Janssen Research & Development*

Clinical Protocol

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of Anti-TNFα Refractory Subjects With Active Radiographic Axial Spondyloarthritis

Protocol CNTO1275AKS3002; Phase 3
AMENDMENT 1

STELARA® (ustekinumab)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Date: 13 July 2015
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	09 April 2015
Amendment 1	13 July 2015

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (13 July 2015)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: To clarify that the Sponsor intends to enroll up to 10% of the study population with total spinal ankylosis.

Applicable Section(s)	Description of Change(s)
Rationale: All subjects regardless of self-administration or assisted administration of study agent must return to the study site for assessment of primary and major secondary endpoints, and safety assessments at the required study time points.	
Time and Events Schedule Table Footnote f	**Subjects in the 3 treatment groups who qualify for early escape will have different dosing and assessment schedules. These subjects may begin self-administration of open-label golimumab at home.** Subjects unable to have ~~injection~~ **golimumab** administered away from study site will be required to return to the site for administration of study agent injection. **Early escape subjects will return to the study site at Week 24 for assessments related to the primary and major secondary endpoints (ASAS response, BASDAI, BASFI, ASDAS [CRP]) and Week 24 safety assessments, then at Weeks 28, 40, and 52 for BASDAI and safety assessments, and lastly the final safety visit/Week 64**.
Rationale: Clarification of the Sponsor's intention to enroll up to 10% of the study population with total spinal ankyloses has been made by deletion exclusion criterion #10.	
Section 4.2 Exclusion Criteria #10	~~Have total spinal ankylosis.~~
Rationale: Two separate visits at screening for subjects have been eliminated.	
Section 9.1.2 Screening Phase	~~The screening visit may be divided into no more than 2 visits. For example, after obtaining informed consent, the investigator will complete all laboratory tests at the first visit. The subject will then return for the remainder of the screening procedures only if the subject is eligible for the study as determined by the central laboratory test results.~~
Rationale: Details regarding the physical examination assessment have been added.	

Applicable Section(s)	Description of Change(s)
Section 9.7 Safety Evaluations	**Physical examination** **A physical examination will be performed at screening and the Week 64/Final safety follow up visit. The chest, abdomen, and extremities should be examined, but otherwise the examination can be a focused one based upon the individual's medical history and manifestations of spondyloarthritis, including axial and extra-articular (uveitis, psoriasis, inflammatory bowel disease, etc.).**
Rationale: Clarification on the posttreatment assessments for subjects who discontinue study agent administration has been made.	
Section 10.3 Withdrawal from the Study	~~If a subject withdraws from the study before the end of the treatment, posttreatment assessments should be obtained (Section 9.1.4).~~ If a subject discontinues study agent administrations before the end of the treatment but does not withdraw consent for study participation, posttreatment assessments should be obtained (Section 9.1.4).
Rationale: Clarification of reporting of subject pregnancies and pregnancy outcomes has been made.	
Section 12.3.3 Pregnancy	Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. **Pregnancies must be reported by study-site personnel within 24 hours of knowledge of the event using the appropriate pregnancy notification form.** **Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.**
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of Anti-TNFα Refractory Subjects With Active Radiographic Axial Spondyloarthritis

Ustekinumab is a fully human monoclonal antibody (mAb) that binds to the IL-12/23p40 protein subunit of human interleukin (IL)-12 and IL-23 with high affinity and specificity. The binding of ustekinumab to the IL-12p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of NK and CD4+ T cells, inhibiting IL-12- and IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, ustekinumab inhibits the biological activity of IL-12 and IL-23 in all in vitro assays examined.

Elevated IL-23 levels have been reported in ankylosing spondylitis (AS), and increased numbers of IL-23 responsive Th17 cells have been demonstrated in peripheral blood mononuclear cells from spondyloarthritis (SpA) patients. Ustekinumab has shown preliminary efficacy in the radiographic axial spondyloarthritis (AxSpA) population in a small open-label study.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to assess the efficacy of ustekinumab, in adult anti-TNFα refractory subjects with active radiographic AxSpA, as measured by the reduction in signs and symptoms of radiographic AxSpA.

Secondary Objectives

The secondary objectives are to assess the effect of treatment with ustekinumab in anti-TNFα refractory subjects with active radiographic AxSpA on the following:

- Efficacy related to improving physical function, range of motion, health-related quality of life, and other health outcomes.
- Safety.
- Pharmacokinetics (PK) and immunogenicity.

Exploratory Objective

The exploratory objectives are to evaluate the effect of ustekinumab on pharmacodynamics, on the microbiome, and on pharmacogenomics in anti-TNFα refractory subjects with radiographic AxSpA.

Hypothesis

The primary hypothesis for this study is that at least 1 of the ustekinumab groups is statistically superior to placebo in reducing the signs and symptoms in subjects with active radiographic AxSpA, as assessed at Week 24 by the composite endpoint of Assessment of SpondyloArthritis International Society (ASAS) 40 response and the outcome of continuing originally assigned treatment.

OVERVIEW OF STUDY DESIGN

CNTO1275AKS3002 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of ustekinumab 45 mg and 90 mg in subjects with active radiographic AxSpA and who have been refractory to anti-TNFα therapy.

Approximately 483 subjects will be randomized at approximately 150 investigational sites. Subjects will be randomly assigned in a 1:1:1 ratio to receive subcutaneous (SC) ustekinumab 45 or 90 mg or placebo administrations at Weeks 0, 4, and 16. Permuted block randomization by interactive web response system (IWRS) will be used. Randomization will be stratified by region.

At Week 16, subjects in all 3 treatment groups who qualify for early escape (EE; subjects with <10% improvement from baseline in both total back pain and morning stiffness measures at both Week 12 and Week 16), will begin receiving open-label golimumab 50 mg SC injections at Week 16 and every 4 weeks (q4w) thereafter through Week 52.

At Week 24, all remaining placebo subjects who did not meet EE criteria will be rerandomized using IWRS to begin receiving ustekinumab 45 or 90 mg at Weeks 24 and 28 followed by q12w therapy with the last study agent administration at Week 52 and have the final follow-up visit at Week 64. All subjects in the ustekinumab 45 mg and 90 mg treatment groups who do not qualify for EE will continue to receive the treatment they were randomized to at Week 0 through Week 52 and have the final follow-up visit at Week 64.

Database locks (DBL) will occur at the time of the interim analysis, Week 24, and Week 64.

An independent Data Monitoring Committee (DMC) will be commissioned for this study.

A group sequential design using the O'Brien and Fleming boundary will be applied with 1 interim analysis at the time when approximately 50% of subjects have completed the Week 24 visit or end study participation before the Week 24 visit.

Subjects will be followed for adverse events (AE) and serious adverse events (SAE) at least 12 weeks following the last study treatment administration. The end of study is defined as the time the last subject completes the Week 64 visit.

SUBJECT POPULATION

The target study population is adult subjects who have been refractory to anti-TNFα therapy and have active radiographic AxSpA, as evidenced by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and a visual analog scale (VAS) for total back pain of ≥4, each on a scale of 0 to 10. All subjects are required to have a screening high sensitivity C-reactive protein (hsCRP) level ≥0.300 mg/dL. Background treatment with nonsteroidal anti-inflammatory drugs (NSAID), select non-biologic disease-modifying antirheumatic drugs (DMARD), and low dose corticosteroids will be allowed during the study at stable doses through Week 24.

- Subjects must have a diagnosis of definite AS, as defined by the 1984 modified New York criteria.
- The radiographic criterion and at least 1 clinical criterion must be met:
  a. Radiographic criterion: Sacroiliitis Grade ≥2 bilaterally or sacroiliitis Grade 3 to 4 unilaterally as assessed by the central reader.
  b. Clinical criteria (at least 1):
     1) Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest.
     2) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
     3) Limitation of chest expansion relative to normal values corrected for age and sex.

Screening for eligible subjects will be performed within 8 weeks before the first administrations of the study agent. Subjects with complete ankylosis of the spine, defined as bridging syndesmophytes present at all intervertebral levels of the cervical and lumbar spine visualized on lateral-view spinal radiographs are permitted to be included in the study, but will be limited to approximately 10% of the study population.

Subjects must also meet the inclusion and exclusion criteria.

DOSAGE AND ADMINISTRATION

Before the first study agent administration, subjects will be randomly assigned in a ratio of 1:1:1 to 1 of 3 treatment groups:

- Group 1 (placebo): Placebo at Weeks 0, 4, and 16. At Week 24 all subjects (with the exception of subjects who qualified for EE) will be rerandomized to receive either ustekinumab 45 or 90 mg SC at Weeks 24 and 28 followed by q12w dosing, with the last administration of study agent at Week 52.
- Group 2 (ustekinumab 45 mg): Ustekinumab 45 mg at Weeks 0 and 4, followed by q12w dosing, with the last administration of study agent at Week 52. At Week 24, subjects will receive placebo SC to maintain the blind.
- Group 3 (ustekinumab 90 mg): Ustekinumab 90 mg at Weeks 0 and 4, followed by q12w dosing, with the last administration of study agent at Week 52. At Week 24, subjects will receive placebo SC to maintain the blind.

Subjects who qualify for EE at Week 16 will be administered golimumab 50 mg SC q4w.

To maintain the blind, all randomized subjects will receive each administration of ustekinumab/placebo as 2 SC injections totaling 1.5 mL in 2 different locations as follows:

- Placebo: 0.5 mL placebo injection and 1.0 mL placebo injection.
- Ustekinumab 45 mg: 0.5 mL ustekinumab 45 mg injection and 1.0 mL placebo injection.
- Ustekinumab 90 mg: 1.0 mL ustekinumab 90 mg injection and 0.5 mL placebo injection.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy evaluations chosen for this study were established in previous trials of therapeutic biologic agents for the treatment of radiographic AxSpA. Patient reported outcomes (PRO) chosen for this study are consistent with clinically relevant measurements that are accepted in the medical literature for other studies in AS and applicable regulatory guidance documents.

Axial spondyloarthritis response evaluations include:

- Assessment in Ankylosing Spondylitis Response Criteria
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Patient's Global Assessment
- Total Back Pain
- Night Back Pain
- Morning Stiffness

- Musculoskeletal Assessments
  - Bath Ankylosing Spondylitis Metrology Index (BASMI)
  - Chest Expansion
  - Maastricht Ankylosing Spondylitis Enthesitis Score
- Ankylosing Spondylitis Disease Activity Score
- Imaging Evaluations
  - X-rays of sacroiliac joints
- 36-item short form health survey (SF-36)
- Medical Outcomes Study Sleep Scale
- Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire
- Functional Assessment of Chronic Illness Therapy - Fatigue Questionnaire
- EuroQol 5 Dimension (EQ-5D) Questionnaire
- Work Productivity and Activity Impairment Questionnaire (WPAI-SHP)

Primary Endpoint

The primary endpoint is the proportion of subjects achieving an ASAS 40 response at Week 24.

Major Secondary Endpoints

The following major secondary analyses will be performed. The major secondary endpoints are listed in order of importance as specified below:

1. The proportion of subjects who achieve an ASAS 20 at Week 24.
2. The proportion of subjects who achieve at least 50% improvement from baseline in BASDAI at Week 24.
3. The change from baseline in BASFI at Week 24.
4. The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24.

PHARMACOKINETIC EVALUATIONS

All serum ustekinumab concentrations below the limit of quantification (BLQ) of the assay or missing data will be labeled as such in the concentration data listing or SAS dataset. Concentrations below the BLQ of the assay will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

Descriptive statistics, including arithmetic mean, standard deviation, median, interquartile range, minimum, and maximum will be calculated at each sampling time point.

Serum ustekinumab concentrations will be summarized for each treatment group over time. If feasible, a population PK analysis using nonlinear mixed effects modeling approach (NONMEM) will be used to characterize the disposition characteristics of ustekinumab in the current study. The CL/F and V/F will be estimated. The influence of important variables (such as body weight, positive for antibodies to ustekinumab, and the use of methotrexate [MTX], etc.) on the population PK parameter estimates may be evaluated. Details will be given in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

IMMUNOGENICITY EVALUATIONS

The incidence and titers of antibodies to ustekinumab will be summarized by treatment group over time. The impact of antibodies to ustekinumab on PK, efficacy, and safety will be assessed.

PHARMACODYNAMIC EVALUATIONS

Pharmacodynamic markers are considered exploratory.

BIOMARKER AND MICROBIOME EVALUATIONS

Changes in serum, RNA, fecal microbial profiles, and other biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and clinical response will be explored. All biomarker analyses will be summarized in a separate technical report.

PHARMACOGENOMIC (DNA) EVALUATIONS

Pharmacogenomic and epigenetics analyses are considered exploratory.

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Subject participation in the pharmacogenomic research is optional.

SAFETY EVALUATIONS

Subject safety evaluations including assessments of the following: adverse events (including injection-site reactions and infections), clinical laboratory tests (hematology, chemistry, and pregnancy testing), vital signs, physical examinations, concomitant medication review, electrocardiograms, and early detection of tuberculosis will be monitored through the end of the study as delineated in the Time and Events Schedule.

Based upon the safety profile of ustekinumab, as well as the golimumab safety data to date, several AEs of interest have been identified and will be monitored and assessed in this study. These include: injection reactions, major cardiovascular events (MACE), demyelination, hepatobiliary laboratory abnormalities, infections including TB, and malignancies.

STATISTICAL METHODS

Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for categorical variables will be used to summarize most data.

Unless otherwise specified, the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by region will be used to compare categorical variables such as the proportion of subjects responding to treatment. In general, continuous response parameters will be compared using an analysis of variance model, with region as covariate if appropriate. All statistical testing will be performed 2-sided. In addition to statistical analyses, graphical data displays (eg, line plots) and subject listings may also be used to summarize/present the data. Specific details will be provided in the Statistical Analysis Plan (SAP).

Population Set

The population set will be a modified intention-to-treat (mITT; ie, all randomized subjects who received at least 1 administration of study treatment). Subjects included in the efficacy analyses will be summarized according to their assigned treatment group regardless of whether or not they receive the assigned treatment.

Safety and PK analyses will include all subjects who received at least 1 administration of study treatment.

Endpoint Analyses

Primary Endpoint Analysis

The primary endpoint is the proportion of subjects who achieve an ASAS 40 response at Week 24. The primary hypothesis is to compare at Week 24 the composite endpoint of ASAS40 response and the outcome of continuing originally assigned treatment. Hence, subjects who early escape to golimumab, meet treatment failure criteria, or have missing ASAS assessment are nonresponders for the composite endpoint.

The proportion of subjects who achieve the composite endpoint at Week 24 will be compared between the ustekinumab groups and placebo group using a CMH test stratified by region at a significance level of 0.05 (2-sided). Data from all randomized subjects who received at least 1 administration of study treatment (mITT) will be analyzed according to their assigned treatment group regardless of their actual treatment received.

Sensitivity analyses with modified analysis sets and different rules may be conducted, and will be documented in detail in the SAP.

In addition, subgroup analysis will be performed to evaluate consistency in the primary efficacy endpoint by demographic characteristics, baseline disease characteristics, and baseline medications. Interaction test between the subgroups and treatment group will also be provided if appropriate.

Major Secondary Analyses

To control for multiplicity for the primary endpoint analysis and the major secondary endpoint analyses, the 4 major secondary analyses listed below will be performed sequentially contingent upon the success of the primary statistical analysis in that treatment group comparison. Otherwise, the p-values for the subsequent endpoints will be considered as supportive analyses. The following prespecified order will be used to analyze the major secondary endpoints.

- The proportion of subjects who achieve an ASAS 20 at Week 24.
- The proportion of subjects who achieve at least a 50% improvement from baseline in BASDAI at Week 24.
- The change from baseline in BASFI at Week 24.
- The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24.

Safety Analysis Overview

Routine safety evaluations will be performed. The occurrences and type of AEs, SAEs, and reasonably related AEs including injection reactions and infections will be summarized by treatment groups. The number of subjects with abnormal laboratory parameters (hematology and chemistry) based on NCI-CTCAE toxicity grading will be summarized.

All safety analyses will be performed using the population of all subjects who received at least 1 administration of study agent.

In addition, graphical data displays (eg, line plots) and subject listings may also be used to summarize/present data.

TIME AND EVENTS SCHEDULE

Table 1: Times and Events from Study Initiation Through Week 64

Phase	Screening	Placebo-controlled and Active treatment										Safety follow-up
Week	-8	0	4	8	12	16	20	24	28	40	52/Final Efficacy Visit[a]	64/Final Safety Visit[b]
Study Procedures[c]												
Screening/Administrative[d]												
Informed consent[e]	X											
Informed consent for pharmacogenomics (DNA; optional)	X											
Inclusion/exclusion criteria	X	X										
Medical history and demographics	X											
Study agent Administration												
Randomization		X						X				
Study agent administration[f,g]		X	X			X		X	X	X	X	
Injection site reaction evaluation[h]		X	X			X		X	X	X	X	
Safety Assessments												
Physical examination	X											X
ECG	X											
HIV, HBV, and HCV	X											
QuantiFERON-TB Gold test	X											
Tuberculin skin test[i]	X											
TB evaluation[j]	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[k]	X											
Urine pregnancy test[k]		X	X			X		X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Weight	X							X			X	X
Chest X-ray[l]	X											
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments												
BASDAI	X	X	X	X	X	X	X	X	X	X	X	
BASFI		X	X	X	X	X	X	X	X	X	X	
Patient's Global assessment		X	X	X	X	X	X	X	X	X	X	
Total Back Pain assessment	X	X	X	X	X	X	X	X	X	X	X	
Night Back Pain assessment		X	X	X	X	X	X	X	X	X	X	
BASMI		X				X		X			X	

Table 1: Times and Events from Study Initiation Through Week 64

Phase	Screening	Placebo-controlled and Active treatment										Safety follow-up
Week	-8	0	4	8	12	16	20	24	28	40	52/Final Efficacy Visit[a]	64/Final Safety Visit[b]
Study Procedures[c]												
Chest expansion		X				X		X			X	
Enthesitis evaluation		X				X		X			X	
IWRS for total back pain and morning stiffness					X	X						
SF-36[m]		X				X		X			X	
ASQOL[m]		X				X		X			X	
EQ-5D[m]		X				X		X			X	
FACIT-F[m]		X				X		X			X	
MOS-SS[m]		X				X		X			X	
WPAI-SHP[m]		X				X		X			X	
X-ray (SI joints)	X[n]											
Clinical Laboratory Assessments												
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X[f]	X	X	X
hsCRP	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics/Immunogenicity												
Serum ustekinumab concentrations[o]		X	X	X	X	X	X	X	X	X	X	X
Antibodies to study agent[o]		X	X	X	X			X		X	X	X
Pharmacogenomics (DNA)												
Whole blood DNA[p]		X						X			X	
Biomarkers												
HLA-B27 status[q]	X											
Whole blood for RNA gene expression		X						X			X	
Serum for biomarker assessment		X						X			X	
Microbiome stool sample[r]		X	X					X			X	

Table 1: Times and Events from Study Initiation Through Week 64

a. Subjects who discontinue study agent administrations before the Week 24 visit should return for all visits through Week 24. Subjects who discontinue study agent after Week 24 and before the Week 52 visit, must return as soon as possible for a final efficacy follow-up visit (refer to Week 52 assessments).
b. For subjects who discontinue study agent administrations prematurely, a final safety visit (refer to Week 64 assessments) must be performed 12 weeks after last study agent administration.
c. All assessments are to be completed prior to study agent injection, except at Weeks 8, 12, and 20 (no study agent injection), unless otherwise specified. For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety assessments.
d. X-ray assessments may be performed after all other screening assessments are performed.
e. The informed consent to participate in the optional microbiome substudy at selected sites is offered in the main informed consent form.
f. Subjects in the 3 treatment groups who qualify for early escape will have different dosing and assessment schedules. These subjects may begin self-administration of open-label golimumab at home. Subjects unable to have golimumab administered away from study site will be required to return to the site for administration of study agent injection. Early escape subjects will return to the study site at Week 24 for assessments related to the primary and major secondary endpoints (ASAS response, BASDAI, BASFI, ASDAS [CRP]) and Week 24 safety assessments, then at Weeks 28, 40, and 52 for BASDAI and safety assessments, and lastly the final safety visit/Week 64.
g. Ustekinumab/placebo study agent SC injections will be administered as indicated in Table 1, except that subjects who qualify for early escape will switch to administration of golimumab SC every 4 weeks from Week 16 through Week 52.
h. Subjects should be monitored for the occurrence of injection site reactions for 30 minutes after the injection.
i. Only required if QuantiFERON is not registered/approved locally or the tuberculin skin test (TST) is mandated by local health authorities.
j. If TB is suspected at any time during the study, a chest x-ray, and QuantiFERON-TB Gold test should be performed. A TST is additionally required if the QuantiFERON-TB Gold test is not registered/approved locally or the TST as mandated by local health authorities.
k. Pregnancy testing may be repeated at any time at the discretion of investigator or subject, or as required by local regulation.
l. May be taken within 3 months prior to the first administration of study agent.
m. All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.
n. An existing x-ray may be sent for central reading in lieu of screening x-ray. If x-ray is not of adequate quality a new screening x-ray must be submitted.
o. The same serum samples will be used for the measurement of ustekinumab concentration and detection of antibodies to ustekinumab. For visits with study agent administration, all blood samples for assessing pre-injection ustekinumab concentration and antibodies to ustekinumab MUST be collected BEFORE the administration of the study agent.
p. Participation is optional and subjects must sign a separate pharmacogenomics informed consent.
q. This test should be performed if previous results are not available, in which case a sample will be collected for HLA-B27 at screening.
r. Only from approximately 100 subjects who consent and are randomized to participate in the microbiome substudy at selected sites.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AS	ankylosing spondylitis
ASAS	Assessment in SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life questionnaire
AST	aspartate aminotransferase
AxSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacille Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
CMH	Cochran-Mantel-Haenszel
DBL	database lock
DMARD	disease-modifying antirheumatic drugs
eCRF	electronic case report form
EE	early escape
EQ-5D	EuroQol 5 Dimension
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
hs-CRP	high sensitivity C-reactive protein
IWRS	interactive web response system
MA	musculoskeletal assessor
mAb	monoclonal antibody
MACE	major cardiovascular events
MCS	Mental Component Summary
mITT	modified intention-to-treat
MOS-SS	Medical Outcomes Study Sleep Scale
MTX	methotrexate
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NONMEM	nonlinear mixed effects modeling approach
NSAID	nonsteroidal anti-inflammatory drugs
PCS	Physical Component Summary
PFS	prefilled syringe
PGA	Patient's Global Assessment
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	Patient Reported Outcome
PsA	psoriatic arthritis
q12w	every 12 weeks
q4w	every 4 weeks
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SpA	spondyloarthritis
SSZ	sulfasalazine
TB	tuberculosis
TNFα	tumor necrosis factor alpha

TST	tuberculin skin test
ULN	upper limit of normal
VAS	visual analog scale
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire - Specific Health Problem

1. INTRODUCTION

Ustekinumab is a fully human monoclonal antibody (mAb) that binds to the interleukin (IL)-12/23p40 protein subunit of human (IL)-12 and IL-23 with high affinity and specificity. The binding of ustekinumab to the IL-12p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of NK and CD4+ T cells, inhibiting IL-12- and IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, ustekinumab inhibits the biological activity of IL-12 and IL-23 in all in vitro assays examined.

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure (IB) and Addenda for ustekinumab.

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Disease Background

The spondyloarthritides (ankylosing spondylitis [AS], psoriatic arthritis [PsA], enthesitis-related arthritis [a subset of juvenile inflammatory arthritis], the enthesitis/arthritis associated with inflammatory bowel disease, and reactive arthritis) are a family of chronic inflammatory disorders of unknown etiology characterized by enthesitis (inflammation at the sites where tendons or ligaments insert into the bone) and a high association with the HLA-B27 antigen. These disorders have been more recently distinguished by focusing on the peripheral or axial predominance of their inflammatory manifestations. Axial spondyloarthritis (AxSpA) is a chronic inflammatory disease of the axial skeleton manifested by back pain and progressive stiffness of the spine.

Axial spondyloarthritis is defined using the Assessment of SpondyloArthritis international Society (ASAS) 2009 classification criteria as a condition characterized by back pain for at least 3 months and an age of onset less than 45 years. In addition, evidence of sacroiliitis by radiographs or by magnetic resonance imaging (MRI) with at least 1 typical spondyloarthritis (SpA) feature or the presence of human leucocyte antigen (HLA)-B27 and at least 2 typical SpA features needs to be present. AxSpA encompasses the continuum of disease presentation, with that 10 to 12% of patients progress from a nonradiographic state to AS.[37] Radiographic AxSpA is thus synonymous with established AS with radiographic evidence of sacroiliitis defined by the modified New York criteria[53] and therefore radiographic AxSpA and AS have been used interchangeably throughout the document.

While nonsteroidal anti-inflammatory drugs (NSAID) are effective in treating the signs and symptoms of AxSpA in many patients, traditional disease-modifying anti-rheumatic drugs (DMARD) are not effective for the axial component, and the use of systemic corticosteroids is not supported by evidence; however, anti-tumor necrosis factor alpha (TNFα) therapies have been approved for use in AS for several years.

While anti-TNFα agents show efficacy in patients with radiographic AxSpA, there are reasons to study the effectiveness of new agents targeting different mechanisms of action. For example, there is a large subset of the patient population who do not achieve a clinical response, as defined by at least 20% improvement from baseline in ASAS measures. Furthermore, an even smaller proportion of patients achieve a higher level of ASAS response (40% improvement) following treatment with current anti-TNFα therapies, and these products, while efficacious, also have significant potential risks. Current ASAS treatment guidelines note that, according to several case report studies and as well as a large retrospective registry study, those patients who do not achieve clinical response during treatment with an anti-TNFα agent may often achieve an adequate response by switching to a different anti-TNFα agent.[6] In those studies, approximately 30% of patients switched anti-TNFα agents over time, primarily for lack of efficacy. While subsequent response rates were lower than in primary responders, over half of the patients who switched to another anti-TNFα agent achieved a response.[20]

Therefore, new therapies targeting pathways other than TNFα, especially those with an improved benefit/risk profile, may result in improved alternative options for patients with radiographic AxSpA.

1.2. Overall Rationale for the Study

1.2.1. Scientific Rationale for Use of Anti-IL-12/23p40 Therapy in Radiographic AxSpA

Ankylosing spondylitis (radiographic AxSpA) is thought to be triggered by a combination of both environmental and genetic factors. Genetically, AS is most strongly associated with the HLA-B27 gene, a major histocompatibility complex Class I molecule expressed ubiquitously across cell types. Misfolding and accumulation of HLA-B27 proteins can activate cellular stress responses that are linked to cytokine dysregulation, including upregulation of IL-23 production and induction of the T-helper (Th)17 axis.[12] The IL-23/Th-17 axis is emerging as an important inflammatory pathway, with strong genetic associations with IL23R and polymorphisms having been shown in AS,[7,13,41] suggesting that IL-23 is involved in the disease pathogenesis.[24] Interestingly, protection from AS, as well as from other spondyloarthritis-associated disorders like Crohn's disease and psoriasis, is conferred by an IL23R variant due to reductions in responsiveness to IL-23 and downstream factors, including IL-17.[15] Genetic as well as clinical correlations with the IL-23/Th17 pathway are also evident in another spondyloarthropathy, PsA.[5,25,35,38,39]

In terms of cytokine overexpression, elevated IL-23 levels been reported in AS,[46] and increased numbers of IL-23 responsive Th17 cells have been demonstrated in peripheral blood mononuclear cells from SpA patients.[45] IL-23 levels in blood and synovial fluid can be higher than normal in SpA patients;[33,43] however, serum IL-23 levels have not been shown to correlate with disease activity in SpA.[34] Cells expressing IL-12 and IL-23 have been detected in the subchondral bone marrow and fibrous tissue replacing bone marrow in the facet joints of patients with AS.[3] Subclinical bowel inflammation is commonly associated with 70% of spondyloarthropathy patients, and IL-23 expression is upregulated in the ileum of patients with

AS.[11] Clinical studies of the anti-IL-17 agent, secukinumab, have shown that blocking the Th17 axis in AS can be an effective approach.[4,14,48]

Structural damage in AxSpA is characterized by 2 distinct features: erosive bone damage and pathological new bone formation. Chronic inflammation in the spine and pelvis stimulates bone erosion followed by osteoproliferation and formation of bony spurs that create the ankylosis characteristic of the structural damage observed in radiographic AxSpA. In the preclinical setting, a pivotal study showed that over-expression of IL-23 in a mouse spondylitis model leads to axial and peripheral enthesitis and new bone formation by stimulating a population of inflammatory CD4-, CD8- resident T cells in the entheses.[47] While IL-23 and other cytokines, including TNF, IL-1, and IL-6, have been shown to mediate inflammatory processes responsible for bone resorption,[1,10,24] the link between chronic inflammation and new bone formation are not fully understood. Interferon gamma and cytokines downstream of IL-23, including IL-17 and IL-22, have been shown to play a role in new bone formation.[17,29,47] Therefore, by blocking IL-23 and its downstream mediators, ustekinumab may theoretically lead to improvement in structural damage over time.

1.2.2. Rationale for Ustekinumab in Axial Spondyloarthritis

The benefits of treatment with ustekinumab have been demonstrated in the PsA population.[26,31,42] and are summarized in Section 1.2.3, including improvements in symptoms in the subgroups of PsA subjects with spondylitis. Ustekinumab has shown preliminary efficacy in the radiographic AxSpA population in a small open-label study (Section 1.2.4).

1.2.3. CNTO1275PSA3001 and CNTO1275PSA3002 PsA Studies

The Sponsor has conducted 2 Phase 3 placebo-controlled studies with ustekinumab in over 900 subjects with active PsA, CNTO1275PSA3001 and CNTO1275PSA3002. Study CNTO1275PSA3001 included biologic naïve subjects and in study CNTO1275PSA3002, approximately 60% of subjects were exposed to anti-TNFα agents prior to study entry. [26,31,42] The 24-week data from these studies formed the basis for the approval of ustekinumab for the treatment of subjects with active PsA. These 2 studies clearly demonstrated improvements in peripheral arthritis, physical function, dermatologic manifestation, soft tissue disease (dactylitis and enthesitis), and improvements in health-related quality of life in subjects with active PsA.

Approximately 30% of subjects in study CNTO1275PSA3001 and 22% in study CNTO1275PSA3002 in addition to peripheral joint involvement, had evidence of spondylitis (axial inflammation) at baseline as judged by investigators. Over 70% of subjects in both trials had also evidence of enthesitis based on investigators' assessment.

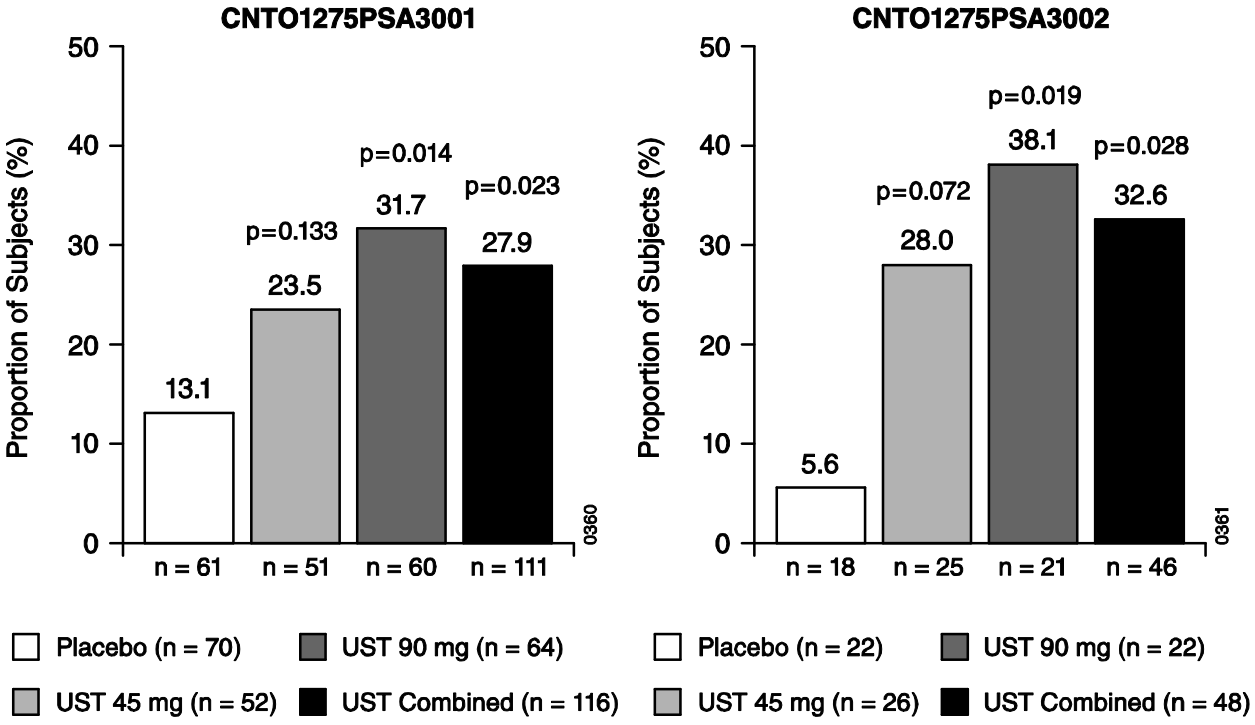
1.2.3.1. Subgroup of Subjects with Spondylitis

Efficacy analyses in the spondylitis subset showed improvement for both ustekinumab 45 mg and 90 mg in the signs and symptoms of PsA as measured by American College of Rheumatology (ACR) 20 at Week 24 which focuses on peripheral manifestations of the disease. Results were comparable with other subtypes of PsA.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questionnaire (a validated tool for the assessment of spinal disease in subjects with AS) was used as an exploratory analysis in the ustekinumab PsA studies for the purpose of providing data on axial manifestations of PsA.

The number of subjects in each study included in the BASDAI analyses was 186 subjects in CNTO1275PSA3001 and 70 subjects in CNTO1275PSA3002. In both studies, a significantly higher proportion of subjects achieved a BASDAI 50 response at Week 24 in the ustekinumab 90 mg group compared with placebo (31.7% vs 13.1% [p=0.014] in CNTO1275PSA3001 and (38.1% vs 5.6% [p=0.019] in CNTO1275PSA3002; Figure 1). Numerically higher proportions of subjects achieved a BASDAI 50 response in the ustekinumab 45 mg group compared with placebo (23.5% vs 13.1% in CNTO1275PSA3001 and 28.0% vs 5.6% in CNTO1275PSA3002; (Figure 1).

Figure 1: Proportion of subjects with BASDAI 50 responses at Week 24 in CNTO1275PSA3001 and CNTO1275PSA3002 trials in subjects with active PsA



1.2.3.2. Enthesitis Evaluation

In both Phase 3 studies, a dose response was observed in the percent improvement in enthesitis from baseline at Week 24 based on the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES). Statistical significance was reached for both dose groups as compared with placebo in CNTO1275PSA3001 (median percent change in MASES was -50.00 vs 0.00 for 90 mg vs placebo [p<0.001] and -42.86 vs 0.00 for 45 mg vs placebo [p=0.002]), while significance was only reached for 90 mg as compared with placebo in CNTO1275PSA3002 (median percent

change in MASES was -48.33 vs 0.00 for 90 mg vs placebo [p=0.008] and -33.33 vs 0.00 for 45 mg vs placebo [p=0.098]).

1.2.4. Investigator-Initiated Study in AS

Ustekinumab was evaluated for the treatment of subjects with active AS in an open-label, proof-of-concept investigator-initiated study TOPAS.[36]

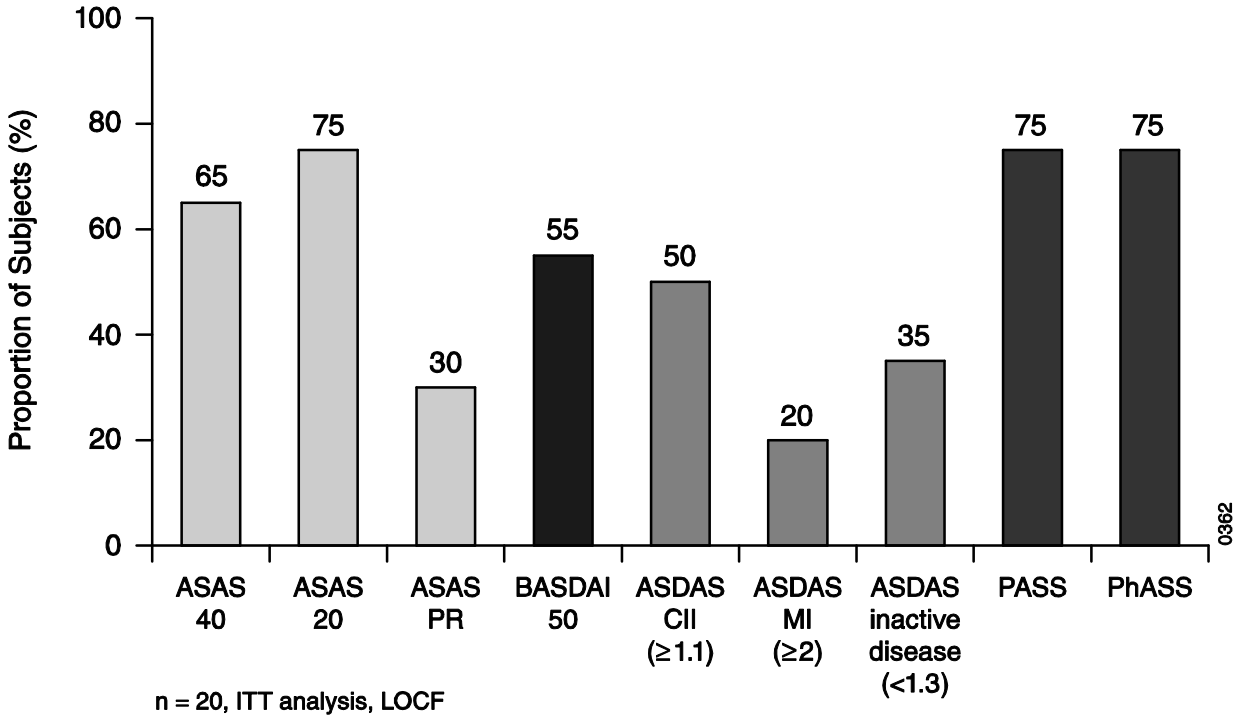
In this study, 20 subjects with active AS (defined as meeting the modified New York criteria and having active disease defined as a BASDAI score ≥4 despite concomitant treatment with a NSAID) received ustekinumab 90 mg at Weeks 0, 4, and 16, and were followed through Week 28. One (5%) of the subjects had previously received anti-TNFα therapy. Subjects who had a history of lack of efficacy to an anti-TNFα agent were excluded, but otherwise previous exposure to anti-TNFα agents was allowed.

The proportion of subjects who achieved the primary endpoint, ASAS 40 response at Week 24, was 65% (Figure 2). Key secondary endpoints also showed clinically meaningful improvement: 75% of subjects achieved an ASAS 20 response at Week 24 and 55% achieved a BASDAI 50 response at Week 24 (Figure 2). Significant mean improvement from baseline to Week 24 was observed for the MRI imaging parameters (sacroiliac [SI] joint osteitis score and spine osteitis score).[36]

Ustekinumab was well tolerated in this study. There was 1 serious adverse event (SAE) of hospitalization for back pain due to an uncomplicated flare of AS. No new safety signals were detected.

Although this was a small, uncontrolled open-label study, the efficacy and safety data showed promising results for ustekinumab use in the AS population.

Figure 2: Summary of Efficacy Results in Investigator Initiated Study in AS (TOPAS)



ASAS=Assessment of SpondyloArthritis international Society; ASAS PR=Assessment of SpondyloArthritis international Society-Partial remission; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; ASDAS CII=Ankylosing Spondylitis Disease Activity Score-Clinically Important Improvement; ASDAS MI =Ankylosing Spondylitis Disease Activity Score-Major Improvement; PASS=Patient Acceptable Symptom State; PhASS=Physician Acceptable Symptom State.

1.3. Dose Justification

The proposed dose regimen for the CNTO1275AKS3001 Phase 3 study is selected primarily based on the dosing regimen used in the Phase 3 CNTO1275PSA3001 and CNTO1275PSA3002 studies in PsA, supplemented with data from the TOPAS study. In general, ustekinumab 45 and 90 mg (for patients weighing >100 kg with moderate to severe psoriasis) at Weeks 0 and 4 followed by every 12 weeks (q12w) maintenance therapy are the approved doses for the treatment of patients with active PsA.

The proposed dosing regimens for this Phase 3 study in radiographic AxSpA are ustekinumab 45 and 90 mg administered subcutaneously at Weeks 0 and 4, then q12w. The rationale for the 45 and 90 mg q12w dose regimens is as follows:

- In studies CNTO1275PSA3001 and CNTO1275PSA3002 in PsA, improvement in the joint, soft tissue, and skin manifestations of active PsA improved through the 24-week placebo-controlled observation period and over time for subjects treated with both ustekinumab 45 and 90 mg.
- Most relevant to the proposed study, CNTO1275PSA3001 and CNTO1275PSA3002 included a subset of total 256 (27.6%) subjects with spondylitis (in addition to peripheral arthritis; see Section 1.2.3.1 and Figure 1). These subjects were included in the BASDAI analyses. In both studies, and although not powered to show a difference, a significantly higher proportion of subjects achieved a BASDAI 50 response at Week 24 in the ustekinumab 90 mg group compared with placebo and there were numerical improvements in subjects receiving 45 mg ustekinumab compared with placebo (Section 1.2.3.1).
- In both ustekinumab Phase 3 studies in PsA, over 70% of the subjects randomized in each of the studies were diagnosed with enthesitis using a modified MASES. In both Phase 3 studies, a dose response was observed in the percent improvement from baseline in MASES at Week 24. Statistical significance was reached for both ustekinumab 45 mg and 90 mg dose groups as compared with placebo in CNTO1275PSA3001 while significance was only reached for 90 mg as compared with placebo in CNTO1275PSA3002 (Section 1.2.3.2).
- Ustekinumab 90 mg was the only dose evaluated for the treatment of patients with active AS in an open-label, proof-of-concept investigator-initiated study (TOPAS; Section 1.2.4). Although this was a small, uncontrolled study in 20 patients, the efficacy data showed promising results for the AS population treated with the 90 mg dose. In addition to the primary endpoint (ASAS 40), key secondary endpoints (ASAS 20 and BASDAI 50 at Week 24) also showed clinically meaningful improvement. The 90 mg dose was well tolerated with no safety signals identified. These data at the 90 mg dose, were generally comparable to other open-label studies of TNFα blockers in AS.[27,44]
- In the global psoriasis and PsA studies, ustekinumab at doses 45 mg and 90 mg was generally well tolerated with no clear impact of ustekinumab on the targeted events including death, malignancy, serious infections, or major cardiovascular events (MACE). Ustekinumab has been commercially available since 2009 and the cumulative global exposure through 31 December 2014 has been estimated as 379,596 person-years.

In summary, both the ustekinumab 45 mg and 90 mg doses were demonstrated to be efficacious in the treatment of PsA. Improvements in enthesitis in PsA subjects were observed with both doses even though the 90 mg dose was associated with somewhat greater improvements that were consistently statistically significant across the 2 randomized controlled trials. Reductions in the signs and symptoms of spondylitis in patients with PsA in large randomized controlled trials were statistically significantly greater in those treated with ustekinumab 90 mg as compared with placebo, and numerically greater with 45 mg as compared with placebo, and treatment with ustekinumab 90 mg was associated with good efficacy responses in patients with active AS in an open-label, proof-of concept study. Overall, the data suggests efficacy in reducing spondylitis and enthesitis signs and symptoms may be more robust with the 90 mg dose versus the 45 mg dose, supporting a dose-response relationship.

Based on these considerations, it is reasonable to study ustekinumab both 45 and 90 mg dose regimens in the radiographic AxSpA Phase 3 trial as was studied in the Phase 3 PsA and psoriasis clinical programs.

In addition to this radiographic AxSpA study, the ustekinumab AxSpA development program will include 2 other trials in the AxSpA population which will evaluate 45 and 90 mg ustekinumab doses in subjects with radiographic AxSpA who are naïve to anti-TNFα agents (CNTO1275AKS3001) and in subjects with active nonradiographic-AxSpA (CNTO1275AKS3003).

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to assess the efficacy of ustekinumab, in adult anti-TNFα refractory subjects with active radiographic AxSpA, as measured by the reduction in signs and symptoms of radiographic AxSpA.

Secondary Objectives

The secondary objectives are to assess the effect of treatment with ustekinumab in anti-TNFα refractory subjects with active radiographic AxSpA on the following:

- Efficacy related to improving physical function, range of motion, health-related quality of life, and other health outcomes.
- Safety.
- Pharmacokinetics (PK) and immunogenicity.

Exploratory Objective

The exploratory objectives are to evaluate the effect of ustekinumab on pharmacodynamics, on the microbiome, and on pharmacogenomics in anti-TNFα refractory subjects with radiographic AxSpA.

2.2. Hypothesis

The primary hypothesis for this study is that at least 1 of the ustekinumab groups is statistically superior to placebo in reducing the signs and symptoms in subjects with active radiographic AxSpA, as assessed at Week 24 by the composite endpoint of ASAS 40 response and the outcome of continuing originally assigned treatment.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

CNTO1275AKS3002 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of ustekinumab 45 mg and 90 mg in subjects with active radiographic AxSpA and who have been refractory to anti-TNFα therapy.

Approximately 483 subjects will be randomized at approximately 150 investigational sites. Subjects will be randomly assigned in a 1:1:1 ratio to receive subcutaneous (SC) ustekinumab 45 or 90 mg or placebo administrations at Weeks 0, 4, and 16. Block randomization will be used. Randomization will be stratified by region.

At Week 16, subjects in all 3 treatment groups who qualify for early escape (EE; subjects with <10% improvement from baseline in both total back pain and morning stiffness measures at both Week 12 and Week 16), will begin receiving open-label golimumab 50 mg SC administrations at Week 16 and every 4 weeks (q4w) thereafter through Week 52. These subjects will return to the study site at Week 24 for assessments related to primary and major secondary endpoints (ASAS response, BASDAI, BASFI, ASDAS), then for BASDAI and safety evaluations at Weeks 28, 40, and 52, and for the final safety visit at Week 64.

At Week 24, all remaining placebo subjects who did not meet EE criteria will be rerandomized by interactive web response system (IWRS) to begin receiving ustekinumab 45 or 90 mg at Weeks 24 and 28 followed by q12w therapy with the last study agent administration at Week 52. All subjects in the ustekinumab 45 mg and 90 mg treatment groups who do not qualify for EE will continue to receive the treatment they were randomized to at Week 0 through Week 52.

Subjects will be followed for adverse events (AE) and SAEs at least 12 weeks following the last study treatment administration. The end of study is defined as the time the last subject completes the Week 64 visit.

An independent Data Monitoring Committee (DMC) will be commissioned for this study. For details, refer to Section 11.13.

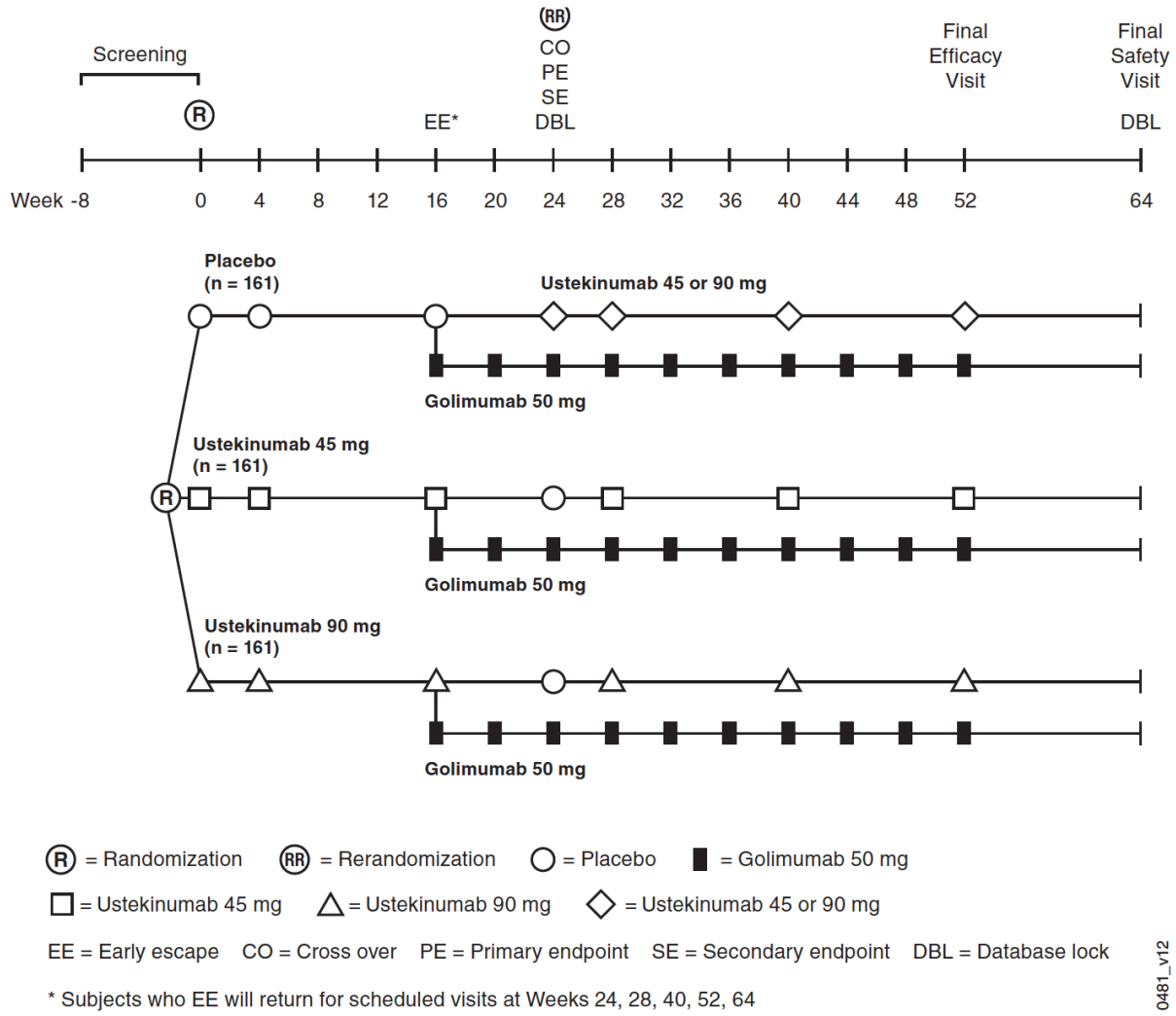
A group sequential design using the O'Brien and Fleming boundary will be applied with one interim analysis based on a database lock (DBL) at the time when approximately 50% of subjects have completed the Week 24 visit or end study participation before the Week 24 visit. The Sponsor will be kept blinded to the interim data. Details for the prespecified decision rules will be provided in the Interim Analysis Plan.

The other 2 DBLs will occur when all subjects complete the Weeks 24 and 64 visits, respectively.

A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study where local regulations permit. Subject participation in pharmacogenomics research is optional.

A diagram of the study design is provided below in Figure 3.

Figure 3: Schematic Overview of the Study



3.1.1. Study Population

The target study population is adult subjects who have been refractory to anti-TNFα therapy and have active radiographic AxSpA, as evidenced by BASDAI ≥4 and a visual analog scale (VAS) for total back pain of ≥4, each on a scale of 0 to 10. All subjects are required to have a screening high sensitivity C-reactive protein (hsCRP) level ≥0.300 mg/dL. The study population will include subjects who have been refractory to anti-TNFα therapy. Background treatment with NSAIDs, select non-biologic DMARDs, and low dose corticosteroids will be allowed during the study at stable doses through Week 24 and may be adjusted after Week 24.

- Subjects must have a diagnosis of definite AS, as defined by the 1984 modified New York criteria.

- The radiographic criterion and at least 1 clinical criterion must be met:
  a. Radiographic criterion: Sacroiliitis Grade ≥2 bilaterally or sacroiliitis Grade 3 to 4 unilaterally as assessed by the central reader.
  b. Clinical criteria (at least 1):
     1) Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest.
     2) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
     3) Limitation of chest expansion relative to normal values corrected for age and sex.

3.1.2. Study Phases and Duration of Treatment

There will be 3 phases in this study: Screening, placebo-controlled and active treatment, and safety follow-up. The screening phase of up to 8 weeks will allow for sufficient time to perform screening study evaluations and determine subject eligibility. The second treatment phase of the study will be the placebo-controlled (Week 0 to 24) and active treatment periods (Week 24 to Week 52). The third phase of the study will be the safety follow-up phase and will be 12 weeks from the last administration of study agent.

3.1.3. Study Control, Randomization, and Blinding

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Block randomization by IWRS will be used. Randomization will be stratified by region.

Individual subjects and investigators will remain blinded for the duration of the study, until the Week 64 DBL has occurred. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. The first of the 3 DBLs planned for the study will be for the interim analysis. The Sponsor will be kept blinded to the interim data. The other 2 planned DBLs are at Week 24 and at Week 64. Limited Sponsor personnel will be unblinded to subject-level data at the Week 24 DBL for data analyses and data review. Identification of Sponsor personnel who will have access to the unblinded subject-level data for the Week 24 DBL will be documented prior to unblinding.

3.2. Study Design Rationale

As described in Section 1.2.1 there is substantial scientific evidence supporting the critical role of IL-23 in the pathogenesis of radiographic AxSpA. Specifically, the clinical response to ustekinumab observed in Phase 3 PsA trials, especially the spondylitis/enthesitis subset of subjects and the fact that there is a close genetic/pathophysiologic connection between PsA and Axial SpA and the response noted in the open-label 'TOPAS' trial supports this approach. The dose justification for this study is described in Section 1.3.

Study Population Rationale

The target study population is subjects who have definite AS, as defined by the modified New York criteria. All eligible subjects will be required to have active disease based on symptoms (defined as BASDAI score ≥4 and total back pain ≥4) which should assure selection of subjects being the most appropriate candidates for a treatment with a biologic. The rationale for studying the anti-TNFα-refractory population in this clinical trial is that ustekinumab may be a better, alternative biologic treatment option over using a second, anti-TNFα agent in these patients.

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. The primary endpoint is evaluated at Week 24, which is the time point used in the ustekinumab PsA Phase 3 studies.[26,31,42] Ustekinumab is expected to achieve maximal efficacy by Week 20 to Week 28 of treatment based on the findings in the ustekinumab Phase 3 studies in subjects with PsA. The 64-week study duration is preferred over a shorter study (eg, 24 or 28 weeks) to ensure that ustekinumab reaches steady-state exposures and to allow sufficient time to evaluate the durability of the effect and safety of ustekinumab in subjects with active radiographic AxSpA over a prolonged period of time after reaching steady state. Subjects in all treatment groups will always have the option to withdraw from the study at any time for any reason, including inadequate response.

Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of ustekinumab or help to explain inter-individual variability in clinical outcomes or may lead to identification of population subgroups that respond differently to this study agent. The goal of the biomarker analyses is to evaluate the pharmacodynamics effects of ustekinumab and aid in evaluating the drug-clinical response relationship.

Biomarker samples may be used to help address emerging issues, better understand the natural history of radiographic AxSpA and to enable the development of safer, more effective, and ultimately individualized therapies for patients with radiographic AxSpA.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 8 weeks before administration of the study agent. Subjects with complete ankylosis of the spine, defined as bridging syndesmophytes present at all intervertebral levels of the cervical and lumbar spine visualized on lateral-view spinal radiographs are permitted to be included in the study, but will be limited to approximately 10% of the study population.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate Sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

Each potential radiographic AxSpA subject must satisfy all of the following criteria to be enrolled in the study.

1. Subjects must be 18 years of age or older (or of legal age of consent in the country if older than 18 years)
2. Subjects must have a diagnosis of definite AS, as defined by the modified 1984 New York criteria.[53] The radiographic criterion must be confirmed by a central x-ray reader and at least 1 clinical criterion must be met:

    a. Radiographic criterion: Sacroiliitis Grade ≥ 2 bilaterally or sacroiliitis Grade 3 to 4 unilaterally.

    b. Clinical criteria (at least 1):
    1) Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest.
    2) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
    3) Limitation of chest expansion relative to normal values corrected for age and sex.

3. Subjects must have symptoms of active disease at screening and at baseline, as evidenced by both a BASDAI score of ≥4 and a VAS score for total back pain of ≥4, each on a scale of 0 to 10.

4. Have an elevated hsCRP level of ≥0.300 mg/dL at screening.

    NOTE: A one-time repeat assessment of hsCRP level is allowed during the 8-week screening period and the Investigator may consider the subject eligible if the test result is within acceptable range on repeat testing in the central laboratory.

5. Refractory to no more than 1 anti-TNFα therapy by either of the following 2 reasons:

    - Lack of benefit from anti-TNFα therapy, as assessed by the treating physician, after at least 12 weeks of infliximab (Remicade®, Remsima®, Inflectra®, Infimab®), certolizumab pegol, etanercept, (Enbrel®, YiSaiPu®, Etanar®), or adalimumab (Humira®, Exemptia®). Documented lack of benefit may include inadequate improvement in disease activity.
    - Received infliximab (Remicade®, Remsima®, Inflectra®, Infimab®), certolizumab pegol, etanercept (Enbrel®, YiSaiPu®, Etanar®), or adalimumab (Humira®, Exemptia®) and have documented intolerance to anti-TNFα therapy (eg, infusion/injection site reaction, or other AE(s) that precludes continuation of that anti-TNFα agent).

6. Has an inadequate response to at least 2 NSAIDs over a 4-week period in total with maximal recommended doses of NSAID(s), or is unable to receive a full 4 weeks of maximal NSAID therapy because of intolerance, toxicity, or contraindications to NSAIDs.
7. If using NSAIDs or other analgesics for AS, must be on a stable dose for at least 2 weeks prior to the first administration of study agent. If currently not using NSAIDs or other analgesics for AS, must not have received NSAIDs or other analgesics for AS for at least 2 weeks prior to the first administration of the study agent.
8. If using oral corticosteroids, must be on a stable dose equivalent to ≤10 mg of prednisone/day for at least 2 weeks prior to the first administration of study agent. If currently not using corticosteroids, must have not received oral corticosteroids for at least 2 weeks prior to the first administration of the study agent.
9. If using methotrexate (MTX), sulfasalazine (SSZ), or hydroxychloroquine (HCQ), should have started treatment at least 3 months prior to the first administration of study agent and should have no serious toxic side effects attributable to those DMARDs. MTX routes of administration and doses (not to exceed 25 mg/week) should be stable for at least 4 weeks prior to the first administration of the study agent. If using SSZ or HCQ, must also be on a stable dose for at least 4 weeks prior to the first administration of study agent. If currently not using MTX, SSZ, or HCQ, must have not received these DMARDs for at least 4 weeks prior to the first administration of the study agent.
10. Subjects with complete ankylosis of the spine, defined as bridging syndesmophytes present at all intervertebral levels of the cervical and lumbar spine visualized on lateral-view spinal radiographs are permitted to be included in the study, but will be limited to approximately 10% of the study population.
11. Before randomization, a woman must be either:
    - Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months); permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,
    - Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception associated with inhibition of ovulation; placement of an intrauterine device (IUD) or intrauterine system (IUS); male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above.

12. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test at Week 0 before randomization.

13. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 5 months after receiving the last dose of study agent.

14. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 5 months after receiving the last dose of study agent.

15. Are considered eligible according to the following tuberculosis (TB) screening criteria:

    a. Have no history of latent or active TB prior to screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB prior to first administration of study agent, or have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation.

    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to the first administration of study agent.

    d. Within 8 weeks prior to the first administration of study agent, have a negative QuantiFERON®-TB Gold test result (Appendix A), or have a newly identified positive QuantiFERON®-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent. Within 8 weeks prior to the first administration of study agent, a negative tuberculin skin test (TST;

Appendix B), or a newly identified positive TST in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent, is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in that country or the TST is mandated by local health authorities.

- Subjects with 2 indeterminate QuantiFERON®-TB Gold test results may be enrolled without treatment for latent TB, if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

e. The QuantiFERON®-TB Gold test and the TST are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; Subjects with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

f. Have a chest radiograph (both posterior-anterior and lateral views or per country regulations where applicable) taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

16. Have screening laboratory test results within the following parameters:

a. Hemoglobin ≥ 8.5 g/dL (SI: ≥85 g/L)

b. White blood cells ≥ 3.5 x 10^3/μL (SI: ≥3.5 GI/L)

c. Neutrophils ≥ 1.5 x 10^3/μL (SI: ≥1.5 GI/L)

d. Platelets ≥ 100 x 10^3/μL (SI: ≥100 GI/L)

e. Serum creatinine ≤ 1.5 mg/dL (SI: ≤129 μmol/L)

f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be within 1.5 times the upper limit of normal (ULN) range for the laboratory conducting the test.

NOTE: A one-time repeat of these screening laboratory tests is allowed during the 8-week screening period and the Investigator may consider the subject eligible if the previously abnormal laboratory test result is within acceptable range on repeat testing in the central laboratory.

17. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

18. Be able to read, write, understand, and complete study questionnaires.

19. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study**.**

20. Each subject must sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

21. Are willing to refrain from the use of complementary therapies including ayurvedic medicine, traditional Chinese medication(s), and acupuncture within 2 weeks prior to the first study agent administration and throughout the duration of the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Have other inflammatory diseases that might confound the evaluations of benefit from the ustekinumab therapy, including but not limited to, rheumatoid arthritis, systemic lupus erythematosus, or Lyme disease.

2.
- Has received infliximab or infliximab biosimilar, within 12 weeks of the first study agent administration.
- Has received adalimumab, adalimumab biosimilar, or certolizumab pegol within 6 weeks of the first study agent administration.
- Has received etanercept or etanercept biosimilar within 6 weeks of the first study agent administration.

Anti-TNFα therapy	**Ineligible if last treatment prior to first study agent administration is:**
Infliximab, infliximab biosimilar	<12 weeks prior
Adalimumab, adalimumab biosimilar, certolizumab pegol	<6 weeks prior
Etanercept, etancercept biosimilar or yisaipu	<6 weeks prior

3. Has ever received golimumab

4. Are pregnant, nursing, or planning a pregnancy or fathering a child while enrolled in the study or within 5 months after receiving the last administration of study agent.

5. Have received any systemic immunosuppressives or DMARDs other than MTX, SSZ, or HCQ within 4 weeks prior to first administration of study agent. Medications in these categories include, but are not limited to chloroquine, azathioprine, cyclosporine, mycophenolate mofetil, gold, and penicillamine. Corticosteroids are not included in this criterion; see other eligibility criteria regarding corticosteroids.

6. Have received leflunomide within 3 months prior to the first administration of study agent (irrespective of undergoing a drug elimination procedure), or have received leflunomide within 12 months prior to the first administration of study agent and have not undergone a drug elimination procedure.

7. Have received epidural, intra-articular, IM, or IV corticosteroids, including adrenocorticotropic hormone during the 4 weeks prior to first administration of study agent.

8. Have received any prior biologic therapy other than TNFα inhibitors, including, but not limited to ustekinumab, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, and B-cell depleting therapies.

9. Have ever received tofacitinib or any other Janus kinase (JAK) inhibitor.

10. ~~Have total spinal ankylosis.~~

11. Have a known hypersensitivity to human immunoglobulin proteins.

12. Have used cytotoxic drugs, including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents.

13. Have a history of active granulomatous infection, including histoplasmosis, or coccidioidomycosis, prior to screening. Refer to inclusion criterion #15 for information regarding eligibility with a history of latent TB.

14. Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

15. Have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.

16. Have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

17. Have received, or are expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent, during the study, or within 3 months after the last administration of study agent. For BCG vaccination criterion, refer to Exclusion Criterion #14.

18. Have a history of an infected joint prosthesis, or have received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

19. Have had a serious infection (including but not limited to, hepatitis, pneumonia, sepsis, or pyelonephritis), or have been hospitalized for an infection, or have been treated with intravenous antibiotics for an infection within 2 months prior to first administration of study agent. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

20. Have a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis), an open, draining, or infected skin wound or ulcer.

21. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.

22. Has a hepatitis B infection. Subjects must undergo screening for hepatitis B virus (HBV; Appendix C). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total).

23. Subjects who are seropositive for antibodies to hepatitis C virus (HCV), unless they have 2 negative HCV RNA test results 6 months apart prior to screening and have a third negative HCV RNA test result at screening.

24. Have a history of known demyelinating diseases such as multiple sclerosis or optic neuritis (contraindication for the use of anti-TNFα agent as rescue therapy).

25. Has a diagnosis of congestive heart failure Class III or IV.

26. Have current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.

27. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, clinically significant splenomegaly, or history of monoclonal gammopathy of undetermined significance.

28. Subject has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin that have been treated with no evidence of recurrence for at least 3 months before the first study agent administration and carcinoma in situ of the cervix that has been surgically cured).

29. Subject has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients and/or golimumab or its excipients (refer to the ustekinumab Investigator's Brochure and the golimumab Investigator's Brochure).

30. Are currently receiving venom immunotherapy (honeybee, wasp, yellow jacket, hornet, or fire ant).

31. Subject has taken any disallowed therapies as noted in Section 8, before the planned first dose of study agent.

32. Subject has received an investigational drug (including investigational vaccines) within 5 half-lives or 3 months, whichever is longer, or used an invasive investigational medical device within 3 months before the planned first dose of study agent or is currently enrolled in an investigational study.

33. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

34. Subject has had major surgery, (eg, requiring general anesthesia) within 1 month before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 1 month after the last dose of study agent administration.

    Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate

35. Have a transplanted organ (with the exception of a corneal transplant performed >3 months prior to first administration of study agent).

36. Have or have had a substance abuse (drug or alcohol) problem within the previous 3 years.

37. Are unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy access.

38. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study agent is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Both heterosexually active women of childbearing potential and men capable of fathering a child must consent to use a highly effective method of contraception and continue to use contraception for the duration of the study and for 5 months after the last administration of study agent.
2. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 5 months after receiving the last dose of study agent.
3. All men must also not donate sperm during the study and for 5 months after receiving the last dose of study agent.
4. Must agree not to receive an investigational medical device for the duration of this study.
5. The use of the following drugs is not permitted concomitantly with study agent administration and within 12 weeks after the last study agent administration:

    - Systemic immunosuppressives or DMARDs (other than MTX, SSZ, and HCQ) including chloroquine, azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, leflunomide, oral or parenteral gold. Systemic immunosuppressives do not refer to corticosteroids; see Section 8.2 regarding corticosteroid restrictions.
    - Biologic agents targeted at reducing TNFα (including but not limited to infliximab [Remicade®, Remsima®, Inflectra®, Infimab®], commercial golimumab, certolizumab pegol, etanercept [Enbrel®, Etanar®, YiSaiPu®], and adalimumab [Humira®, Exemptia®]
    - Biologic agents targeting IL-1ra (anakinra).
    - Tocilizumab or any other biologic targeting IL-6 or IL-6 receptor.
    - Tofacitinib or other JAK inhibitor.
    - B-cell depleting agents (eg, rituximab).
    - Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.
    - Abatacept.
    - Anti-IL-17 agents (eg, brodalumab, secukinumab, and ixekizumab).
    - Anti-integrin therapy (eg, natalizumab or vedolizumab).
    - Investigational drugs other than the study agent.

6. Subjects must not receive a live virus or bacterial vaccination during the study and for 3 months after the last administration of study agent.
7. Subjects must not receive a BCG vaccination during the study and for 12 months after the last administration of study agent.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Randomization at Week 0 and the rerandomization at Week 24 for placebo subjects will be conducted using permuted block method by the IWRS.

At Week 0, eligible subjects will be randomly assigned to receive ustekinumab 45 or 90 mg or placebo based on a computer-generated randomization schedule prepared before the study under the supervision of the Sponsor. Subject allocation to a treatment group will be done using a stratified block randomization method in a 1:1:1 ratio to 1 of 3 treatment groups. Randomization will be stratified by region.

At Week 16, subjects in all 3 treatment groups who meet EE criteria: <10% improvement from baseline in both total back pain and morning stiffness measures at both Week 12 and Week 16, will begin receiving open-label golimumab 50 mg q4w through Week 52. At Week 24, all remaining placebo subjects not meeting EE criteria will crossover to ustekinumab 45 mg or 90 mg randomly at Weeks 24 and 28 followed by q12w therapy through Week 52.

Blinding

To maintain the study blind, the study agent container will have a multipart label containing the study name, study agent number, and reference number, and other information on each part. A tear-off label is designed to be torn off, separated from the study agent container, and attached to the subject's source documents. The label will not identify the study agent in the container. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study agent ascertained. The study agent number will be entered in the case report form when the study agent is administered. The study agents will be identical in appearance and will be packaged in identical containers.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, study agent serum concentrations, antibodies to study agent, and treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained, and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date of unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document; the reason for unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. The decision to continue or discontinue study treatment for these subjects will be based upon consultation of the investigator with the study responsible physician.

The study responsible physician will remain blinded throughout the study to subject level treatment assignment and dosing regimen. At the Week 24 DBL, the data will be unblinded for analysis while subjects are still participating in the study. Identification of Sponsor personnel who will have access to the unblinded subject level data will be documented prior to unblinding.

6. DOSAGE AND ADMINISTRATION

6.1. Dosing Regimen and Blinding

Before the first study agent administration, subjects will be randomly assigned in a ratio of 1:1:1 to 1 of 3 treatment groups:

- Group 1 (placebo): Placebo SC at Weeks 0, 4, and 16. At Week 24 all subjects (with the exception of subjects who qualified for EE) will be rerandomized to receive either ustekinumab 45 or 90 mg SC at Weeks 24 and 28 followed by q12w dosing, with the last administration of study agent at Week 52.
- Group 2 (ustekinumab 45 mg): Ustekinumab 45 mg SC at Weeks 0 and 4, followed by q12w dosing, with the last administration of study agent at Week 52. At Week 24, subjects will receive placebo SC to maintain the blind.

- Group 3 (ustekinumab 90 mg): Ustekinumab 90 mg SC at Weeks 0 and 4, followed by q12w dosing, with the last administration of study agent at Week 52. At Week 24, subjects will receive placebo SC to maintain the blind.

Subjects who qualify for EE at Week 16 will be administered open-label golimumab 50 mg SC q4w.

To maintain the blind, all randomized subjects will receive each administration of ustekinumab/placebo as 2 SC injections totaling 1.5 mL in 2 different locations as follows:

- Placebo: 0.5 mL placebo injection and 1.0 mL placebo injection.
- Ustekinumab 45 mg: 0.5 mL ustekinumab 45 mg injection and 1.0 mL placebo injection.
- Ustekinumab 90 mg: 1.0 mL ustekinumab 90 mg injection and 0.5 mL placebo injection.

Early Escape

At Week 16, subjects in all 3 treatment groups who qualify for EE criteria (<10% improvement from baseline in both total back pain and morning stiffness measures at both Week 12 and Week 16) will begin receiving open-label golimumab 50 mg SC administrations at Week 16 and q4w thereafter through Week 52. These subjects will return to the study site at Week 24 for assessments related to the primary and major secondary endpoints (ASAS response, BASDAI, BASFI, ASDAS [CRP]), then for BASDAI and safety evaluations at Weeks 28, 40, and 52, and for the final safety visit at Week 64.

At the discretion of the investigator and subject and after appropriate and documented training, subjects who qualify for EE in all 3 treatment groups will self-administer golimumab 50 mg SC, initially at the investigative site under the supervision of a health care professional. A caregiver may also be trained to administer study agent.

Subjects (or a caregiver) who are able to self-administer will be supplied golimumab 50 mg prefilled syringe (PFS) for self-administration away from the site, ie, at home. Subjects unable to have injection administered away from site will be required to return to the site every 4 weeks for administration of study agent injection by a health care professional.

Study personnel will instruct subjects on how to store medication for at-home use.

At the Week 24 DBL, the data will be unblinded for analysis to the Sponsor only, and not to investigative study site and/or subjects. Subjects and investigative study sites will remain blinded until after the final Week 64 DBL.

6.2. Study Agent Administration and Timing

All postbaseline visits through Week 24 may occur at the indicated week ±4 days. After Week 24 and throughout the study, visits may occur at the indicated week ±7 days. In case it is not possible to administer the missed injection in time, site personnel should discuss the issue with the medical monitor.

7. TREATMENT COMPLIANCE

Study agent will be administered SC by a qualified individual who administers study agent at the study sites throughout the study. Study personnel will maintain a log of all study agent administrations. Study personnel will inventory and account for study agent supplies for each subject. All ongoing therapies administered at the time of screening must be recorded.

It is understood that treatment may be interrupted for health-related or safety reasons, but compliance with the treatment schedule is strongly encouraged.

For subjects who qualify for EE at Week 16 and begin self-administration at home, the investigator or designated study personnel will maintain a log of all golimumab 50 mg PFS dispensed and returned. When golimumab is self-administered by subjects at home, the amount of golimumab (number of syringes) dispensed will be recorded and compared with the amount (number of syringes) returned.

Subjects will receive instructions on compliance with study treatment when they begin self-administration SC of golimumab 50 mg at home. During the course of the study, the investigator or designated study research personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the golimumab.

8. CONCOMITANT THERAPY

Every effort should be made to keep subjects' concomitant medications stable through Week 24 or as specified in the following sections. The concomitant medication dose may be reduced or the medication temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the change and reason for the change should be clearly documented in the subject's medical record.

Concomitant medication review will occur at study visits identified in the Time and Events Schedule.

8.1. Methotrexate, Sulfasalazine, or Hydroxychloroquine

Subjects are permitted to enter the study on stable doses of MTX, SSZ, or HCQ.

If subjects are using MTX, SSZ, or HCQ, treatment should have started at least 3 months prior to the first administration of study agent. MTX routes of administration and doses ≤25 mg/week should be stable for at least 4 weeks prior to the first administration of the study agent. It is recommended that all subjects taking MTX in this study receive at least 5 mg oral folate or 5 mg folinic acid weekly. If using SSZ or HCQ, subjects must also be on a stable dose for at least 4 weeks prior to the first administration of study agent. Every effort should be made to maintain stable doses and routes of administration of MTX, SSZ, and HCQ through Week 24 of the study in subjects receiving this medication. After Week 24 and through Week 52, dose adjustment in MTX, SSZ, and HCQ is allowed, except the dose should not be increased above the study entry level dose. After Week 52, the dose can be adjusted as needed.

Subjects not on treatment with MTX, SSZ, or HCQ must have discontinued the treatment for at least 4 weeks prior to the first administration of study agent, and must not receive MTX, SSZ, or HCQ through Week 52. After Week 52, these medications can be introduced and adjusted as needed. Guidelines for dose adjustment in the event of MTX toxicity are included in the Trial Center File.

8.2. Corticosteroid Therapy

Subjects treated with oral corticosteroids for AxSpA should receive a stable dose equivalent to ≤10 mg prednisone per day for at least 2 weeks prior to first administration of study agent and continue to receive this dose through Week 24; the dose and type of oral corticosteroid may be changed at the discretion of the investigator only if the subject develops unacceptable side effects. After Week 24 and through Week 52, dose adjustment in oral corticosteroids is allowed, except the dose should not be increased above the study entry level dose. After Week 52, the dose of oral corticosteroids can be adjusted as needed.

Subjects not treated with oral corticosteroids at baseline must have discontinued oral corticosteroids at least 2 weeks prior to the first administration of study agent, and they must not receive oral corticosteroids for AxSpA through Week 52. After Week 52, oral corticosteroids can be introduced and adjusted as needed.

Intravenous, intramuscular, or epidural administration of corticosteroids for the treatment of AxSpA is not allowed through Week 52.

Short-term (≤2 weeks) oral, IV, IM, or epidural corticosteroid used for indications other than AxSpA should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives. Long-term (>2 weeks) oral or IV corticosteroids use for indications other than AxSpA are not allowed throughout the course of the study.

Inhaled, otic, ophthalmic, intranasal, and other routes of mucosal delivery of corticosteroids are allowed throughout the course of the study.

Attempts should be made to avoid intra-articular corticosteroid injections especially during the first 24 weeks of the study. However if necessary, subjects may receive up to 2 intra-articular, tendon sheath, or bursal corticosteroid injections in no more than 2 affected sites during the study. In the case of severe tenderness or swelling in a single joint, it is suggested that the subject be evaluated for infection prior to receiving an intra-articular corticosteroid injection.

8.3. Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

The use of stable doses of NSAIDs and other analgesics is allowed.

Subjects treated with NSAIDs, including aspirin and selective cyclooxygenase-2 inhibitors, and other analgesics should receive the usual marketed doses approved in the country in which the study is being conducted, and should have been on a stable dose at least 2 weeks prior to the first administration of the study agent. Through Week 24, the dose and type of NSAIDs and other

analgesics generally should not be changed unless the subject develops unacceptable side effects. After Week 24, dose adjustment is allowed.

The use of topical analgesics including capsaicin and diclofenac is allowed. The dose of topical analgesics may be adjusted, except for analgesic patches. For transdermal analgesic patches, the dose should be stable through Week 24 and generally should not be changed unless the subject develops unacceptable side effects. After Week 24, dose adjustment in analgesic patches is allowed.

Subjects not treated with NSAIDs or other analgesics at baseline must not have received NSAIDs and other analgesics at least 2 weeks prior to the first administration of study agent, and they must not receive NSAIDs and other analgesics for AxSpA through Week 24. After Week 24, NSAIDs and other analgesics can be introduced and adjusted as needed.

In this trial, aspirin is considered an NSAID, except for low-dose aspirin prescribed for cardiovascular or cerebrovascular disease.

8.4. Disease Modifying Antirheumatic Drugs/Systemic Immunosuppressives

Disease modifying antirheumatic drugs/systemic immunosuppressive agents, with the exception of MTX, SSZ, and HCQ must be discontinued at least 4 weeks prior to the first administration of study agent and are prohibited throughout the study. These DMARDs include, but are not limited to chloroquine, gold preparations, penicillamine, and leflunomide. If a subject received leflunomide within 12 months prior to the first administration of study agent, the subject must have undergone a drug elimination procedure. Prohibited systemic immunosuppressive drugs throughout the study (ie up to 12 weeks post last study agent dose), include, but are not limited to, cyclosporine, tacrolimus, mycophenolate mofetil, and azathioprine (see Section 4.3). Systemic immunosuppressives do not refer to corticosteroids; see Section 8.2 for restrictions regarding the use of corticosteroids.

8.5. Biologic Agents or Investigational Agents

The use of biologic agents (eg, commercial golimumab, anakinra, etanercept, adalimumab, infliximab, tocilizumab, alefacept, efalizumab, rituximab, natalizumab, abetacept, commercial ustekinumab, brodalumab, secukinumab, ixekizumab), cytotoxic agents (eg, chlorambucil, cyclophosphamide, nitrogen mustard, other alkylating agents), tildrakizumab and other anti-IL-23 biologics, or investigational drugs is not allowed throughout the study (ie, up to 12 weeks post last study agent dose). If any of these medications are used, the subject will be discontinued from further study agent injections.

8.6. Complementary Therapies

The use of complementary therapies including but not limited to ayurvedic medicine, traditional Chinese medications, or non-medicinal therapy such as acupuncture is not allowed throughout the study.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, pharmacogenomic, medical resource utilization, health economic, and safety measurements applicable to this study.

All visit-specific patient reported outcomes (PRO) assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. For additional details, refer to the PRO user manual.

For women of childbearing potential only, additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Also additional TB tests may be performed as determined necessary by the investigator or required by local regulation.

Health economics data will be collected. For details see Section 9.6.

Every effort should be made to perform all other assessments as specified in the Time and Events Schedule unless logistically not feasible, and if possible, the same individual(s) should perform the assessments at each visit.

Serum for the analysis of biomarkers and whole blood (for gene expression analysis) will be collected from all subjects. At Weeks 0, 24, and 52, a single whole blood sample for DNA analysis will be collected only from subjects who have consented to participate in the optional pharmacogenomics (DNA) component of the study. Blood samples for DNA analyses will only be collected if permitted by local regulations. Refer to the Laboratory Reference Manual for the Pharmacogenomics Sample Collection and Shipment Procedures for details on collecting and handling blood samples for pharmacogenomics research. In the event of DNA extraction failure, a replacement pharmacogenomics blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample.

The total blood volume to be collected from each subject will be approximately 221 mL.

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

9.1.2. Screening Phase

Screening procedures will be performed as indicated in Table 1.

After written informed consent has been obtained and within a period of 8 weeks before randomization, all screening evaluations will be performed. Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study. Every effort should be made to adhere to the study Time and Events Schedule for each subject. Subjects must provide a separate written pharmacogenomics informed consent to participate in the optional pharmacogenomics research component of the study.

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before randomization. Women of childbearing potential and men capable of fathering a child must agree to use a highly effective method of contraception and continue to use contraception for the duration of the study and for 5 months after. The method(s) of contraception used by each subject must be documented. For details, see Section 4.1.

A 12-lead electrocardiogram (ECG) will be performed locally at screening to ensure that if a subject should require an ECG during the study for any reason, an ECG prior to first study agent administration is available for comparison to detect changes.

A chest radiograph will be performed at screening to ensure that the subject does not have any abnormality suggestive of a malignancy or current active infection, including TB. Chest x-rays taken up to 3 months prior to the first administration of study agent may be used.

Subjects must undergo testing for TB (Appendix A and Appendix B) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON®-TB Gold test result (and a negative TST result in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the TST is mandated by local health authorities) are eligible to continue with prerandomization procedures. Subjects with a newly identified positive QuantiFERON®-TB Gold test (or TST) result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB prior to the administration of the first dose of study agent. An exception is made for subjects currently receiving treatment for latent TB with no evidence of active TB, or who have a history of latent TB and documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study agent. These subjects do not need to be retested with the QuantiFERON®-TB Gold test (or TST) during screening. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed or the subject must be excluded from the study. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

A subject whose first QuantiFERON®-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON®-TB Gold test result is also indeterminate, the subject may be enrolled without treatment for latent TB, if active TB is ruled out, their chest

radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

Retesting

The re-testing of abnormal screening laboratory blood tests and C-reactive protein (CRP) levels that lead to exclusion is allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

If a subject has signed the Informed Consent Form (ICF) and failed to meet 1 or more entry requirement, the site may retest lab values or repeat a study entry procedure once during the screening period. This is inclusive of only 1 additional blood draw to be completed for retesting, regardless of whether an additional lab value is found to be out of range. The goal of the re-test procedure is to assess if the subject is eligible for randomization within the screening window or should be considered a screen failure.

Subjects that have lab values that do not meet entry criteria following the re-test are to be deemed a screen failure. An exception to this is a positive QuantiFERON-TB Gold test which may not be repeated to meet eligibility criteria.

Rescreening

If a subject is a screen failure but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on one occasion only after consultation with the Sponsor. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

9.1.3. Treatment Phase

Treatment phases include the placebo-controlled (Week 0 to 24) and active treatment phases (Week 24 to 52). At Week 0, eligible subjects will be randomly assigned to receive 1 of 3 treatments: Placebo, ustekinumab 45 mg, or ustekinumab 90 mg. Safety and efficacy assessments will be performed as noted in Table 1. Details for the early detection of active TB are provided in Section 9.7.

At Week 16, subjects in the placebo treatment group who qualify for EE will be treated with open-label golimumab 50 mg q4w through Week 52. At Week 24, all remaining subjects in the placebo group will cross over to receive ustekinumab 45 or 90 mg.

At Week 16, subjects in the ustekinumab 45 mg and 90 mg treatment groups who qualify for EE will be treated with open-label golimumab 50 mg q4w through Week 52. All other subjects will continue to receive the treatment regimen assigned at Week 0.

Starting at the Week 16 visit subjects in all 3 treatment groups who qualify for EE may begin self-administration of golimumab. For details, see Section 7.

9.1.4. Posttreatment Phase (Follow-Up)

Subjects will be instructed that study agent will not be made available to them after they have completed/discontinued study agent and that they should return to their primary physician to determine standard of care.

All subjects who complete the Week 52 visit assessments will be asked to return for a final safety visit at Week 64.

If a subject discontinues study agent at any time before the Week 24 visit, the subject should return for all visits through Week 24. If a subject discontinues study agent after Week 24 and before the Week 52 visit, the efficacy-related assessments for the Week 52 visit (Table 1) should be performed as soon as possible. All subjects who discontinue study agent prematurely should return 12 weeks after their last dose for safety-related assessments (refer to the Week 64 visit in Table 1).

No procedures and evaluations should be conducted after a subject withdraws consent.

9.2. Efficacy

9.2.1. Evaluations

9.2.1.1. Assessment of SpondyloArthritis International Society Response Criteria

A 20% improvement in response according to the criteria of the ASAS 20[2,49,52] is defined as:

1. An improvement of ≥ 20% from baseline and absolute improvement from baseline of at least 1 on a 0 to 10 scale in at least 3 of the following 4 domains:

    i. Patient global
    ii. Total back pain
    iii. Function (Bath Ankylosing Spondylitis Functional Index [BASFI])
    iv. Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness)

2. Absence of deterioration from baseline (≥20% and worsening of at least 1 on a 0 to 10 scale) in the potential remaining domain.

ASAS 40 is defined as a ≥40% improvement in 3 of 4 domains, with an absolute improvement of at least 2 on a 0 to 10 scale, and no deterioration at all in the remaining domain.

ASAS 5/6 is defined as a ≥20% improvement in any 5 of the 6 domains of pain (VAS 0 to 10), patient global (VAS 0 to 10), function (BASFI score), morning stiffness (from BASDAI), hsCRP, and spine mobility (lumbar side flexion).

ASAS partial remission is defined as a value below 2 on a scale of 0 to 10 in each of the 4 ASAS domains described above.

9.2.1.2. Bath Ankylosing Spondylitis Disease Activity Index

The Bath Ankylosing Spondylitis Disease Activity Index[19] is defined below:

Subject self-assessment using a visual analog scale (VAS; 0 to 10) on the following criteria:

A. Fatigue
B. Spinal pain
C. Joint pain
D. Enthesitis
E. Qualitative morning stiffness
F. Quantitative morning stiffness

The BASDAI = 0.2 (A + B + C + D + 0.5[E + F]).

9.2.1.3. Bath Ankylosing Spondylitis Functional Index

The BASFI is a subject's self-assessment represented as a mean (VAS; 0 to 10) of 10 questions, 8 of which relate to the subject's functional anatomy and 2 of which relate to a subject's ability to cope with everyday life.[8] An increase along the scale indicates a worsening condition.

9.2.1.4. Patient's Global Assessment

Patient's global assessment of disease activity will be recorded on a VAS (0 to 10; 0 = very well, 10 = very poor).

9.2.1.5. Total Back Pain

Subjects will be asked to assess their average total back pain over the past week on a VAS (0 to 10; 0 = no pain, 10 = most severe pain).

9.2.1.6. Night Back Pain

Subjects will be asked to assess their nighttime back pain during the past week on a VAS (0 to 10; 0 = no pain, 10 = most severe pain).

9.2.1.7. Morning Stiffness

Morning stiffness will be measured by the average of the responses to last 2 questions of the BASDAI.

9.2.1.8. Musculoskeletal Assessments

The musculoskeletal assessments will include each component of the BASMI (Section 9.2.1.8.1), chest expansion (Section 9.2.1.8.2), and enthesitis index (Section 9.2.1.8.3).

A musculoskeletal assessor (MA) with adequate training and experience in performing musculoskeletal assessments will be designated at each study site to perform all musculoskeletal assessments. The MA should preferably be a rheumatologist but if a rheumatologist is not available, should be a health care provider with at least 1 year of experience in performing musculoskeletal assessments (for additional details, see the Investigative Site File). Health care providers with less than 1 year of experience may serve as an MA based upon the discretion and approval of the Sponsor. It is recommended that the designated MA identifies an appropriate back-up MA for coverage in the event of absences of the designated MA. It is strongly recommended that the same MA who performs the baseline musculoskeletal assessments for a subject should also perform the musculoskeletal assessments for that subject at every subsequent visit through Week 52.

The Sponsor will provide training for each site's designated MA prior to the screening of the first subject at each site. A back-up MA must complete training before performing a musculoskeletal assessment for a subject's study visit. Training documentation of each MA should be maintained at the study site, and especially through Week 24. However, it is recommended that the MA should not be changed during the study.

If an MA was trained by the Sponsor in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study; however, repeat training prior to start of the trial is encouraged.

All MAs performing the musculoskeletal evaluation at a site must be listed on the Delegation Log at the study site and should be documented in the source documents at each visit.

9.2.1.8.1. Bath Ankylosing Spondylitis Metrology Index

The Bath Ankylosing Spondylitis Metrology Index (BASMI) is represented as an aggregate score of 5 components (ranging from 0 to 10) and will be calculated using the van der Heijde calculation[50] as shown in Table 2. A musculoskeletal assessor (MA; see Section 9.2.1.8) will perform all BASMI assessments.

Table 2: Scores (S) for the five components of the $BASMI_{lin}$

	S = 0 if:	Between 0 and 10:	S = 10 if:
Lateral lumbar flexion* (cm)	A ≥21.1	S = (21.1-A)/2.1	A ≤0.1
Tragus-to-wall distance* (cm)	A ≤8	S = (A-8)/3	A ≥38
Lumbar flexion (modified Schober) (cm)	A ≥7.4	S = (7.4-A)/0.7	A ≤0.4
Intermalleolar distance (cm)	A ≥124.5	S = (124.5-A)/10	A ≤24.5
Cervical rotation angle* (°)	A ≥89.3	S = (89.3-A)/8.5	A ≤4.3

* For lateral lumbar flexion, tragus-to-wall distance, and cervical rotation the average of right and left should be taken. If a score lies beyond the range 0–10, the values 0 or 10 have to be used, respectively.

- The $BASMI_{lin}$ is the mean of the five S scores.

- The assessments (A) of the 5 components will be collected at the sites when analysis is performed and the scores (S) will be calculated programmatically based on assessments when analysis is performed.

9.2.1.8.2. Chest Expansion

Chest expansion is the difference, in cm, between the circumference of the chest in maximal inspiration and maximal expiration. It is measured at the level of the fourth intercostal space in males, and just below the breasts in females. The MA will perform all chest expansion assessments.

9.2.1.8.3. Enthesitis Index

Enthesitis will be assessed using MASES index.[23] The MASES index was developed to assess enthesitis in subjects with ankylosing spondylitis, and evaluates the presence or absence of pain by applying local pressure to the following entheses:

- 1st costochondral joint, left and right;
- 7th costochondral joint, left and right;
- posterior superior iliac spine, left and right;
- anterior superior iliac spine, left and right;
- iliac crest, left and right;
- 5th lumbar spinous process;
- proximal insertion of Achilles tendon, left and right.

The range of MASES is 0 to 13.

The MA will perform all enthesitis assessments. The Sponsor will provide enthesitis assessment training. Documentation of this training will be maintained in the study site's training files.

9.2.1.9. Ankylosing Spondylitis Disease Activity Score

The ASAS has developed a disease activity score (DAS) for use in AS, the Ankylosing Spondylitis Disease Activity Score (ASDAS).[30,51] For this study, the following formula will be used to calculate the ASDAS score:

ASDAS (CRP) = 0.121 x Total back pain + 0.058 x Duration of morning stiffness + 0.110 x Patient global assessment + 0.073 x Peripheral pain/ swelling + 0.579 x Ln (hsCRP (mg/L) +1).

Major improvement in ASDAS (CRP) is defined as a decrease ≥2.0. Inactive disease is defined as an ASDAS (CRP) score <1.3.

Clinically important improvement in ASDAS (CRP) is defined as a decrease ≥1.1 (www.asas-group.org).

9.2.1.10. Imaging Evaluations

9.2.1.10.1. X-ray of Sacroiliac Joints

All subjects will have x-rays of SI joints at screening. An existing x-ray may be sent for central reading in lieu of screening x-ray. All subjects will have x-rays of SI joints as specified in Table 1. Detailed information on the acquisition of x-rays will be provided in the Imaging Manual.

Sacroiliac joints will be scored for the presence of sacroiliitis by the central readers using the following sacroiliitis scoring system for x-rays.[53]

- Grade 0: normal
- Grade 1: suspicious changes
- Grade 2: minimum abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width)
- Grade 3: unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis widening, narrowing, or partial ankylosis)
- Grade 4: severe abnormality (total ankylosis)

9.2.1.11. 36-Item Short-form Health Survey

The 36-item short form health survey (SF-36) questionnaire was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item scales:

- limitations in physical functioning due to health problems;
- limitations in usual role activities due to physical health problems;
- bodily pain;
- general mental health (psychological distress and well-being);
- limitations in usual role activities due to personal or emotional problems;
- limitations in social functioning due to physical or mental health problems;
- vitality (energy and fatigue);
- general health perception.

These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These summary scores are also scaled with higher scores indicating better health but are scored using a norm-based system where linear transformations are performed to transform scores to a mean of 50 and standard deviations of 10, based upon general US population norms.[54] The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.[55]

9.2.1.12. Medical Outcomes Study Sleep Scale

The extent of sleep problems will be assessed using the Medical Outcomes Study Sleep Scale (MOS-SS).[22] MOS-SS measures six dimensions of sleep, including initiation, maintenance (eg, staying asleep), quantity, adequacy, somnolence (eg, drowsiness), and respiratory impairments (eg, shortness of breath, snoring). The MOS-SS is a generic health measure, assessing a health-related quality of life concept-sleep that is relevant to everyone's health status and wellbeing and known to be directly affected by disease and treatment. As such, the MOS-SS is not specific to any age, disease, or treatment group. The reliability and validity of the MOS-SS have been evaluated in a number of disease areas, including neuropathic pain and rheumatoid arthritis.

9.2.1.13. Ankylosing Spondylitis Quality of Life (ASQoL) Questionnaire

Ankylosing Spondylitis Quality of Life questionnaire (ASQoL) is a self-administered patient-reported outcomes instrument.[16] It consists of 18 items requesting a Yes or No response to questions related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. A score of 1 is given to a response of 'YES" on each item and all item scores are summed to a total score with a range of 0 to 18. Higher scores indicate worse health related quality of life. Subjects can complete the instrument in less than four minutes.

9.2.1.14. Functional Assessment of Chronic Illness Therapy−Fatigue Questionnaire

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire consists of 13 questions that assess a subject's level of fatigue and tiredness over the last 7 days. Each question is graded on a 5-point scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much) then scored 0 to 4; accordingly, total scores can range from 0 to 52. Lower score reflects more severe fatigue. Although not developed for radiographic AxSpA, FACIT-F has demonstrated strong internal consistency and test-retest reliability. It distinguishes between healthy and PsA patients and is correlated with swollen joint count and actively inflamed joint count. In rheumatology, a change of 4 points is considered meaningful[9] and has been used in the PsA population.[32]

9.2.1.15. EuroQol 5 Dimension Questionnaire

The EuroQol 5 Dimension Questionnaire (EQ-5D) is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal.[18] The EQ-5D is applicable to a wide range of health conditions and treatments. EQ-5D essentially consists of 2 elements: The EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state

which can be converted into a single summary index (EQ-5D index) by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The EQ VAS records the respondent's self-rated health on a vertical line, VAS where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. The EQ VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.

9.2.2. Endpoints

Primary Endpoint

The primary endpoint is the proportion of subjects achieving an ASAS 40 response at Week 24.

Major Secondary Endpoints

The following major secondary analyses will be performed. The major secondary endpoints are listed in order of importance as specified below:

1. The proportion of subjects who achieve an ASAS 20 at Week 24.
2. The proportion of subjects who achieve at least 50% improvement from baseline in BASDAI at Week 24.
3. The change from baseline in BASFI at Week 24.
4. The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24.

Other Secondary Endpoints

- The proportion of subjects who achieve ASAS partial remission
- The proportion of subjects who achieve ASAS 20
- The proportion of subjects who achieve ASAS 40
- The proportion of subjects who achieve an ASAS 5/6 response.
- The proportion of subjects who achieve a ≥20%, ≥50%, ≥70%, ≥90% improvement from baseline in BASDAI.
- The change from baseline in hsCRP.
- The change from baseline in ASDAS (CRP).
- The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3).
- The proportion of subjects who achieve ASDAS (CRP) major improvement (decrease ≥2.0).
- The proportion of subjects who achieve ASDAS (CRP) clinically important improvement (decrease ≥1.1).
- The change from baseline in BASMI.
- The change from baseline in chest expansion.
- The change from baseline in the MASES enthesitis scores in subjects with enthesitis at baseline.

- The change from baseline in inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness).
- The change from baseline in total back pain
- The change from baseline in night back pain
- The change from baseline in Patient Global Assessment
- The change from baseline in SF-36 subscales.
- The change from baseline in the PCS scores of SF-36.
- The change from baseline in the MCS scores of SF-36.
- The change from baseline in domain scores of MOS-SS.
- The change from baseline in ASQoL scores.
- The change from baseline in EQ-5D VAS and in EQ-5D index.
- The change from baseline in FACIT-Fatigue.
- The change from baseline in WPAI.

9.3. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK of ustekinumab, as well as the immunogenicity of ustekinumab (antibodies to ustekinumab). Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.3.1. Serum Collection and Handling

Venous blood samples will be collected at the time points shown in the Time and Events Schedule for the determination of serum ustekinumab concentrations and antibodies to ustekinumab. Serum samples will also be collected at the final visit from subjects who terminate study participation early. At visits where PK and immunogenicity will be evaluated, 1 blood draw of sufficient volume can be used. Each sample will be split into 3 aliquots (1 aliquot for serum ustekinumab concentration, 1 aliquot for antibodies to study agent, and 1 aliquot as a back-up). Samples must be collected before study agent administration at visits when a study agent administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.3.2. Analytical Procedures

9.3.2.1. Pharmacokinetics of Ustekinumab

Serum samples will be analyzed to determine serum ustekinumab concentrations using a validated, specific, and sensitive immunoassay method by Sponsor's bioanalytical facility or under the supervision of the Sponsor. The Sponsor, or its designee, under conditions in which the subjects' identity remains blinded, will assay these samples.

9.3.2.2. Immunogenicity [Antibodies to Ustekinumab]

Antibodies to ustekinumab will be detected using a validated immunoassay method in serum samples collected from all subjects. Serum samples that test positive for antibodies to ustekinumab will be further characterized to determine if antibodies to ustekinumab could neutralize the biological effects of ustekinumab in vitro (ie, neutralizing antibodies to ustekinumab). All samples will be tested by the Sponsor or Sponsor's designee.

9.4. Pharmacodynamic Evaluations

9.4.1. Serum and Whole Blood Biomarkers

Samples for the analysis of pharmacodynamic markers will be collected at Weeks 0, 24, and 52. The samples will be used to better understand the biology of AxSpA, to provide a biological assessment of the response of patients to treatment with ustekinumab, to analyze differences between responders and non-responders, and to determine if the markers can be used to classify patients as potential responders prior to treatment. Serum samples will be used to analyze inflammation and spondyloarthropathy related proteins. Markers related to the biology of AxSpA, including (but not limited to) Th17, IL12/23, and bone homeostasis pathways will also be measured. RNA from whole blood samples will be used for gene expression analysis to determine the molecular profile of AxSpA and assess changes in gene expression post ustekinumab treatment.

9.4.2. Microbiome Substudy

This study will include a fecal microbiome substudy. Approximately 100 subjects will be asked to provide stool samples. The objective of the fecal biomarker study is to assess whether bacterial species, products of bacterial species, and products of host:bacterial interactions are associated with radiographic AxSpA or response to ustekinumab. Samples will be collected at baseline, Week 4, Week 24, and Week 52.

Participation in this portion of the study is optional and subjects must consent to participate in the microbiome substudy in the ICF. Note that genetic analyses of the subject's DNA or RNA will not be performed on these samples. Further, a subject may withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

9.5. Pharmacogenomic (DNA) Evaluations

In addition to HLA-B27 genotyping prior to study agent administration, complete genomic testing and/or targeted sequencing will be performed to search for links of specific genes to disease or response to drug. DNA methylation testing will also be performed to evaluate epigenetics, ie, modifications in DNA characteristics other than its sequence. Only DNA research related to ustekinumab or to the pathobiology of AxSpA will be performed. Genome wide pharmacogenetics testing as well as methylation testing will be undertaken in this study in consenting subjects only. Participation in this portion of the study is optional and subjects must sign a separate pharmacogenetics informed consent. Further, a subject may withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

9.6. Health Economics

9.6.1. Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment Questionnaire - Specific Health Problem (WPAI-SHP) is a validated instrument that has been used to study the impact of various diseases on patients' ability to work and perform daily activities.[40] The WPAI:SpA assesses the impact of AS on work and other daily activities during the past 7 days. The WPAI:SpA consists of six questions to determine employment status, hours missed from work due to AS, hours missed from work for other reasons, hours actually worked, the degree to which AS affected work productivity while at work and the degree to which AS affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment.

9.7. Safety Evaluations

Details regarding the independent DMC are provided in Section 11.13.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Safety and tolerability will be assessed by collecting information on AEs, clinical laboratory tests, vital signs, physical examinations, concomitant medication review, injection evaluations, allergic reactions, and early detection of TB.

Hematology assessments will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.

Blood chemistry assessments will include but are not limited to the following: chemistry panel (total and direct bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen/urea, and creatinine).

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator 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 eCRF.

Tests being performed by the central laboratory include, but are not limited to, the following:

- Hematology Panel

-hemoglobin	-WBC (neutrophils, lymphocytes, monocytes, eosinophils, basophils [%, absolute])
-hematocrit	-platelet count
-Red blood cells (RBC)	-mean corpuscular volume
-mean corpuscular hemoglobin	-mean corpuscular hemoglobin concentration
-RBC morphology	-WBC morphology (if present)

- Serum Chemistry Panel

-sodium	-total bilirubin
-potassium	-bilirubin (direct and indirect)
-urea nitrogen	-calcium
-creatinine	-phosphorous
	-albumin
-AST	-total protein
-ALT	
-alkaline phosphatase	-chloride
-bicarbonate	
-nonfasting glucose	

- Serum pregnancy testing for women of childbearing potential will be conducted at screening.
- Urine pregnancy testing for women of childbearing potential.

During the study, all abnormal laboratory values will require further explanation from the investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the investigator.

Vital Signs

Pulse and blood pressure will be collected.

Height and Weight

Height and weight will be measured as specified in the Time and Events Schedule.

Physical Examination

A physical examination will be performed at screening and the Week 64/Final safety follow up visit. The chest, abdomen, and extremities should be examined, but otherwise the examination can be a focused one based upon the individual's medical history and manifestations of spondyloarthritis, including axial and extra-articular (uveitis, psoriasis, inflammatory bowel disease, etc.).

Electrocardiogram

A 12-lead ECG will be performed at screening.

Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

Injection-site Reactions

A study agent injection-site reaction is any adverse reaction at an SC study agent injection site. The injection sites will be evaluated for reactions and any injection site reactions will be recorded as an AE. For injections administered at the study site, subjects should be carefully monitored for the occurrence of injection-site reactions for 30 minutes after the injection.

Allergic Reactions

Through Week 52, all subjects except those who qualify for EE and who choose to self-administer open-label golimumab must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives) for at least 30 minutes after the injection. If mild or moderate allergic reaction is observed, acetaminophen 650 mg PO or NSAIDs and diphenhydramine 25 mg PO or IV may be administered.

Subjects with reactions following an injection resulting in bronchospasm with wheezing and/or dyspnea requiring ventilator support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm mercury (Hg) will not be permitted to receive any additional study agent injections. In the case of such reactions, appropriate medical treatment should be administered.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the Time and Events Schedule) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of > 14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, study agent administration should be interrupted and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB Gold test, a repeat TST in countries in which the QuantiFERON®-TB Gold test is not approved/registered or TST is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. If the QuantiFERON®-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form.

Refer to the Time and Events Schedule (Table 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 64 of the study. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

If a subject discontinues study agent administrations at or before Week 52, he/she must return for specific efficacy and final safety visits (see Section 9.1.4).

Study agent administrations must be permanently discontinued if any of the following occur:

- Pregnancy or pregnancy planned within the study period or within 5 months after the last study agent administration.
- Reaction resulting in bronchospasm with wheezing and/or dyspnea requiring ventilator support, or symptomatic hypotension that occurs following a study agent administration.
- Reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study agent. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Opportunistic infection.
- Malignancy, excluding nonmelanoma skin cancer.
- Subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.

  - A subject undergoing continued evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB Gold test result (and/or a positive TST result in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the TST is mandated by local health authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study agent and continued to completion. Indeterminate QuantiFERON®-TB Gold test results should be handled as in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON®-TB Gold test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

- The initiation of protocol-prohibited medications (see Section 4.3).
- Investigator or Sponsor's medical monitor believes that for safety reasons it is in the subject's best interest.

Discontinuation of study agent administration must be considered for subjects who develop a serious infection.

10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study agent assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject discontinues study agent administrations before the end of the treatment but does not withdraw consent for study participation, posttreatment assessments should be obtained (Section 9.1.4).

A subject who withdraws from the study will have the following options regarding the optional research samples (DNA and microbiome stool samples):

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.

- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the Sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The Sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

Withdrawal of Participation in the Collection of Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

Descriptive statistics will include counts and proportions for categorical data, and median, mean, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data.

Unless otherwise specified, the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by region will be used to compare categorical variables such as the proportion of subjects responding to treatment. In general, continuous response parameters will be compared using an analysis of variance model, with region as covariate if appropriate. All statistical testing will be performed 2-sided.

Subject baseline data, demographic and baseline clinical disease characteristics will be summarized. The baseline measurement is defined as the closest measurement taken at or before the time of the Week 0 administration.

Efficacy analyses and summaries of subject information will be based on the modified intent-to-treat population (mITT; ie, all randomized subjects who received at least 1 administration of study treatment). Subjects included in the efficacy analyses will be summarized according to their assigned treatment group regardless of whether or not they receive the assigned treatment.

Safety and PK analyses will include all subjects who received at least 1 administration of study treatment.

11.1. Subject Information

Subjects' demographics data (eg, age, race, sex, height, weight) and baseline disease characteristics (eg, duration of disease, total back pain, and CRP) will be summarized by treatment group.

11.2. Sample Size Determination

The sample size of 483 subjects was chosen to achieve 90% power to detect a treatment difference between ustekinumab and placebo for the primary endpoint at a significance level of 0.05 (2-sided).

The assumptions for the sample size and power calculations were based on Week 24 data from the ustekinumab investigator-initiated study in AS and the certolizumab pegol AxSpA study[28] (Table 3).

Table 3: Power to detect a significant treatment difference in achieving an ASAS 40 Response at Week 24

	Treatment group	Sample size	ASAS 40 response	Power
1	Placebo ustekinumab	161 161	15% 25%	0.6123
2	**Placebo** **ustekinumab**	**161** **161**	**15%** **30%**	**0.9004**
3	placebo ustekinumab	161 161	15% 35%	0.9876
4	placebo ustekinumab	161 161	15% 40%	0.9993

11.3. Efficacy Analyses

11.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of subjects who achieve an ASAS 40 response at Week 24. The primary hypothesis is to compare at Week 24 the composite endpoint of ASAS 40 response and the outcome of continuing originally assigned treatment. Hence, subjects who early escape to golimumab, meet treatment failure criteria, or have missing ASAS assessment are nonresponders for the composite endpoint.

The proportion of subjects who achieve the composite endpoint at Week 24 will be compared between the ustekinumab groups and placebo group using a CMH test stratified by region at a significance level of 0.05 (2-sided). Data from all randomized subjects who received at least 1 administration of study treatment (mITT) will be analyzed according to their assigned treatment group regardless of their actual treatment received.

The critical values of the group sequential test design were calculated for the O'Brien and Fleming design. The following table outlines the critical values and 1-sided alpha levels for the interim analysis and the final analysis (Table 4):

Table 4: Critical values and 1-sided alpha levels for the interim analysis and final analysis

Information rate	Bounds reject H_0	Significant level (one-sided)	Alpha spent
0.5	2.797	0.0026	0.0026
1.0	1.977	0.0240	0.0250

Sensitivity analyses with modified analysis sets and different rules may be conducted, and will be documented in detail in the SAP.

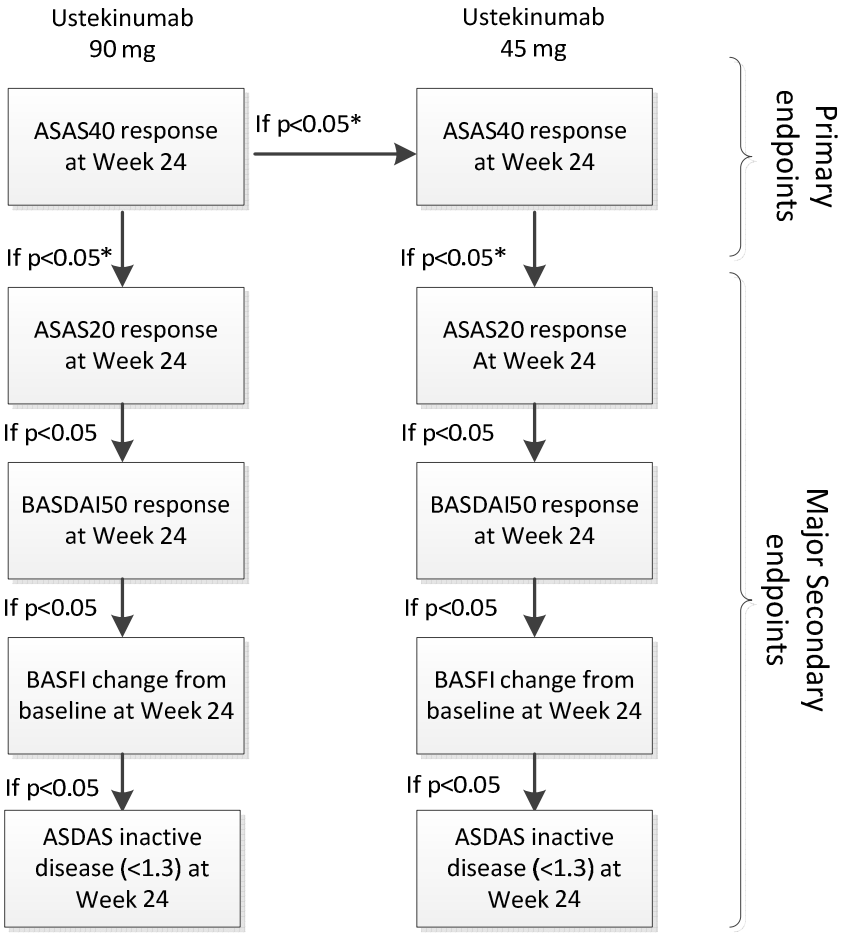
In addition, subgroup analysis will be performed to evaluate consistency in the primary efficacy endpoint by demographic characteristics, baseline disease characteristics, and baseline medications. Interaction test between the subgroups and treatment group will also be provided if appropriate.

11.3.2. Major Secondary Analyses

To control for multiplicity for the primary endpoint analysis and the major secondary endpoint analyses, the 4 major secondary analyses listed below will be performed sequentially contingent upon the success of the primary statistical analysis in that treatment group comparison (Figure 4). Otherwise, the p-values for the subsequent endpoints will be considered as supportive analyses. The following prespecified order will be used to analyze the major secondary endpoints.

1. The proportion of subjects who achieve an ASAS 20 response at Week 24.
2. The proportion of subjects who achieve at least a 50% improvement from baseline in BASDAI at Week 24.
3. The change from baseline in BASFI at Week 24.
4. The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24.

Figure 4: Overview of Multiplicity Control



* $p < 0.05$ refers to the rejection of null hypothesis according to the group sequential design specified in Section 11.3.1.

Because of regional differences in the regulatory approach to the statistical methods for controlling the type I error for the primary and secondary hypotheses, a different multiple comparison procedure will be prespecified and added to the SAP to address the requirement of regions with the family-wise control of the primary and secondary endpoints across doses.

11.3.3. Other Planned Efficacy Analyses

In addition to the primary and major secondary analyses, statistical analyses will be performed at visits prior to or at Week 24 for selected endpoints (eg, ASAS 20 at Week 16, the change from baseline in BASMI at Week 24). All endpoints described in Sections 9.2.2 will be summarized over time by treatment groups.

11.4. Pharmacokinetic Analyses

All serum ustekinumab concentrations below the limit of quantification (BLQ) of the assay or missing data will be labeled as such in the concentration data listing or SAS dataset. Concentrations below the BLQ of the assay will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each sampling timepoint.

Serum ustekinumab concentrations will be summarized for each treatment group over time. If feasible, a population PK analysis using nonlinear mixed effects modeling approach (NONMEM) will be used to characterize the disposition characteristics of ustekinumab in the current study. The CL/F and V/F will be estimated. The influence of important variables (such as body weight, positive for antibodies to ustekinumab, and the use of MTX, etc.) on the population PK parameter estimates may be evaluated. Details will be given in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

11.5. Immunogenicity Analyses

The incidence and titers of antibodies to ustekinumab will be summarized by treatment group over time. The impact of antibodies to ustekinumab on PK, efficacy, and safety will be assessed.

11.6. Pharmacodynamic Biomarker Analyses

Pharmacodynamic markers are considered exploratory and results will be summarized in a separate technical report.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum ustekinumab concentration and efficacy may be explored.

11.8. Biomarker and Microbiome Analyses

Changes in serum, RNA, fecal microbial profiles, and or other biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and clinical response will be explored.

Results will be presented in a separate report.

11.9. Pharmacogenomic Analyses

Pharmacogenomic and epigenetic analyses are considered exploratory and results will be summarized in a separate technical report.

11.10. Health Economics Analyses

1. The change from baseline in impact of disease on work productivity and daily activity via WPAI-SHP will be descriptively summarized by treatment group over time and compared between treatment groups at Week 24.
2. The change from baseline in impact of disease on overall health status via EQ-5D-5L will be descriptively summarized by treatment group over time and compared between treatment groups at Week 24.

11.11. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent AEs and AEs that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Based upon the safety profile of ustekinumab, as well as the golimumab safety data to date, several AEs of interest have been identified and will be monitored and assessed in this study. These include: injection reactions, MACE, demyelination, hepatobiliary laboratory abnormalities, infections including TB, and malignancies.

Clinical Laboratory Tests

Routine safety evaluations will be performed. Adverse events, SAEs, reasonably-related AEs, and AEs by severity will be summarized by treatment group. The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry), and the number of subjects with abnormal laboratory parameters (hematology and chemistry) based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grading will be summarized treatment group. Listings of SAEs will also be provided. All safety analyses will be based on the population of subjects who received at least 1 injection of study agent; subjects will be summarized by the treatment they actually received in placebo controlled period. Additional analyses will be conducted by ustekinumab dose groups for the entire study period.

11.12. Interim Analysis

An interim analysis based on the group sequential design will be conducted when approximately 50% of subjects have completed the Week 24 visit or ended study participation before the

Week 24 visit. O'Brien-Fleming alpha spending function will be used to determine the critical value for early stopping for efficacy of the primary endpoint. In addition, futility stopping rules will be specified in the interim analysis plan. An independent DMC will review these interim analysis results and make recommendations to the Sponsor whether the study should be stopped for futility or efficacy.

11.13. Data Monitoring Committee

The independent DMC will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to review the interim analysis results. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. Any safety concerns will be communicated to the Sponsor.

The DMC are independent of the Sponsor. None of the members will be participating in the current study. The independent DMC will consist of at least 2 medical experts in a relevant therapeutic area and 1 statistician. The members of the committee will be specified prior to study initiation. The major function of this committee will be to monitor the safety of the study agent and to provide recommendations for placing the study on hold or stopping the study in the event that any unanticipated serious events occur. In addition, the committee will review the interim unblinded efficacy results of CNTO1275AKS3001, CNTO1275AKS3002, and CNTO1275AKS3003, and recommend the continuation or stopping of the trial according to the specification of each protocol.

Periodic safety reviews will occur every 4 months. The DMC may change the frequency or number of reviews based on interim safety findings. The safety reviews will focus on particular AEs, SAEs, and mortality.

Serious adverse events (SAE) reports will be provided to the DMC members on an ongoing basis. The DMC will have access to unblinded data and review tabulated safety summaries (if appropriate) and any additional data that the DMC may request. No formal statistical hypothesis testing is planned. In addition, during the study, the Sponsor's study responsible physician (or designee) will regularly review blinded safety data from the sites and notify the DMC and appropriate Sponsor personnel of any issues.

The content of the efficacy and safety summaries, the DMC role and responsibilities and the general procedures (including communications) and their recommendations on the study conduct will be defined and documented in the DMC charter prior to the first DMC review.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety

information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a Sponsor study agent that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study agent
- Suspected abuse/misuse of a Sponsor study agent
- Inadvertent or accidental exposure to a Sponsor study agent
- Unexpected therapeutic or clinical benefit from use of a Sponsor study agent
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study agent, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study agent, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All adverse events, regardless of seriousness, severity, or presumed relationship to study agent, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The

investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

The subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax). Serious adverse events related to the disease under study will be collected per protocol but will not be unblinded and expedited if they fall into the following categories: exacerbation of spondylitis or worsening of pain related to AxSpA.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study agent or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization)

that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within 20 weeks of the last dose of study agent, whether or not the event is expected or associated with the study agent, is considered a serious adverse event.

12.3.3. Pregnancy

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. Pregnancies must be reported by study-site personnel within 24 hours of knowledge of the event using the appropriate pregnancy notification form.

Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators,

and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY AGENT INFORMATION

14.1. Physical Description of Study agents

Ustekinumab for this study will be supplied as a sterile solution in a single use PFS at a volume of either 0.5 ml (45 mg dose) or 1 ml (90 mg dose) as follows:

- Ustekinumab 45 mg, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0 in 0.5 mL nominal volume.
- Ustekinumab 90 mg, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0 in 1.0 mL nominal volume.

No preservatives are present.

Golimumab will be supplied as a sterile liquid for SC injection in single-use PFSs. Each PFS contains 50 mg (0.5 mL fill of liquid) of golimumab, in addition to histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives are present.

Liquid placebo will be supplied in both a 0.5 mL and a 1 mL PFS.

The needle cover on the PFS for ustekinumab and its placebo and golimumab contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

14.3. Labeling

Study agent labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Ustekinumab product must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C). The ustekinumab product should not be frozen and should be protected from light. Vigorous shaking of the ustekinumab product should be avoided. The formulation does not contain preservatives. Prior to administration, the drug product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Golimumab must also be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C). Golimumab must be handled in strict accordance with the protocol and the container label and be stored in a limited access area or in a locked cabinet under appropriate environmental conditions.

Subjects who are able and who have been appropriately trained in the self-administration of golimumab self-administer study agent at home in accordance with Section 7. Study personnel will instruct subjects on how to transport, store and administer medication for at-home use as indicated for this protocol.

Refer to the Site Investigational Product Procedures Manual for additional guidance on the preparation and handling of ustekinumab and golimumab.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study agents received at the site is inventoried and accounted for throughout the study. The study agents administered to the subject must be documented on the drug accountability form. All study agents will be stored and disposed of according to the Sponsor's instructions. Study-site personnel must not combine contents of the study agent containers.

Study agents must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study agents must be available for verification by the Sponsor's study site monitor during on-site monitoring visits. The return to the Sponsor of unused study agent will be documented on the drug return form. When the study site is an authorized destruction unit and study agent supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study agents should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study agents will be supplied only to subjects participating in the study. Study agents may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agents from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure
- Site Investigational Product Procedures Manual Laboratory Manual and laboratory supplies
- Electronic PRO device and user manual
- IWRS user guide and user manual
- Electronic data capture (eDC) Manual
- Sample ICF
- Imaging Manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected in this study from each subject will be approximately 191 mL for the main study and 30 mL for optional DNA testing, which is less than the typical blood donation of 500 mL.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written or electronic materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects (unless not required, as documented by the IEC/IRB)
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written or electronic materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study agent
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not

affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject. A limited number of subjects will be asked to consent to participate in a microbiome substudy. Refusal to participate in the microbiome substudy will not result in ineligibility for the clinical study.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, pharmacodynamics, and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand the mechanism of action of ustekinumab, to understand radiographic AxSpA, to understand responses to treatment in subjects with radiographic AxSpA, differential drug responders, and to develop tests/assays related to ustekinumab and radiographic AxSpA. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal from the Study, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative (see Contact Information page(s) provided separately). Except in emergency

situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study agent to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators

- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study agent administration information; and date of study completion and reason for early discontinuation of study agent or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following subject- and investigator-completed AS scales and assessments designated by the Sponsor will be recorded directly into an electronic device and will be considered source data: PGA, SF-36, MOS-SS, ASQoL, EQ-5D, FACIT-F, WPAI-SHP, AxSpA response evaluations (BASDAI, BASFI, Total back pain, Night back pain), and Musculoskeletal assessments (BASMI, enthesitis index, chest expansion).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between the Sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the Sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory, IWRS, and PRO data into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The Sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must 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 the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRFs with the hospital or clinic records (source documents); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the Sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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 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 IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study agent development

17.10. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ustekinumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including pharmacogenomics or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of ustekinumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory, IWRS, and PRO data into the Sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomics or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any

work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs) or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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APPENDIX A: QUANTIFERON®-TB GOLD TESTING

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON®-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

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APPENDIX B: TUBERCULIN SKIN TESTING

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

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APPENDIX C: HEPATITIS B VIRUS (HBV) SCREENING WITH HBV DNA TESTING

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+
* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.			

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Anna Beutler, MD

Institution: Janssen Research & Development

Signature: [redacted] Date: Jul 13, 2015
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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