjusting for the baseline PASI value and the stratification factors. The point estimate and 90% CI of the risk difference in PASI 75 response rate and PASI 100 response rate at week 64 will be estimated from a generalized linear model with an identity link adjusting for the stratification factors. Missing data will be imputed by multiple imputation method for PASI percent improvement from day 1 at week 64 and by non-responder imputation for PASI 75 response rate and PASI 100 response rate at week 64. In addition, the PASI percent improvement from day 1 at weeks 28, 40, and 52 and the PASI 75 and PASI 100 response rates at weeks 28, 40, and 52 will be summarized descriptively by treatment group.

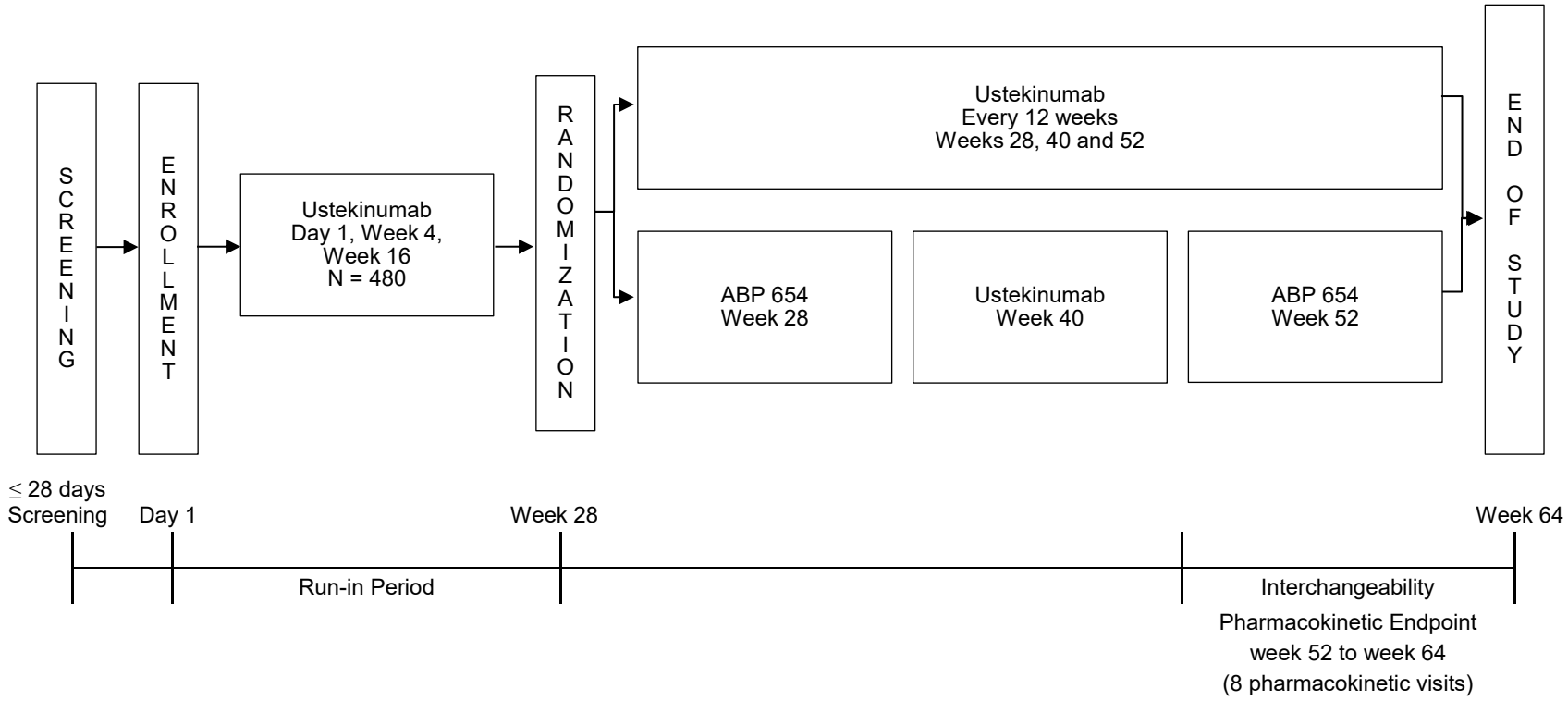
All reported adverse events will be categorized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version at the time of final analysis) dictionary and graded by Common Terminology Criteria for Adverse Events, version 4.03. Safety analyses of the safety endpoints will be performed based on the Safety Analysis Set (consisting of all subjects who are randomized and receive any investigational product post randomization) according to the actual treatment groups (switching group versus continued-use group). Treatment-emergent adverse events post randomization are defined as adverse events that start or worsen on or after the first dose of investigational product post randomization and prior to the End of Study. The numbers and percentages of subjects reporting treatment-emergent adverse events, serious adverse events and events of interests will be tabulated by treatment group. The number and percent of subjects developing binding or neutralizing antidrug antibody (ADA) in the subset of Safety Analysis Set who have never tested positive (ie, tested negative or no results) prior to the first dose of investigational product post randomization and have at least one ADA result post randomization will be tabulated descriptively by treatment group and by visit.

In addition, safety analyses prior to randomization will be performed based on the Run-in Treated Set (consisting of all enrolled subjects treated with at least 1 dose of ustekinumab during the run-in period). The number and percentage of subjects reporting treatment-emergent

adverse events, serious adverse events and events of interest while receiving ustekinumab during the run-in period will be summarized. The number and percentage of subjects developing binding or neutralizing ADAs for ustekinumab during the run-in period will be summarized.

1.2 Schema

Figure 1–1. Study Schema



PASI: Psoriasis Area and Severity Index

Subjects with ≤ 100 kg will receive 45 mg of investigational product and subjects with > 100 kg will receive 90 mg of investigational product.

At week 28, run-in failures (eg, subjects achieving PASI improvement < 50%) will not be randomized and will complete an End of Study visit at week 28. The run-in period will occur from day 1 until prior to randomization at week 28.

Subjects achieving PASI improvement ≥ 50% will be randomized at week 28 (1:1) to continue ustekinumab or the switching group, at the same 45 mg or 90 mg dose stratified by geographic region, prior biologic use for psoriasis at baseline (week 0, "yes" versus "no") and body weight at baseline (week 0, ≤ 100 kg and > 100 kg).

1.3 Schedule of Assessments

Table 1-1. Schedule of Assessments

	Screening	Baseline	Study Visits (Week ± 5 days)[f]					Pharmacokinetic Endpoint Assessments Post Actual Week 52 Dose Date						End of Study[d]
Study Visit	**≤ 28 days**	**day 1/ week 0**	**4**	**16**	**28**	**40**	**52**	**2d**	**7d**	**10d**	**2w**	**4w**	**8w**	**12w post week 52 (week 64[g])**
Informed Consent	X													
Medical/Medication History	X													
Physical Examination	X	X												X
Height	X	X												
Body Weight	X	X			X									X
Vital Signs	X	X	X	X	X	X	X							X
Adverse Events	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
PASI/sPGA/Affected BSA	X	X			X	X	X							X
Laboratory Assessments														
Tuberculosis Testing	X													
Tuberculosis Worksheet	X[b]													
Chest X-ray	X[c]													
Serum Pregnancy Test	X													
Serology (HBsAg, HCV, HIV)	X													
12-lead ECG	X	X		X	X	X	X							
Urine Pregnancy Test		X	X	X	X	X	X							X
Hematology	X	X			X		X							X
Chemistry	X	X			X		X							X
Urinalysis	X	X												X
Pharmacokinetics		X	X	X	X	X	X	X	X	X	X	X	X	X
Antidrug Antibodies		X	X	X	X	X	X							X

	Screening	Baseline	Study Visits (Week ± 5 days)[f]					Pharmacokinetic Endpoint Assessments Post Actual Week 52 Dose Date						End of Study[d]
Study Visit	**≤ 28 days**	**day 1/ week 0**	**4**	**16**	**28**	**40**	**52**	**2d**	**7d**	**10d**	**2w**	**4w**	**8w**	**12w post week 52 (week 64[g])**
Investigational Product														
Randomization					X									
Investigational Product Administration[e]		X	X	X	X	X	X							

BSA: body surface area; ECG: electrocardiogram; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus antibody; HIV: human immunodeficiency virus; PASI: Psoriasis Area and Severity Index; PPD: purified protein derivative; sPGA: static Physician's Global Assessment

[a]Report serious adverse events that occur after signing informed consent form. Nonserious adverse events are reported as medical history prior to enrollment.

[b]Only for subjects with a positive tuberculosis test (ie, positive PPD or positive or indeterminate Quantiferon®/T-spot®)

[c]Prior radiography or formal reports signed off by a radiologist within 3 months of screening is acceptable.

[d]Subjects who missed week 28 visit or terminated early from the study should complete all procedures scheduled for week 64 within 28 days after withdrawal/discontinuation if possible. Subjects not achieving PASI 50 at week 28 will not be randomized and will complete End of Study procedures at week 28.

[e]ABP 654/ ustekinumab will be administered after all other procedures are completed for each dosing visit. Pharmacokinetic and antidrug antibody blood draws must be done prior to dosing at the visits where pharmacokinetic and antidrug antibody blood draws and investigational product administration occur.

[f]Dosing should be delayed if subject has a serious infection (up to 5 days). Refer to Section 6.7 for details.

[g]For subjects completing the study, the End of Study visit should be conducted 12 weeks post actual week 52 dose date. If the subject is adhering to protocol schedule, this visit will be completed at week 64.

Table 1-2. Tolerance Windows for Pharmacokinetic Endpoint Sample Collection

Study Visit	Tolerance Windows[a]
Week 52 predose	Within 1 hour prior to week 52 investigational product administration
2 days post week 52 dose	± 5 hours
7 days post week 52 dose	± 5 hours
10 days post week 52 dose	± 24 hours
2 weeks post week 52 dose	± 24 hours
4 weeks post week 52 dose	± 48 hours
8 weeks post week 52 dose	± 72 hours
12 weeks post week 52 dose (End of Study Visit)	± 72 hours

[a]The week 52 visit should be performed 52 weeks from day 1, with a window of ± 5 days. Subsequent visits are done in relation to the actual week 52 investigational product dose date (eg, for the 2 days post week 52 dose timepoint, the pharmacokinetic sample should be collected 2 days after the actual week 52 dose, with a collection window of ± 5 hours).

2 Introduction

ABP 654 is a biosimilar candidate to ustekinumab (Stelara®) which is an interleukin 12 (IL-12) and IL-23 antagonist.

The term “investigational product” throughout the protocol, refers to ABP 654 or ustekinumab.

2.1 Study Rationale

Amgen Inc. is developing ABP 654 as a biosimilar candidate to ustekinumab. The current study is designed to investigate the pharmacokinetic (PK) similarity, efficacy, safety, and immunogenicity of multiple switches between ustekinumab and ABP 654 compared with continued use of ustekinumab in subjects with moderate to severe plaque psoriasis. This study is being conducted to support a demonstration of interchangeability of ABP 654 and ustekinumab as defined by the United States (US) Biologic Price Competition and Innovation Act of 2009 (BPCI Act). An interchangeable biosimilar is defined as a biosimilar that can be expected to produce the same clinical result as the reference product in any given patient and the risk in terms of safety or diminished efficacy of switching between use of the biosimilar and the reference product is not greater than the risk of using the reference product without such switch (BPCI Act).

ABP 654 and ustekinumab belong to the pharmacologic class of IL-12 and IL-23 antagonists. The mechanism of action across indications involves the ustekinumab protein molecule binding with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. This binding disrupts IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell surface receptor chain, IL-12 receptor subunit beta 1 (IL-12Rβ).

In the US, ustekinumab is approved for subcutaneous (SC) administration in the treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and active psoriatic arthritis in adults alone or in combination with methotrexate, as well as maintenance dosing for adult patients with moderate to severe active Crohn’s disease and moderate to severe active ulcerative colitis; ustekinumab is also approved for intravenous (IV) administration in the initial treatment of moderate to severe active Crohn’s disease in adults and moderate to severe active ulcerative colitis in adults (Stelara® United States Prescribing Information [USPI], July 2020). In the European Union (EU), ustekinumab is approved for SC administration in the treatment of patients 6 years or older with

moderate to severe plaque psoriasis, and active psoriatic arthritis in adults (Stelara® Summary of Product Characteristics [SmPC], February 2020).

A biosimilar product, generally, is one that is highly similar to a licensed biologic reference product, and there are no clinically meaningful differences between the biosimilar and reference products in terms of safety, purity, and potency. Biosimilarity is demonstrated by the totality of the evidence, including quality, nonclinical, and clinical evidence. The quality and nonclinical data for ABP 654 and ustekinumab are summarized in the Investigator's Brochure.

2.2 Background

ABP 654 is designed to have an identical amino acid sequence and the same biological and functional characteristics as ustekinumab. ABP 654 has the same dosage form (solution for injection), product strengths, and formulation as ustekinumab (US and EU).

The totality of evidence available from an ongoing analytical program suggests that ABP 654 is analytically similar to ustekinumab with respect to its physicochemical properties and biological activities, except for minor differences expected from cell line changes; these minor differences are not expected to be clinically meaningful. ABP 654 and ustekinumab (US and EU) have similar in vitro binding to IL-23, IL-12, and neonatal fragment crystallizable receptor (FcRn), similar inhibition of IL-23 and IL-12, and similar binding kinetics and affinity to IL-23 and IL-12. Effector functions (antibody-dependent cell-mediated cytotoxicity [ADCC] and complement-dependent cytotoxicity [CDC]) towards cells expressing IL-12 and/or IL-23 receptors are not expected to occur with ABP 654 and ustekinumab. The lack of ADCC was confirmed when ABP 654 and ustekinumab were tested for effector functions using human IL-12 expressing U937 cells. Lack of CDC activity is currently being investigated.

As of the date of this protocol, ABP 654 has not been approved as a biosimilar to ustekinumab; however, based on the analytical similarity of ABP 654 and ustekinumab established to date, clinical experience with ustekinumab is deemed relevant to predicting the effects of ABP 654 in humans and is summarized in the following paragraphs. Additionally, ABP 654 is being used in 2 ongoing clinical studies. Study 20190230 is being conducted to evaluate the single-dose PK, safety, tolerability, and immunogenicity of ABP 654 (90 mg SC injection) compared to ustekinumab (US and EU) in healthy subjects. Study 20190232 is being conducted to demonstrate that there is no clinically meaningful difference between ABP 654 and ustekinumab

in terms of PK, efficacy, safety, and immunogenicity in adult subjects with moderate to severe plaque psoriasis.

Ustekinumab has been investigated in a number of clinical studies and for a number of different indications. In healthy subjects, the median time of maximum concentration (t_{max}) value following a single SC administration of 90 mg of ustekinumab was comparable to subjects with psoriasis. The maximum concentration (C_{max}) and area under the curve (AUC) in healthy subjects were higher than values seen in subjects with psoriasis. This is likely attributed to differing pharmacokinetic sampling schedules between the 2 studies, differences in body weight between the 2 populations, or increased IL-12/IL-23 binding target concentrations in subjects with psoriasis. In healthy subjects following a single 90 mg SC dose, the apparent volume of distribution was 90.2 mL/kg and the terminal half-life ($t_{½}$) was 22.1 days with an apparent systemic clearance of 3.1 mL/day/kg (BLA 125261 Clinical Pharmacology and Biopharmaceutics Review, 2009).

In subjects with plaque psoriasis, exposure increased in an approximately dose proportional manner after a single SC administration at doses range from 0.27 mg/kg to 2.7 mg/kg. Serum concentrations of ustekinumab were higher in the group receiving the 90 mg dose, as opposed to the 45 mg dose. However, when comparing the difference among the 2 groups, dose proportionality was also shown. Assessment of intrinsic factors including body weight, age, and sex were performed. When given the same dose of ustekinumab, subjects that weighed > 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing ≤ 100 kg. Subgroup analysis showed that age, sex, and race had no effects on clinical response (Stelara® USPI, July 2020; BLA 125261 Clinical Pharmacology and Biopharmaceutics Review, 2009).

The clinical efficacy and safety information for ustekinumab as described in the product labeling (Stelara® USPI, July 2020; Stelara® SmPC, February 2020) are considered relevant to predicting the effects of ABP 654 in humans. When ustekinumab was administered to subjects with plaque psoriasis in clinical studies, subjects had a reduction in disease as measured by Psoriasis Area and Severity Index (PASI) score (≥ 75% improvement in PASI [PASI 75]) from baseline to week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA) as compared with the placebo arm. Adverse events reflected in the warnings and precautions section of the product labeling for ustekinumab that may be serious include bacterial, fungal, and viral infections including tuberculosis, malignancies,

hypersensitivity reactions, posterior reversible encephalopathy syndrome, noninfectious pneumonia and serious dermatological conditions (eg, erythrodermic psoriasis, exfoliative dermatitis, hypersensitivity vasculitis).

A detailed description of the chemistry, pharmacology, efficacy, and safety of ABP 654 is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

ABP 654 is expected to be biosimilar to ustekinumab. The risks and benefits of ABP 654 are therefore expected to be the same as those of ustekinumab, as specified in the product labeling; therefore, there are no anticipated risks for switching between ABP 654 and ustekinumab. All subjects in this study will receive an active treatment. More detailed information about the expected benefits, risks, and reasonably expected adverse events of ABP 654 can be found in the Investigator's Brochure.

A risk assessment will be performed on an ongoing basis to evaluate the potential impact of coronavirus disease 2019 (COVID-19) on subjects. Risk mitigation measures, including COVID-19 related precautions and procedures (including severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] testing/screening) will be implemented based on the prevailing situation during study conduct, at the investigator's discretion and in accordance with local and institutional guidelines, as applicable.

2.3.1 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with ABP 654, as well as switching between ABP 654 and ustekinumab, are justified by the anticipated benefits to subjects with moderate to severe plaque psoriasis.

3 Objectives and Endpoints

Table 3-1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective: • To demonstrate similarity of pharmacokinetics in subjects with multiple switches between ustekinumab and ABP 654 compared to subjects receiving continued use of ustekinumab	Primary Endpoints: Pharmacokinetic parameters: • AUC_{tau} between week 52 and week 64 • C_{max} between week 52 and week 64
Secondary Objective: • To assess the efficacy, safety and immunogenicity in subjects with multiple switches between ABP 654 and ustekinumab compared with subjects receiving continued use of ustekinumab	Secondary Endpoints: Pharmacokinetic-related Endpoints: • t_{max} between week 52 and week 64 • $C_{trough,ss}$ between week 28 and week 52 Efficacy-related Endpoints: • PASI percent improvement from baseline (day 1) to week 64 • PASI 75 response at week 64 • PASI 100 response at week 64 Safety-related Endpoints: • Treatment-emergent adverse events and serious adverse events, post randomization • Events of interest, post randomization • Incidence of antidrug antibodies, post randomization

AUC_{tau}: area under the curve from time 0 over the dosing interval; C_{max}: maximum concentration; $C_{trough,ss}$: trough concentration at steady state; PASI: Psoriasis Area and Severity Index; t_{max}: time of maximum concentration

4 Study Design

4.1 Overall Design

This is a randomized, double-blinded, phase 3 study in adult subjects with moderate to severe plaque psoriasis. This study is planned to be conducted globally at study centers including but not limited to North America and Europe.

The total duration of study participation for each subject will be 68 weeks, with up to 4 weeks for screening and 64 weeks after the first investigational product administration.

Table 4-1. Investigational Product Groups

Reference Group **Continued-use Group**	Continued use of ustekinumab administered by subcutaneous injection using a blinded prefilled syringe at a dose of 45 mg (baseline body weight ≤ 100 kg) or 90 mg (baseline body weight > 100 kg) at day 1, week 4, and week 16. Subsequent dosing will be done at the same dose every 12 weeks at weeks 28, 40, and 52.
Test Group **Switching Group**	Switching group with ustekinumab administered by subcutaneous injection using a blinded prefilled syringe at a dose of 45 mg (baseline body weight ≤ 100 kg) or 90 mg (baseline body weight > 100 kg) at day 1, week 4 and week 16. Subject will then be switched to ABP 654 at week 28, back to ustekinumab at week 40, and again to ABP 654 at week 52.

Subjects will receive an initial 3 doses of ustekinumab on day 1 (week 0), week 4 and week 16. From week 28, subjects in the continued-use group will stay on ustekinumab and subjects in the switching group will switch between ABP 654 and ustekinumab every 12 weeks.

At week 28, efficacy assessments will be conducted including evaluation of PASI.

Subjects who do not achieve a PASI 50 response or better improvement at week 28 are considered as run-in failures and will not be randomized at week 28; these subjects will complete End of Study (EOS) procedures at week 28. The run-in period will occur from day 1 until prior to randomization at week 28. Those unable to complete the week 28 visit or did not have a PASI assessment completed at week 28 will be discontinued from the study. All enrolled subjects not randomized at week 28 will be considered run-in failures and the run-in failure reason will be documented.

4.2 Scientific Rationale for Study Design

ABP 654 is being developed globally as a biosimilar to the reference product ustekinumab. Additionally, ABP 654 is being developed as an interchangeable biosimilar with ustekinumab, as

defined by US regulations. Accordingly, the continued-use group administered with only ustekinumab was chosen as the control group. Analytical similarity data available to date support the conclusion that ABP 654 is analytically similar to ustekinumab.

The current study is designed to investigate the pharmacokinetic similarity, efficacy, safety and immunogenicity of multiple switches between ustekinumab and ABP 654 compared with continued use of ustekinumab in subjects with moderate to severe plaque psoriasis.

4.2.1 Subject Input into Design

Not applicable.

4.3 Justification for Dose

The dose (45 mg or 90 mg, which is based on body weight) is the approved psoriasis dosing regimen for ustekinumab (US and EU) for which ABP 654 is being tested for interchangeability. See Section 6.7 for dose modifications.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including an EOS visit or the last scheduled procedure shown in the Schedule of Assessments (Table 1-1).

The end of the study is defined as the date of the last visit of the last subject in the study or last scheduled procedure shown in the Schedule of Assessments (Table 1-1) for the last subject in the study globally.

5 Study Population

The study population will consist of subjects with moderate to severe plaque psoriasis. Subjects (or legally acceptable representative) must be able to provide written consent and subjects must meet all the inclusion criteria and none of the exclusion criteria.

Approximately 480 subjects will be enrolled. Randomization will be stratified based on geographic region, prior biologic use for psoriasis (“yes” versus “no”) at baseline (week 0), and baseline body weight. Subjects with prior biologic use for psoriasis will be capped at 50% of the total enrolled subjects.

The number of subjects enrolled may be adjusted during the study with the actual run-in failure rate seen to ensure approximately 310 randomized subjects at week 28.

5.1 Inclusion Criteria

Subjects cannot be enrolled before all the inclusion criteria (including test results) are confirmed. Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subject is male or female and is ≥ 18 and ≤ 75 years of age inclusive, at the time of enrollment.
2. Subject has stable moderate to severe plaque psoriasis for at least 6 months (eg, no morphology changes or significant flares of disease activity in the opinion of the investigator).
3. Subject has a score of PASI ≥ 12, involvement of ≥ 10% body surface area (BSA) and static Physician Global Assessment (sPGA) ≥ 3 at screening and at baseline.
4. Subject is a candidate for phototherapy or systemic therapy.
5. Subject has previous failure, inadequate response, intolerance, or contraindication to at least 1 conventional antipsoriatic systemic therapy (eg, methotrexate, cyclosporine, psoralen plus ultraviolet light [PUVA]).
6. Female subject (except if at least 2 years postmenopausal or surgically sterile): a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline.
7. Subject or legally acceptable representative is capable of giving signed Institutional Review Board (IRB)/Independent Ethics Committee (IEC) informed consent.
8. Subject has no known history of latent or active tuberculosis. Subject must meet any 1 of the following 3 criteria:
    1. Subject has a negative test for tuberculosis during screening, defined as either:
        - Negative purified protein derivative (PPD); < 5 mm of induration at 48 hours to 72 hours after test is placed, or
        - Negative Quantiferon®/T-spot® test.
    2. Subject with a positive PPD test and a history of Bacillus Calmette-Guérin (BCG) vaccination is allowed with a negative Quantiferon/T-spot test
    3. Subject with a positive PPD test (without a history of BCG vaccination) or subject with a positive or indeterminate Quantiferon/T-spot test is allowed if he/she has all of the following:
        - No symptoms per tuberculosis worksheet provided by the sponsor, Amgen Inc.

- Documented history of adequate prophylaxis initiation prior to receiving investigational product in accordance with local recommendations
- 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

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Skin Disease Related Conditions

1. Subject has erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication induced psoriasis, or other skin conditions at the time of screening (eg, eczema) that would interfere with evaluations of the effect of investigational product of psoriasis.

Other Medical Conditions

2. Subject has a planned surgical intervention during the duration of the study.
3. Subject has an active infection or history of infections, as follows:
   a. Any active infection for which systemic anti-infectives were used within 28 days prior to enrollment
   b. A serious infection, defined as requiring hospitalization or IV anti-infectives within 8 weeks prior to enrollment
   c. Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject
4. Subject has known history or tests positive of human immunodeficiency virus (HIV) at screening.
5. Subject has hepatitis B surface antigen or hepatitis C virus antibody positivity at screening.
6. Subject has uncontrolled, clinically significant systemic disease, such as uncontrolled diabetes mellitus, cardiovascular disease, renal disease, liver disease, or hypertension.
7. Subject has known malignancy within the previous 5 years (except treated or considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma).
8. Subject has active neurological disease, such as multiple sclerosis, Guillain Barre syndrome, optic neuritis, transverse myelitis, or history of neurologic symptoms suggestive of central nervous system demyelinating disease.

9. Subject has a mean QT internal or abnormal long QT syndrome corrected using Fridericia's formula (QTcF) of > 450 msec (for male subject) or > 470 msec (for female subject) at baseline that, in the opinion of the investigator, is abnormal or clinically significant. If the mean QTcF exceeds the limits above, 1 additional triplicate electrocardiogram (ECG) may be taken.
10. Subject has moderate to severe heart failure (New York Heart Associate class III/IV).
11. Subject has known hypersensitivity to the investigational product or to any of the excipients.
12. Subject has any concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the subject.

Laboratory Abnormalities

13. Subject has laboratory abnormalities at screening, including any of the following:
    a. Hemoglobin < 9 g/dL
    b. Platelet count < 100,000/mm^3
    c. White blood cell count < 3,000 cells/mm^3
    d. Aspartate aminotransferase and/or alanine aminotransferase ≥ 2.0 × the upper limit of normal
    e. Creatinine clearance < 50 mL/min (Cockcroft Gault formula)
    f. Any other laboratory abnormality which, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results

Washouts and Non-permitted Drugs

14. Subject has had previous treatment with any agent specifically targeting IL-12 or IL-23 within 1 year prior to enrollment.
15. Subject has received biologic treatment for psoriasis within the previous month or 5 drug half-lives (whichever is longer) prior to enrollment.
16. Subject has received any investigational agents within the previous month or 5 half-lives (whichever is longer) prior to enrollment.
17. Subject has received non-biologic systemic psoriasis therapy within 4 weeks prior to enrollment (including, but not limited to, oral retinoids, methotrexate, cyclosporine, systemically administered calcineurin inhibitors, azathioprine, thioguanine, hydroxyurea, fumarates, mycophenolate mofetil, Janus kinase inhibitors, or oral or parenteral corticosteroids including intramuscular or intraarticular administration, exception: ophthalmic, otic, nasal, or inhaled corticosteroids within recommended doses is permitted).

18. Subject has received ultraviolet A phototherapy (with or without psoralen) or excimer laser within 4 weeks prior to enrollment, or ultraviolet B phototherapy within 2 weeks prior to enrollment.
19. Subject has received topical psoriasis treatment within 2 weeks prior to enrollment (exception: upper mid-strength to least potent [class III to VII] topical steroids permitted on the palms, soles, face, and intertriginous areas; bland emollients [without urea or α- or β-hydroxy acids]).
20. Subject has received live viral or live bacterial vaccination within 2 weeks prior to enrollment.
21. Subject has received BCG vaccination within 1 year prior to enrollment.
22. Subject has received other investigational procedures within 4 weeks prior to enrollment and during the course of the study.

General

23. Subject has active substance abuse within 24 weeks prior to enrollment.
24. Female subject is pregnant or breastfeeding or planning to become pregnant while participating in the study and for at least 5 months after the last dose of investigational product.
25. Sexually active subjects and their partners who are of childbearing potential (ie, neither surgically nor postmenopausal) and not agreeing to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo-Provera injections, or contraceptive implants) while participating in the study and for 5 months after the last dose of investigational product. Male subjects must agree not to donate sperm during the study and for 5 months following after last dose of investigational product or until the scheduled EOS visit (whichever is longer).
26. Subject is not likely to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator knowledge.
27. Subject has any physical or psychiatric disorder that, in the opinion of the investigator, may compromise the ability of the subject to give informed consent and/or to comply with all the required study procedures.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material.

The subject or legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved ICF before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and has been enrolled in the Interactive Web/Voice Response System (IXRS). The investigator is to document this eligibility decision and date in the subject's medical record.

Each subject will have a unique subject identification number obtained from the IXRS. This will be assigned at screening. The unique 11-digit subject identification number will be assigned in sequential order for each site in the format "417XXXXX###," where "417XXXXX" refers to the site number and "###" refers to the sequential subject ordering as each subject at a site is entered into the IXRS (eg, 41712345001). 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 investigator will keep a record (the subject screening log) that includes limited information (such as date of screening) about the potential candidates for subjects who entered screening.

If a subject withdraws from study participation, his/her unique identification number(s) cannot be re-used for another 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 necessarily be the same as the randomization number assigned for the study.

5.4 Lifestyle Considerations

5.4.1 Meals and Dietary Restrictions

Not applicable.

5.4.2 Caffeine, Alcohol, and Tobacco

Not applicable.

5.4.3 Activity

Not applicable.

5.4.4 Coronavirus Disease 2019 Considerations

Study centers and subjects will follow local and institutional guidelines, as applicable, for the prevention of COVID-19 infection. In the event that a subject experiences any signs/symptoms of COVID-19, the subject should promptly notify the investigator.

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled to the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (eg, eligibility requirements failed), and any serious adverse events.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen failure. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects should be assigned the same subject identification number as for the initial screening. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen failed subjects may be rescreened up to 2 times at the investigator's discretion (ie, a total of 3 screens including initial screening). If screening procedures cannot be completed within 28 days before day 1, the subject will be considered a screen failure but may be eligible for rescreening. These subjects can be rescreened under the same ICF if rescreening and enrollment occurs within 30 days of initial consent date. If it is longer than 30 days from the initial consent date, the subject will need to be re-consented and all screening procedures need to be repeated.

6 Investigational Product

Investigational product is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

The investigator must ensure that the investigational product will be used only in accordance with the protocol. Study treatments and investigational product are described in Table 6-1.

6.1 Investigational Product(s) Administered

Table 6-1. Investigational Product(s) Administered

Intervention Name	ABP 654	Ustekinumab
Type	Biologic	Biologic
Dosage Formulation	Liquid suspension	Liquid suspension
Unit Dose Strength(s)	45 mg/0.5 mL solution in a single dose prefilled syringe for subjects with baseline body weight ≤ 100 kg or 90 mg/1.0 mL solution in a single dose prefilled syringe for subjects with baseline body weight > 100 kg	45 mg/0.5 mL solution in a single dose prefilled syringe for subjects with baseline body weight ≤ 100 kg or 90 mg/1.0 mL solution in a single dose prefilled syringe for subjects with baseline body weight > 100 kg
Dosage Level(s)	Dose based on baseline body weight: • 45 mg (≤ 100 kg) • 90 mg (> 100 kg)	Dose based on baseline body weight: • 45 mg (≤ 100 kg) • 90 mg (> 100 kg)
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Active comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Dosing Instructions	Subjects in the switching group will be administered ABP 654 at week 28 and again at week 52.	Subjects in the switching group will be administered ustekinumab on day 1, week 4, week 16 and week 40. Subjects in the continued-use group will be administered ustekinumab on day 1, week 4, week 16 and every 12 weeks at week 28, week 40 and week 52.
Packaging and Labeling	Investigational product will be provided in a prefilled syringe. Each prefilled syringe will be labeled as required per country requirement.	Investigational product will be provided in a prefilled syringe. Each prefilled syringe will be labeled as required per country requirement.

IMP: investigational medicinal product; NIMP: non-investigational medicinal product

6.1.1 ABP 654 Dosage Form

ABP 654 is a recombinant fully human IgGκ monoclonal antibody produced by recombinant DNA technology and is produced in a glyco-engineered Chinese hamster ovary cell line. ABP 654 is purified by processes that include specific viral inactivation and filtration steps. ABP 654 and ustekinumab have the same amino acid sequence.

ABP 654 is supplied as a sterile, single-dose, preservative-free solution for SC injection and is supplied in a prefilled syringe (PFS) containing 45 mg/0.5 mL ABP 654 or 90 mg/1.0 mL ABP 654.

Each 0.5 mL PFS delivers 45 mg ABP 654, L-histidine and L-histidine monohydrochloride monohydrate, polysorbate 80, and sucrose. Each 1 mL PFS delivers 90 mg ABP 654, L-Histidine and L-Histidine monohydrochloride monohydrate, polysorbate 80, and sucrose. See the Investigator's Brochure for additional details.

6.1.2 Ustekinumab Dosage Form

Ustekinumab is a recombinant fully human IgGκ monoclonal antibody produced by recombinant DNA technology, and is produced by a Sp2/0 cell line.

Ustekinumab is supplied in 45 mg/0.5 mL and 90 mg/1.0 mL single use PFS.

Each single-dose PFS delivers 45 mg or 90 mg ustekinumab, L-Histidine, L-Histidine monohydrochloride monohydrate, polysorbate 80, and sucrose.

6.2 Preparation, Handling, Storage, and Accountability

Investigational product should be stored protected from light and according to the storage and expiration information provided on the label (where required) that is affixed to the package containing the investigational product. The PFS should be stored in a secured refrigerator (2°to 8°C) and monitored (manual or automated) in accordance with the labeled storage conditions and country-specific regulations, with access limited to the investigator and authorized site staff. Investigational product should not be frozen. The investigator or designee must maintain documentation to confirm appropriate temperature conditions have been maintained during transit and storage at site for all investigational product received and any discrepancies are reported and resolved before use of the investigational product.

The PFS should be checked for cracks or damage that may occur during transport. Damaged product should not be administered and should be returned to Amgen or its designee.

Detailed information regarding the labeling, packaging, storage, preparation, and administration of each investigational product is to be provided separately in the Pharmacy Manual.

All supplies of investigational product will be accounted for in accordance with GCP guidelines. The investigator, pharmacist, or designee should maintain accurate records of the disposition of all investigational product supplies received during the study. These records should include the amounts and dates clinical drug supplies were received and returned to Amgen or its designee. If errors or damages in the clinical drug supply shipments occur, the investigator should contact

Amgen or its designee immediately. Copies of the investigational product accountability records will be provided by each investigator for inclusion in the Trial Master File (TMF). The clinical research associate (CRA) will periodically check the supplies of investigational product held by the investigator or pharmacist to verify accountability of all medication used.

The investigator will administer investigational product only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of study, all unused investigational product and all investigational product containers should be destroyed on-site (if approved by the sponsor or designee) or returned to Amgen or its designee for destruction. In either instance, complete documentation will be returned to the sponsor or designee. Further guidance and information for the final disposition of unused investigational product are provided in the Pharmacy Manual.

The investigational product resupply will be managed by the IXRS.

6.3 Investigational Product Complaints

An investigational product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

Any investigational product complaint(s) associated with ABP 654 or ustekinumab supplied by Amgen are to be reported according to the instructions provided in the Pharmacy Manual. Any investigational product complaints associated with an adverse event are to be reported as per adverse event reporting guidelines.

6.4 Measures to Minimize Bias: Blinding and Randomization

6.4.1 Blinding

The study is double-blinded; therefore, the investigators, study personnel (with the exception of the Data Monitoring Committee (DMC), and unblinded Parexel staff supporting DMC activities and randomization list activities) and the study subjects will remain blinded to treatment allocation.

Randomization data will be kept strictly confidential, accessible only to authorized staff and the DMC until the time of unblinding. Authorized staff includes the randomization statistician, who

will store the master randomization list in a secure system, an unblinded statistician, and unblinded programmers, who will provide the DMC with unblinded data for review, as and when required, in accordance with the procedures described in the DMC Charter. All authorized unblinded staff must be documented.

ABP 654 and ustekinumab will be coded and labeled in a manner that protects blinding.

Unblinding is only allowed in the case of an emergency, when knowledge of the investigational product is essential for the clinical management of the subject. The investigator must make every effort to contact the sponsor or designee's medical monitor prior to breaking the blind and must contact the sponsor or designee within 1 working day after the event, without revealing to the sponsor (or clinical research organization [CRO]) the results of the code break, except to the designated global safety representative.

Emergency unblinding will be organized through the IXRS. The investigator must record the date of unblinding and the reason. All unblinding must be adequately documented.

If a serious adverse event is reported, the designated global safety representative may unblind the treatment assignment for the individual subject through IXRS in order to meet regulatory reporting requirements. Authorized staff will be provided with a unique Personal Identification Number (PIN) to access the IXRS to obtain blinding information. The PIN is unique to the individual and must not be shared.

6.4.2 Randomization

The site will contact the IXRS at week 28 (subjects with PASI 50 or better improvement) to receive a unique subject randomization number in order to randomize the subject centrally to either the switching group or continued-use group in a 1:1 manner. Randomization will be stratified according to the following factors: prior biologic use for psoriasis ("yes" versus "no"), baseline body weight (≤ 100 kg versus > 100 kg) at baseline (week 0), and geographic region. All enrolled subjects not randomized at week 28 will be considered run-in failures and the run-in failure reason will be documented.

In the event of a quality assurance (QA) audit, the auditor(s) will be allowed access to unblinded investigational product records to verify that randomization/dispensing has been done accurately.

6.5 Investigational Product Compliance

Records of investigational product used and intervals between visits will be kept during the study. Drug accountability will be noted by the CRA during site visits and at the completion of the study. The study treatment should be dispensed by the investigator, or by a qualified individual under the investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained.

6.6 Concomitant Therapy

6.6.1 Prohibited Treatments

- Nonstudy use of ustekinumab, or therapies that target IL-12 or IL-23, are prohibited (exclusion criterion 14).
- Any biologic treatment for psoriasis, or any experimental (biological or nonbiological) therapy (within or outside of a clinical study), except for investigational product, for subjects are prohibited (exclusion criteria 15 and 16).
- Treatments (exclusion criterion 17) which include nonbiologic systemic psoriasis therapy (including but not limited to oral retinoids, methotrexate, cyclosporine, systemically administered calcineurin inhibitors, azathioprine, thioguanine, hydroxyurea, fumarates, mycophenolate mofetil, Janus kinase inhibitors, or oral or parenteral corticosteroids including intramuscular or intraarticular administration [exception: ophthalmic, otic, nasal, or inhaled corticosteroids within recommended doses is permitted]).
- Any other nonstudy treatment for psoriasis, including UVA or UVB phototherapy and excimer laser (exclusion criterion 18) and topical therapies for psoriasis (except for those specifically allowed, exclusion criterion 19) are prohibited.
- Live viral or live bacterial vaccination (exclusion criterion 20). The investigational product should be withheld for at least 15 weeks before vaccination and only resumed at least 2 weeks after vaccination.

6.6.2 Prior and Concomitant Therapy

Prohibited treatments are described in Section 6.6.1.

Any other treatment (not explicitly excluded) which is considered necessary for the subject's welfare may be given at the discretion of the investigator. Allowed treatments include:

- Bland moisturizers/emollients (without urea or α- or β-hydroxy acids) are allowed, as needed, during the study
- Upper mid-strength to least potent (class III to VII) topical steroids are permitted only on the palms, soles, face, and intertriginous areas
- Otic, nasal, ophthalmic, or inhaled corticosteroids are not considered "systemic immunomodulating treatments" and are allowed during the study.

At screening, prior medication history will be documented.

Any vaccine or medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded.

The medical monitor should be contacted if there are any questions regarding prior or concomitant therapy.

All subjects who discontinue investigational product should be offered alternative treatment, if applicable. Treatment should be given according to normal clinical practice after the EOS visit.

6.7 Dose Modification

There are no dose modifications for investigational products (ABP 654 or ustekinumab) in this study. The ABP 654/ustekinumab dose will be based on the subject's baseline body weight and will remain the same throughout the study. Dosing will not be corrected on the basis of body weight at current visit.

If the subject presents with a serious infection at the dosing visit(s), the administration of investigational product may be delayed (up to 5 days); and subjects with serious infections need to be monitored closely and investigational product should not be administered until the infection resolves.

In the case of delayed or missed dose for any reason, subsequent doses should be administered according to the original schedule (ie, at the planned timepoint relative to first dose) investigational product dose(s).

Any toxicities associated or possibly associated with investigational product treatment should be managed according to standard medical practice. A summary of expected adverse drug reactions is provided in the Investigator's Brochure. Ustekinumab has a terminal half-life of

approximately 28.1 days, therefore discontinuation results in slow elimination over several months and will have no immediate effect.

If unmanageable toxicity due to investigational product occurs at any time during the study, treatment with the investigational product should be discontinued.

6.8 Intervention After the End of the Study

After completing dosing with investigational product at week 52 and the EOS visit at week 64, subjects will have completed the study. ABP 654 or ustekinumab will not be provided for post study use.

7 Discontinuation of Investigational Product and Subject Discontinuation

Subjects have the right to withdraw from treatment with investigational product, protocol procedures, or the study completely at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

7.1 Discontinuation of Investigational Product

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product 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 and must discuss with the subject the possibilities for continuation of the Schedule of Assessments (Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is recommended that these subjects remain in the study to ensure safety surveillance and/or collection of efficacy data, where possible. Reasons for

early removal from protocol-required investigational product(s) or procedural assessments may include:

- Decision by sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Protocol deviation
- Noncompliance
- Pregnancy

7.2 Subject Discontinuation/Withdrawal from the Study

Participation in the study is strictly voluntary. Subjects have the right to withdraw from the study by his/her own request at any time and for any reason without any reprisal, and without prejudice to future medical care by the physician or institution.

Subjects who do not achieve a PASI 50 response or better improvement at week 28 will not be randomized and will complete EOS procedures at week 28. Those unable to complete the week 28 visit or did not have a PASI assessment completed at week 28 will be discontinued from the study. The run-in period will occur from day 1 until randomization at week 28. All enrolled subjects not randomized at week 28 will be considered run-in failures and the run-in failure reason will be documented. Subjects terminating early from the study should complete all procedures scheduled for EOS visit (ie, week 64) within 28 days after withdrawal/discontinuation if possible.

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 and must document the subject's decision to withdraw in the subject's medical records. If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and

not tested, and the investigator must document this in the study center study records and notify the sponsor or designee. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Subjects who are withdrawn will not be replaced. Subjects who prematurely discontinue from the study cannot subsequently rejoin the study.

A subject may be discontinued from the study at any time at the discretion of the investigator for safety, behavioral, or administrative reasons, including, but not limited to:

- Requirement for alternative therapy or alternative dosing schedule per the investigator's determination
- The subject develops a malignancy (exception: subjects may be allowed to continue if they develop no more than 2 non-melanoma skin cancers during the study)
- Adverse events or serious adverse events
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Any other reason relating to the subject's safety or integrity of the study data
- Noncompliance with study procedures
- Withdrawal of consent from the study
- Lost to follow-up
- Decision by sponsor/investigator
- Death

Refer to the Schedule of Assessments (Table 1-1) for data to be collected at the time of study discontinuation and evaluations that need to be completed.

If a subject withdraws or is discontinued from the study, the CRA will be informed immediately.

7.3 Loss of Subjects to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Assessments (Table 1-1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue investigational product.

Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments (Table 1-1).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Investigational product will be administered after all other procedures are completed for each dosing visit.

Informed Consent

Informed consent must be documented according to Section 10.1.2, Appendix 1.

Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or designee to ensure that the subject qualifies for the study.

Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any prior conditions that the investigator considers to be clinically relevant.

Prior and Concomitant Medications Review

The investigator or qualified designee will review prior medication use and record prior medications taken by the subject.

The investigator or qualified designee will record medication, if any, taken by the subject during the study through the last visit.

Demographic Data

Demographic data, including (where permitted), date of birth/age, sex, race, and ethnicity will be documented.

8.1 Efficacy Assessments

8.1.1 Psoriasis Area and Severity Index

The PASI is a measure of the average redness (erythema), thickness (induration), and scaliness (scaling), each graded on a 0 to 4 scale of the lesions, weighted by the area of involvement (Feldman and Krueger, 2005). All assessments for a given subject should be made by the same observer, wherever possible.

8.1.2 Static Physical Global Assessment

The sPGA is a 6-point scale (0 to 5) used to measure the severity of disease (induration, scaling, and erythema, Section 10.3, Appendix 3). The sPGA should be completed by the same assessor performing the PASI assessments. All assessments for a given subject should be made by the same observer, whenever possible.

8.1.3 Affected Body Surface Area

The percent of affected BSA affected is estimated by assuming that the subject's palm, excluding the fingers and thumb, represents roughly 1% of the body's surface (Chandran, 2009). At any given visit, BSA should be performed by the same assessor performing PASI assessment. Because of interobserver variability in estimated BSA, all assessments for a given subject should be made by the same observer, whenever possible.

8.2 Safety Assessments

8.2.1 Physical Examinations

Physical examination findings will be recorded and performed by a physician.

Clinically significant abnormal changes from baseline will be reported as adverse events.

Body weight (kg) and height will be measured with the subject dressed in light clothing, without shoes or jacket. Body weight and height will be determined at screening. The baseline body weight will be measured at baseline.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as adverse events, as appropriate (Section 8.3).

8.2.2 Vital Signs

Vital signs will be measured after the subject has been resting for 5 minutes and will include systolic and diastolic blood pressure, pulse, respiratory rate, and temperature.

Systolic and diastolic blood pressure will be measured on the same arm.

Respiratory rate and temperature will also be recorded.

During the study, the measurement of vital signs may be repeated at the discretion of the investigator for safety reasons. Clinically relevant abnormal findings should be reported as adverse events.

8.2.3 Twelve-lead Electrocardiogram

Routine 12-lead ECGs will be taken as indicated in the Schedule of Assessments (Table 1-1). A routine 12-lead ECG will be taken after the subject has been resting in the supine position for at least 5 minutes. 12-lead ECGs will be taken in triplicate with approximately 1-minute intervals and all 3 ECGs will be completed within 5 minutes.

The investigator will use the study site's system to review, sign and date the ECG after recording to ensure subject safety. The time of the ECG, the interval measurements (measured automatically using the same lead whenever possible), as well as an overall conclusion, will be documented. This overall outcome will be recorded as normal, abnormal not clinically significant, or abnormal clinically significant.

Per time point, the ECGs will be stored electronically and reviewed in a timely manner by the investigator.

8.2.4 Tuberculosis Testing

A tuberculosis test will be performed at screening by PPD or Quantiferon/T-spot test. PPD tests will be performed locally, and Quantiferon/T-spot tests will be performed by the local or central laboratory. Subjects with positive PPD or positive or indeterminate Quantiferon/T-spot test may be eligible based on the sponsor's tuberculosis assessment worksheet and the other criteria listed in inclusion criterion 8.

8.2.5 Chest Radiography

Chest radiography will include anterior/posterior or posterior/anterior and lateral views. Historical films or formal reports signed off by a radiologist obtained in the 3 months prior to screening are acceptable.

8.2.6 Clinical Safety Laboratory Assessments

Refer to the list of clinical laboratory tests (Table 8-1) to be performed and to the Schedule of Assessments (Table 1-1) for the timing and frequency.

Urine pregnancy tests will be performed locally. PPD and Quantiferon/T-spot tests will be performed by the local or central laboratory as described in the Schedule of Assessments (Table 1-1). All other laboratory assessments will be performed by a central laboratory. Blood and urine samples will be collected at the times indicated in the Schedule of Assessments (Table 1-1). At visits when investigational product is administered, clinical laboratory samples will be collected before investigational product administration. Venous blood samples will be taken for hematology and biochemistry testing at visits specified in the Schedule of Assessments (Table 1-1).

Refer to the investigator Laboratory Manual for details regarding the collection, processing, and shipping of the blood and urine samples.

Any blood samples (eg, PK, immunogenicity) collected according to the Schedule of Assessments (Table 1-1) 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.

Additional and repeat laboratory safety testing may be performed at the discretion of the investigator.

The investigator (or designee) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically relevant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

Table 8-1. Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Absolute neutrophil count Hematocrit Hemoglobin	Platelet count RBC count WBC count (total) WBC count (differential)
Clinical Chemistry	Blood urea nitrogen Potassium Total bilirubin Creatinine Sodium Total protein Albumin	Glucose (random) Alkaline phosphatase AST ALT gamma-glutamyl transferase
Routine Urinalysis	pH, specific gravity, creatinine, glucose, bilirubin, blood, and protein	
Other Screening Tests	FSH and estradiol (as needed in non-WOCBP only) at screening Serum hCG pregnancy test (as needed for WOCBP) at screening Serology (HbsAg, HCV, and HIV) at screening TB[1] testing (including a TB worksheet and chest X-ray) at screening 12-lead electrocardiogram Urine pregnancy tests Creatinine clearance Immunology (ADA antibody)	

ADA: antidrug antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; HbsAG: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RBC: red blood cell; TB: tuberculosis; WBC: white blood cell; WOCBP: women of childbearing potential

1. Quantiferon®/T-spot® or purified protein derivative testing.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definitions

8.3.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with the investigational product. An adverse event can therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. 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 as well as the electronic case report form (eCRF).

8.3.1.1.1 Events Meeting the Adverse Event Definition

Events that meet the adverse event definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (e.g., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. In case of overdosage, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse events or serious adverse events if they fulfill the definition of an adverse event or serious adverse event.

8.3.1.1.2 Events NOT Meeting the Adverse Event Definition

Events not meeting the adverse event definition include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital [inpatient hospitalization for less than 24 hours]).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

8.3.1.2 Serious Adverse Event

A serious adverse event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:

- Results in death (fatal)
- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

Definitions

Life-threatening: The term “life-threatening” in the definition of “seriousness” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Disability/incapacity: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively

minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Other medically important serious event: Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.3.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

The investigator is responsible for reviewing all laboratory test results, including review of laboratory test results prior to subject enrollment and reviewing subsequent laboratory test results throughout the study. The investigator will determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. Laboratory abnormalities without clinical significance (based on the investigator's judgment) should not be recorded as adverse events or serious adverse events. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to investigational product interruption, modification, or discontinuation must be recorded as an adverse event or serious adverse event, as applicable. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. In addition, laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an adverse event or serious adverse event if they meet the definition of an adverse event or serious adverse event as described in Section 8.3.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (eg, decreased hemoglobin).

8.3.2 Assessments of Adverse Events

8.3.2.1 Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on Common Terminology Criteria for Adverse Events (CTCAE, version 4.03): http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

8.3.3 Causality

The investigator is obligated to assess the relationship between investigational product and each occurrence of each adverse event or serious adverse event.

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure in his/her assessment.

For each adverse event or serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.

The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.3.4 Documenting and Reporting of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the time of enrollment through the EOS visit are recorded in subject's medical records as well as the applicable CRF Adverse Event Summary page. The adverse event grading scale to be used for this study will be CTCAE version 4.03, as described in Section 8.3.2.1.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity (National Cancer Institute CTCAE version 4.03)
- Assessment of relatedness to investigational product, other protocol-required therapies or devices
- Action taken

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's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. A subject, or subject's legal representative, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an EOS assessment.

It is the investigator's responsibility to review all documentation (eg, hospital notes, laboratory reports, and diagnostic reports) related to an adverse event. Wherever possible, the investigator's diagnosis, not the individual signs and symptoms, will be documented as the adverse event.

It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor or responsible CRO in lieu of completion of the CRF page.

If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the sponsor or responsible CRO.

Investigators are not obligated to actively seek adverse events or serious adverse events after the subject's conclusion of study participation. However, if the investigator learns of any serious adverse event, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the investigational product or study participation, the investigator must promptly notify the sponsor.

8.3.4.1 Reporting of 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 ICF through the EOS visit are reported using the applicable CRF Adverse Event Summary page or via the paper serious adverse event report form for serious adverse events occurring during screening for subjects not enrolled.

All serious adverse events must be documented, recorded and transmitted to Amgen, or its designee, within 24 hours following the investigator's knowledge of the event.

The investigator will submit any updated serious adverse event data to the sponsor or designee within 24 hours of it being available.

The criteria for grade 4 in the CTCAE (version 4.03) 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.

If the electronic data capture (EDC) system is not functional, the serious adverse event can be reported by faxing a completed paper Serious Adverse Event Form or by direct telephone communication with Parexel at the numbers provided below. The event must be updated electronically in the EDC system by the clinical study center once the EDC function resumes.

Global reporting of serious adverse events:

- Phone (Safety line): +1 (781) 434-5010
- NorthAmerica_Medical@parexel.com

After the study is completed at a given center, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. If a center receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the center can report this information on a paper Serious Adverse Event Form.

8.3.4.2 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor (or designee) of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor (or designee) has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor (or designee) will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor (or designee) policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor (or designee) will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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 or designee before submission to regulatory authorities. Aggregate

analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

8.3.4.3 Reporting of Serious Adverse Event After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after the EOS. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after the EOS. If serious adverse events are reported, the investigator is to report them 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 study cases and handled accordingly based on relationship to investigational product.

8.3.4.4 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.3.4.5 Adverse Event and Serious Adverse Event Follow-up

During the study the adverse events and serious adverse events should be followed proactively by the investigator at subsequent visits/contact. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or until the subject is lost to follow-up. At the time the subject's study participation ends, all ongoing adverse events and serious adverse events should be evaluated for resolution. All new or updated information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information and will be recorded in the originally completed Adverse Event CRF. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts

from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Adverse Event CRF.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event and serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. If a subject dies during participation in the study, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology if available.

Events of interest are described in Section 8.3.6. Formal pre-specified evaluations for events of interest are not planned at this time.

8.3.5 Pregnancy

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects that occur after the start of study treatment and until 5 months after the last investigational product injection will be documented.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 10.2, Appendix 2. Amgen or its designee will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 10.2, Appendix 2. Pregnancy is not an adverse event unless there is suspicion of investigational product interference with effectiveness of contraceptive measures.

8.3.6 Events of Interest

Events of interest for ABP 654/ustekinumab will be defined in the Statistical Analysis Plan (SAP) and will be reviewed on an ongoing basis as part of this study. There are no additional

expedited reporting requirements for events of interest, beyond what is defined for any adverse event report that qualifies to be expedited as part of regulatory reporting rules for investigational product.

8.4 Treatment of Overdose

Single doses up to 6 mg/kg have been administered intravenously in Stelara clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

8.5 Pharmacokinetics

Serum samples will be collected for measurement of serum concentrations of investigational product as specified in the Schedule of Assessments (Table 1-1). Instructions for the collection, handling, storage and shipment of biological samples will be provided in the Laboratory Manual. Blood samples for PK testing will be collected from all subjects. Samples should be taken prior to administration of investigational product (predose) on dosing visits.

The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of investigational product serum concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Antibodies (binding and neutralizing) to investigational product will be evaluated in serum samples collected from all subjects. Additionally, serum samples should also be collected at the

final visit from subjects who discontinued investigational product or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. Samples should be taken prior to administration of investigational product (predose) on dosing visits. Samples tested positive for binding antibodies will also be further assessed for neutralizing antibodies. Additional blood samples may be obtained to rule out antidrug antibodies (ADAs) during the study.

The detection and characterization of anti-drug antibodies will be performed using a validated assay method by the sponsor or under the supervision of the sponsor.

9 Statistical Considerations

9.1 General Considerations

All personnel involved with the analysis of the study will remain blinded until database lock. Analysis will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, US) by the sponsor or its representatives.

The SAP will be developed and finalized prior to the unblinding for the final analysis. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol.

All data post randomization will be presented by treatment group (switching group versus continued-use group). Data during the run-in period, where all subjects are receiving ustekinumab, will be presented. Descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variable, and counts and percentages will be presented for categorical variables. Confidence intervals (Cis) and other inferential statistics may also be provided.

In general, baseline will be defined as the last non-missing measurement/procedure before or on the date of first administration of investigational product.

9.2 Statistical Hypotheses

The analysis of the primary PK endpoints will test the following hypotheses for each endpoint:

Null Hypothesis (H_0): The geometric means ratio (GMR) between ABP 654 and ustekinumab is outside a similarity margin of (0.8, 1.25),

versus

Alternative Hypothesis (H_A): The GMR between ABP 654 and ustekinumab is within a similarity margin of (0.8, 1.25).

To support a demonstration of interchangeability, the 90% CI of GMRs of ABP 654 versus ustekinumab for AUC_{tau} and C_{max} from the primary analysis should fall within the pre-specified similarity margin.

9.3 Sample Size Determination

Approximately 480 subjects will be enrolled to receive ustekinumab during the run-in period. Subjects with prior biologic use for psoriasis will be capped at 50% of the total enrolled subjects. This sample size will ensure approximately 310 randomized subjects at week 28 after the run-in period, considering 35% run-in failures. Randomization will be in a 1:1 ratio to the continued-use group or the switching group. The randomization will be stratified by prior biologic use for psoriasis (yes versus no) at baseline (week 0), geographic region, and body weight at baseline (week 0). The number of subjects enrolled may be adjusted during the study with the actual run-in failure rate seen to ensure approximately 310 randomized subjects at week 28. Subjects already enrolled will be allowed to be randomized at week 28. The sample size of 310 randomized subjects will provide 90% power to demonstrate similarity of the primary PK endpoints based on the Two One Sided Tests at a 0.05 significance level, assuming a between-subject variability (as measured by coefficient of variation) of 55% for ABP 654 and ustekinumab, a true GMR of 1 between ABP 654 and ustekinumab, and a similarity margin of (0.8, 1.25), and 25% drop-outs after randomization through week 64 (including subjects who discontinue the study prior to week 52 and those reaching week 52 but do not have evaluable primary PK endpoints between weeks 52 and 64).

9.4 Populations for Analysis

For purposes of analysis, the following analysis sets are defined in Table 9-1. The Full Analysis Set will be analyzed according to the treatment that the subject is randomized to (regardless of actual treatment received). For all other analysis sets, subjects will be analyzed according to the investigational product they actually received. A precise definition of “as actually received” will be added in the SAP.

Table 9-1. Populations for Analysis

Population (Analysis Set)	Description
Run-in Treated Set	The Run-in Treated Set consists of all enrolled subjects treated with at least 1 dose of ustekinumab during the run-in period.
Full Analysis Set	The Full Analysis Set consists of all randomized subjects (randomization occurs at week 28).
Safety Analysis Set	The Safety Analysis Set consists of all randomized subjects who received at least 1 dose of investigational product post randomization.
PK Concentration Analysis Set	The PK Concentration Analysis Set which will include all randomized subjects who received at least 1 dose of investigational product post randomization and have at least 1 reported serum concentration of ABP 654 or ustekinumab.

Population (Analysis Set)	Description
PK Parameter Analysis Set	The PK Parameter Analysis Set consists of all randomized subjects who receive all 3 doses of the assigned investigational product between weeks 28 and 52 and who have an evaluable ABP 654 or ustekinumab serum concentration-time profile between weeks 52 and 64.
Per-protocol PK Parameter Analysis Set	The Per-protocol PK Parameter Analysis Set consists of all subjects in the PK Parameter Set who do not have an important protocol deviation that could affect the primary PK endpoints.
Per-protocol Efficacy Analysis Set	The Per-protocol Efficacy Analysis Set consists of all subjects who are randomized and receive all 3 doses of the assigned investigational product between weeks 28 and 52 and who have not experienced an important protocol deviation that may affect the evaluation of the efficacy endpoints.

ICF: informed consent form; PASI: Psoriasis Area and Severity Index; PK: pharmacokinetic(s); SAP: statistical analysis plan

9.5 Planned Analyses

9.5.1 Primary Endpoints

9.5.1.1 Primary Pharmacokinetic Endpoints

The primary analysis of the primary PK endpoints, AUC_{tau} and C_{max}, between weeks 52 and 64 will be performed based on the PK Parameter Analysis Set according to the actual treatment groups (switching group versus continued-use group). The point estimates and 90% Cis for the GMRs between ABP 654 and ustekinumab for AUC_{tau} and C_{max} between weeks 52 and 64 will be estimated using an analysis of covariance (ANCOVA) model adjusting for stratification factors. Prior to statistical modeling, the PK parameters will be logarithmically-transformed (natural log). Point estimates and 90% Cis for the mean difference in logarithmic PK parameters will be estimated from the ANCOVA model, which will then be transformed back to the original scale to obtain the point estimates and 90% Cis for GMR.

AUC_{tau} and C_{max} of ABP 654 and ustekinumab between weeks 52 and 64 will be listed by subject and summarized descriptively by treatment group.

A sensitivity analysis of the primary PK endpoints will be conducted on the Per-protocol PK Parameter Analysis Set.

9.5.2 Secondary Endpoint(s)

9.5.2.1 Secondary Pharmacokinetic Endpoints

The analyses of the secondary PK endpoints of t_{max} between weeks 52 and 64 and $C_{trough,ss}$ between weeks 28 and 52 will be based on the PK Parameter Analysis Set according to the

actual treatment groups (switching group versus continued-use group); t_{max} will be summarized descriptively by treatment group and $C_{trough,ss}$ between weeks 28 and 52 will be summarized descriptively by visit and treatment group. The point estimates and 90% Cis for GMR for $C_{trough,ss}$ between the two treatment groups will be estimated using an ANCOVA model adjusting for stratification factors.

Mean serum concentration-time data post randomization will be presented graphically using PK Concentration Analysis Set.

9.5.2.2 Secondary Efficacy Endpoints

The analysis of the secondary efficacy endpoints will be based on the Per-protocol Efficacy Analysis Set according to the actual treatment groups (switching group versus continued-use group). A sensitivity analysis will be conducted using observed data based on the Full Analysis Set according to randomized treatment groups.

PASI 75 and PASI 100 are defined as at least 75% and 100% improvement from baseline in PASI, respectively.

The point estimate and 90% CI of the mean difference in PASI percent improvement from day 1 at week 64 will be estimated from an ANCOVA model adjusting for the baseline PASI value and the stratification factors.

The point estimate and 90% CI of the risk difference in PASI 75 response rate and PASI 100 response rate at week 64 will be estimated from a generalized linear model with an identity link adjusting for the stratification factors.

Missing data will be imputed by multiple imputation method for PASI percent improvement from day 1 at week 64 and by non-responder imputation for PASI 75 response rate and PASI 100 response rate at week 64.

9.5.3 Safety Endpoints

All reported adverse events will be categorized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version at the time of final analysis) dictionary and graded by CTCAE, version 4.03.

Safety analyses of the safety endpoints will be performed based on the Safety Analysis Set according to the actual treatment groups (switching group versus continued-use group).

Treatment-emergent adverse events post randomization are defined as adverse events that start or worsen on or after the first dose of investigational product post randomization and prior to the EOS. The numbers and percentages of subjects reporting treatment-emergent adverse events, serious adverse events and events of interests will be tabulated by treatment group. The number and percent of subjects developing binding or neutralizing ADA in the subset of Safety Analysis Set who have never tested positive (ie, tested negative or no results) prior to the first dose of investigational product post randomization and have at least one ADA result post randomization will be tabulated descriptively by treatment group and by visit.

Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting purposes. Absolute values and changes from week 28 for laboratory data post randomization will be summarized descriptively by treatment group and visit.

For vital signs post randomization, absolute values and changes from week 28 will be summarized descriptively by treatment group and visit.

The number of abnormal ECG assessments will be summarized by visit for baseline and for the post-randomization period using SAS® version 9.4 or higher. Associated listing detailing the abnormality will be generated for SAS® version 9.4 or higher.

Physical examination values post randomization will be summarized descriptively by treatment group and by visit.

9.5.4 Other Analyses

9.5.4.1 Efficacy

The analyses of the other efficacy endpoints in this section will be based on the Per-protocol Efficacy Analysis Set.

The PASI percent improvement from day 1 at weeks 28, 40, and 52 and the PASI 75 and PASI 100 response rates at weeks 28, 40, and 52 will be summarized descriptively by treatment group.

BSA absolute values and changes from baseline will be summarized descriptively by visit and actual treatment group; the change from baseline in BSA at week 64 will be analyzed in a similar manner as the PASI percent improvement from baseline at week 64.

sPGA scores will be summarized descriptively by visit and treatment group. sPGA response (0/1) will also be summarized descriptively by visit and actual treatment group; the sPGA response (0/1) at week 64 will be analyzed similarly as the PASI 75 and PASI 100 response rates at week 64.

9.5.4.2 Analyses for the Run-in Period

All analyses for the run-in period will be based on the Run-in Treated Set.

Available serum concentrations over time will be summarized descriptively for each scheduled visit during the run-in period.

Treatment emergent adverse events during the run-in are defined as adverse events that start or worsen on or after the first dose of investigational product and prior to the first dose post randomization or EOS for run-in failures.

The numbers and percentages of subjects reporting treatment-emergent adverse events, serious adverse events and events of interest while receiving ustekinumab during the run-in period will be summarized.

The number and percentage of subjects developing binding or neutralizing ADAs for ustekinumab during the run-in period will be summarized.

9.5.5 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and baseline characteristics (including height, body weight, body mass index, and disease characteristics) will be presented for the ustekinumab arm for the Run-in Treated Set and by treatment group descriptively for the other analysis sets defined in Section 9.4.

9.5.6 Exposure to Investigational Product

Exposure to ABP 654/ustekinumab will be summarized descriptively for the ustekinumab arm for the Run-in Treated Set and for each treatment group in the Safety Analysis Set for the run-in period and post randomization period, respectively.

9.5.7 Exposure to Prior and Concomitant Medication

Prior and concomitant medications will be coded using the latest available World Health Organization Drug Dictionary. For the run-in period concomitant medication will be summarized

descriptively for the Run-in Treated Set. For the Safety Analysis Set, concomitant medications during the run-in period and during the post randomization period will be summarized separately.

9.5.8 Subgroup Analyses and Covariates

The stratification factors (prior biologic use for psoriasis [“yes” versus “no”] at baseline [week 0], geographic region, and body weight at baseline [week 0]) will be included as covariates in the statistical models for the PK and efficacy analyses. Subgroup analyses will be conducted for PK parameter endpoints for ADA negative subgroups.

Full details of the subgroup analyses and covariates will be pre-specified in the SAP.

9.6 Interim Analyses

No interim analysis is planned for this study.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Note for Guidance on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US Food and Drug Administration (FDA) Code of Federal Regulations (CFR) (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC, and all applicable laws and regulations

- The protocol, protocol amendments, ICF, any ICF updates, Investigator's Brochure, subject-facing recruitment materials (eg, advertisements) and other relevant documents to be provided to subjects (if applicable) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- A copy of the written approval of the protocol and ICF must be received by Amgen or designee before recruitment of subjects into the study and shipment of Amgen investigational product. Amgen may amend the protocol at any time. The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed.

- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of serious adverse events or other significant safety findings, including adverse drug reactions that are both serious and expected, as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study center and adherence to the requirements of all applicable regulations
- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study subjects
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen or designee
- Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Informed Consent Process

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to subjects.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the subject or his/her legally acceptable representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary, and consent can be withdrawn at any point.
- 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.
- Subjects or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements where applicable, and the IRB/IEC or study center.

- Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled to the study and the date the written consent was obtained. Subject withdrawal of consent or discontinuation from study, study treatment, and/or procedures must also be documented in the subject's medical records.
- The original copy of the signed ICF will be retained at the study center.
- A copy of the ICF and any other written information must be provided to the subject or the subject's legally acceptable representative.
- If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol.
- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.
- 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 unless it is a local requirement. 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.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and personally date the ICF after:

- The written ICF and any other written information to be provided to subjects is read and explained to the subject or to the subject's legally acceptable representative
- The subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study

- The subject or the subject's legally acceptable representative has signed and personally dated the ICF, if they are capable of doing so

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

10.1.3 Data Monitoring Committee

For details on the DMC, refer to DMC Charter. The DMC will evaluate unblinded safety data throughout the study and convene approximately every 6 months after the first subject is enrolled to review safety data and issue recommendations. The DMC's constitution and the details of their roles and responsibilities are described in the DMC Charter.

A DMC will be formed with members consisting of individuals external to Amgen and the CRO chosen for their expertise in plaque psoriasis. Members of the DMC will include, at a minimum, physicians and statistician(s). The primary role of this independent DMC will be to monitor safety data.

In addition, the DMC will communicate any major safety concerns and recommendations regarding study modification or termination to Amgen senior management at any time during the conduct of the study.

Records of DMC meetings will be maintained by the CRO in a restricted, unblinded location for the duration of the study. Meeting records will be transferred and stored in the study TMF at the conclusion of the study. Selected Amgen, or its designee, staff may serve as liaisons with the DMC, but will not be voting members. Personnel at Amgen or its designee involved in preparation or review of DMC unblinded materials will not be otherwise involved in the study.

10.1.4 Financing and Insurance

10.1.4.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and Amgen, or its designee, will sign a clinical study agreement prior to the start of the study, outlining overall Amgen, or its designee, and investigator responsibilities in relation to the study.

10.1.4.2 Insurance, Indemnity, and Compensation

The sponsor will take out reasonable third-party liability insurance cover in accordance with all legal requirements. The civil liability of the investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.4.3 Financial Disclosure

Investigators and sub-investigators will provide the sponsor or designee with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.5 Data and Records Management

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

A CRF will be used to store and transmit subject information. The CRF must be reviewed and electronically signed and dated by the investigator on an ongoing basis throughout the study. The investigator is responsible for verifying that the data entries are accurate and correct by signing the CRF.

Access to the CRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the CRF completely by authorized site personnel (eg, investigators and the study coordinator). The CRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The CRFs and computers that store them must be accessible to CRAs and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported adverse event, and the investigator's assessment as to whether or not the reported adverse event is related to investigational product
- Changes (including dosages) in concomitant medications/therapies (including over-the-counter medications and vitamins or dietary supplements) or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject by telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the CRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the CRF will be electronically tracked.

10.1.5.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, completed scales, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and

complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, through an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorized persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. They will be carried out giving due consideration to data protection and medical confidentiality. The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

During the study, a CRA will review protocol compliance, compare CRF entries and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements.

10.1.5.2 Case Report Form

The file structure and format for the CRF will be provided by the sponsor or its representative and should be handled in accordance with the instructions provided.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

If corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.5.3 Study Files and Record Retention

All data derived from the study will remain the property of the sponsor. The sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of subjects, source documents, CRFs, and the investigational product inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of ABP 654. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The sponsor is responsible for informing the investigator when these documents need no longer be retained.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The study start date is the date on which the first subject is enrolled to the study. The End of Study date is defined as the date when the last subject across all centers is assessed or receives an intervention for evaluation in the study (ie, last subject visit) or has withdrawn prematurely, as applicable.

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will typically be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further investigational product development

10.1.6 Publication Policy

This study will be registered on ClinicalTrials.gov in accordance with applicable laws and publication policy and may also be registered on other publicly accessible websites, as necessary. The results of the study will be posted for public disclosure within 12 months of study completion.

The sponsor or designee is responsible for preparing and providing the appropriate regulatory authorities with the clinical study report (CSR) according to the applicable regulatory requirements. The sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of CSRs (ICH E3).

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff. The criteria described below are to be met for every publication.

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' (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed. Each author must 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.

10.1.7 Auditing and Monitoring

Sponsor-assigned CRAs will conduct regular center visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing subject recruitment, compliance with protocol procedures, completeness and accuracy of data entered into the CRFs, verification of CRF data against original source documents, occurrence of adverse events and the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

The CRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the CRA. Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the Study Monitoring Plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The sponsor or its representative may conduct audits at the investigative centers including, but not limited to, drug supply, presence of required documents, the informed consent

process, and comparison of CRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study.

The investigator (or designee) should contact the sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner

10.1.7.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study.

The sponsor and CRO will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the CSR.

10.1.7.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the subject.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include randomizing subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study subject. In the event of an important protocol deviation, the investigator will discuss the deviation with the sponsor's medical monitor

and will come to an agreement as to whether the subject should be withdrawn from the study due to the important protocol deviation.

10.1.8 Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.9 Protocol Approval and Amendment

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the sponsor.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the investigator must await approval before implementing the changes. The sponsor or designee will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB/IEC, investigator, and/or sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the subject and/or impact the subject's involvement as a study subject. In such cases, the ICF will be renewed for enrolled subjects before their continued participation in the study.

10.1.10 Study and Site Start and Closure

The study start date is the date on which the first subject is enrolled to the study. The End of Study date is defined as the date when the last subject across all centers is assessed or receives an intervention for evaluation in the study (ie, last subject visit) or has withdrawn prematurely, as applicable.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will typically be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further investigational product development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject follow-up.

10.2 Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Study-specific contraception requirements for males and females of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 5 months after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of investigational product, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential (WOCBP):

1. Premenarchal
2. Premenopausal female with one of the following:
    1. Documented hysterectomy
    2. Documented bilateral salpingectomy
    3. Documented bilateral oophorectomy

NOTE: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    4. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement > 40 IU/L is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male Subjects:

Male subjects with female partners of childbearing potential are eligible to participate if the agree to ONE of the following during the protocol-defined time frame in Section 5.2:

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 5 months after the last dose of investigational product
- The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom])

Note: If the male's sole female partner is of nonchildbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study

Female Subjects:

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below and as described in Section 5.2.

Highly Effective Contraceptive Methods That Are User Dependent[1] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2] *1.* Oral *2.* Intravaginal *3.* Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable

Highly Effective Contraceptive Methods That Are User Independent[1]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[2] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized Partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the women of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

1. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
2. Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the intervention period and for at least 5 months after the last dose of investigational product or until the scheduled End of Study visit (whichever is later).

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed at intervals as per the Schedule of Assessments (Table 1-1), and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 5 mIU/mL will be performed will be performed.

Collection of Pregnancy Information:

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 5 months after the last dose of investigational product, the information will be recorded on the Pregnancy Notification Form. The form must be submitted to Amgen or its designee within 24 hours of the center's awareness of the pregnancy (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen or its designee.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen or its designee regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Subjects Who Become Pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 5 months after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form. The form must be submitted to Amgen or its designee within 24 hours of learning of a subject's pregnancy (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 5 months after the last dose of investigational product. This information will be forwarded to Amgen or its designee. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen or its designee regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen or its designee as a pregnancy exposure case.

- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg. Female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen or its designee. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 5 months after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Form and submitted to Amgen or its designee within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 24 (Section 5.2).
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 5 months after discontinuing protocol-required therapies.

10.3 Appendix 3: Static Physician's Global Assessment Scale

Below is the sPGA scale that will be used in this study.

Score	Category	Category Description
0	Clear	• Plaque elevation = 0 (no elevation over normal skin) • Scaling = 0 (no scale) • Erythema = no evidence, hyperpigmentation may be present
1	Almost Clear	• Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) • Scaling = ± (surface dryness with some white coloration) • Erythema = light red coloration
2	Mild	• Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) • Scaling =fine (fine scale partially or mostly covering lesions) • Erythema = light red coloration
3	Moderate	• Plaque elevation = moderate (moderate elevation with rough or sloped edges) • Scaling = coarser (coarse scale covering most or all of the lesions) • Erythema = moderate (definite red coloration)
4	Severe	• Plaque elevation = marked (marked elevation typically with hard or sharp edges) • Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) • Erythema = severe (very bright red coloration)
5	Very Severe	• Plaque elevation = very marked (very marked elevation typically with hard sharp edges) • Scaling = very coarse (coarse, thick tenacious scale over most of the lesions, rough surface) • Erythema = very severe (extreme red coloration, dusky to deep red coloration)

10.4 Appendix 4: Abbreviations and Trademarks

ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ANCOVA	analysis of covariance
AUC	area under the curve
AUC_{tau}	area under the curve from time 0 over the dosing interval
BCG	Bacillus Calmette-Guérin
BSA	body surface area
CFR	Code of Federal Regulations
CDC	complement-dependent cytotoxicity
CI	confidence interval
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough,ss}$	trough concentration at steady state
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FcRn	neonatal fragment crystallizable receptor
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	geometric mean ratio
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL	interleukin
IL-12Rβ	IL-12 receptor subunit beta 1
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IXRS	Interactive Web/Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PFS	prefilled syringe
PGA	Physician's Global Assessment
PIN	personal identification number
PK	pharmacokinetic(s)
PPD	purified protein derivative
PPS	per-protocol analysis set
QA	quality assurance
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limit
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
sPGA	static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
t_{max}	time of maximum concentration
TMF	Trial Master File
US	United States
USPI	United States Prescribing Information
WOCBP	woman of childbearing potential

11 References

Amgen Inc. ABP 654 – Investigator's Brochure (Version 1-0). 21 July 2020.

BLA 125261 Clinical Pharmacology and Biopharmaceutics Review, 2009.

Chandran V, Gottlieb A, Cook RJ, Duffin KC, Garg A, Helliwell P, et al. International Multicenter Psoriasis and Psoriatic Arthritis Reliability Trial for the Assessment of Skin, Joints, Nails, and Dactylitis. Arthritis Rhem. 2009;61(9):1235-1242. doi: 10.1002/art.24562

Feldman SR, Krueger GG. Psoriasis Assessment Tools in Clinical Trials. Ann Rheum Dis. 2005;64 suppl 2(Suppl2):ii65-ii68;discussion ii69-ii73. doi 10.1136/ard.2004.031237

Stelara® Summary of Product Characteristics [SmPC], February 2020.

Stelara® United States Prescribing Information [USPI], July 2020.