Janssen Research & Development *

Statistical Analysis Plan

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

Protocol CNTO1275AKS3001; Phase 3

STELARA® (ustekinumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
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
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRP	c-reactive protein
DAS	disease activity score
DBL	database lock
DMARD	disease-modifying antirheumatic drugs
DMC	Data Monitoring Committee
eCRF	electronic case report form
EE	early escape
EQ-5D	EuroQol 5 Dimension
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCQ	Hydroxychloroquine
HRQOL	Health-related quality of life
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
ITT	Intent-to-Treat
IWRS	interactive web response system
LLOQ	Lower limit of quantification
LOCF	last observation carried forward
LSMeans	Least-Squares Means
MA	musculoskeletal assessor
mAb	monoclonal antibody
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MOS-SS	Medical Outcomes Study Sleep Scale
MRI	magnetic resonance imaging
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NONMEM	nonlinear mixed effects modeling approach
NSAID	nonsteroidal anti-inflammatory drug
PCS	Physical Component Summary
PD	Pharmacodynamics
PFS	prefilled syringe
PGA	Patient's Global Assessment

PK	Pharmacokinetics
PQC	Product Quality Complaint
PRO	Patient Reported Outcome
PsA	psoriatic arthritis
q4w	every 4 weeks
q12w	every 12 weeks
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	36-item short form health survey
SpA	Spondyloarthritis
SSZ	Sulfasalazine
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
TNFα	tumor necrosis factor alpha
TST	tuberculin skin test
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell (count)
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire - Specific Health Problem

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses.

1.1. Trial Objectives

This Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study is to evaluate the efficacy and safety of ustekinumab (previously named CNTO1275), a human anti- IL-12/23p40 monoclonal antibody, administered subcutaneously (SC) in subjects with active radiographic AxSpA who have had an inadequate response or intolerance to NSAIDs and are naïve to anti-TNFα therapy.

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

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

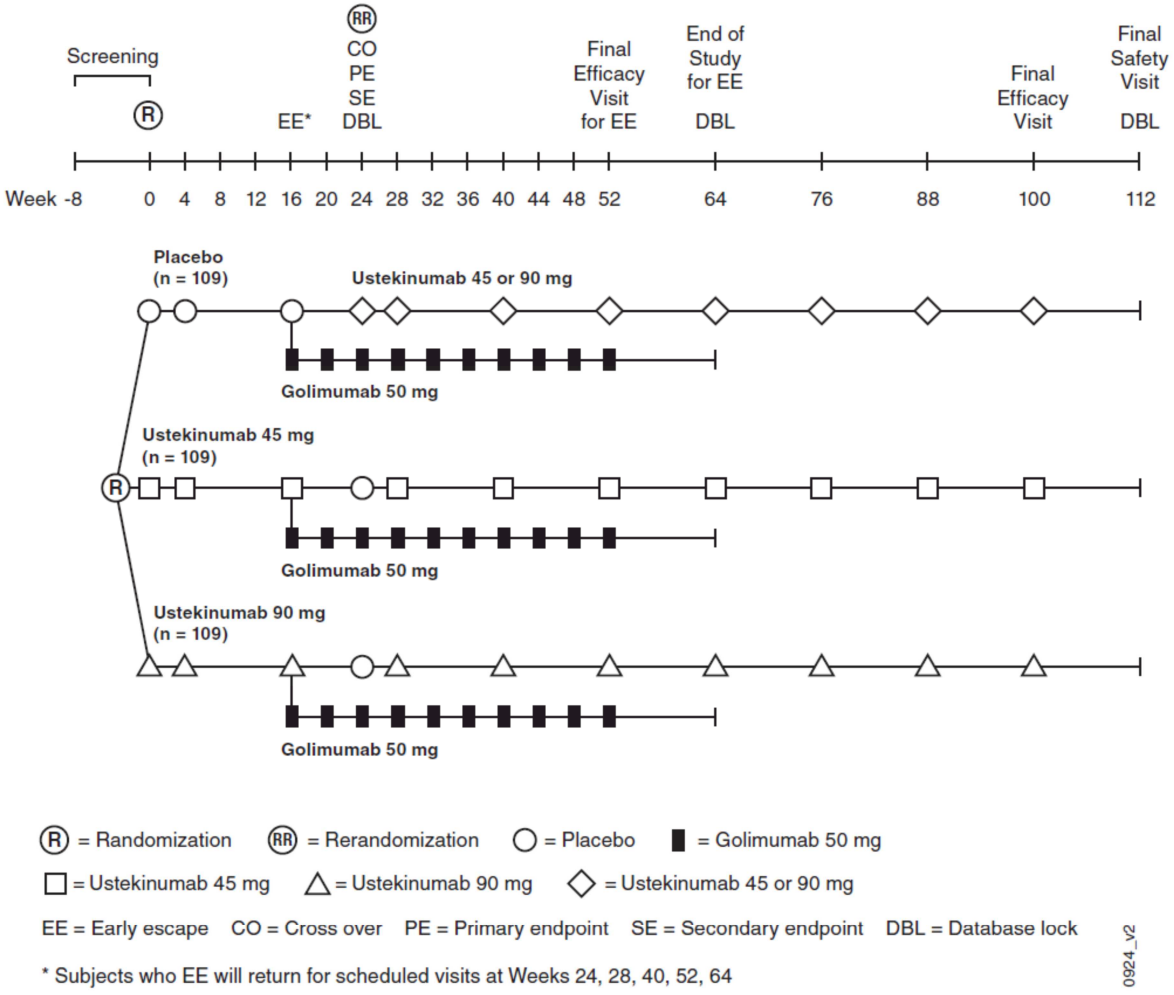
- Efficacy related to improving physical function, range of motion, health-related quality of life, other health outcomes, and radiographic progression
- Safety
- Pharmacokinetics (PK) and immunogenicity

1.2. Trial Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of ustekinumab 45 mg and 90 mg in subjects with active radiographic AxSpA who have had an inadequate response or intolerance to NSAIDs and are naïve to anti-TNFα therapy.

The study consists of a screening phase of up to 8 weeks, a blinded treatment phase of approximately 2 years (i.e., 100 weeks) including a **placebo controlled period** from Week 0 to Week 24 and an **active controlled period** from Week 24 to Week 100, and, a safety follow-up phase of 12 weeks after the last administration of study treatment. An overview of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



At Week 0, approximately 327 subjects are to be randomized in a blinded fashion in a 1:1:1 ratio to 1 of the following 3 treatment groups using permuted block randomization stratified by the region (North America, Latin America, Europe, and Asia Pacific):

- 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 100.
- 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 100. 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 100. At Week 24, subjects will receive placebo SC to maintain the blind.

Subjects in all 3 treatment groups who have <10% improvement from baseline in both total back pain and morning stiffness measures at both Week 12 and Week 16 will be considered as meeting EE criteria. Subjects who meet EE criteria will begin receiving open label golimumab 50 mg SC administrations at Week 16 and every 4 weeks (q4w) thereafter through Week 52.

At selected participating sites, a subset of the first approximately 100 subjects will be enrolled in the MRI substudy to explore the effect of ustekinumab on the structural changes in bone and soft tissue within the spine.

The end of the study is defined as the last visit for the last subject. The last visit is the Week 112 visit.

There are 3 database locks (DBL) planned. They will occur when all subjects complete the Week 24, Week 64, and Week 112 visits.

1.3. Statistical Hypotheses for Trial Objectives

The primary endpoint in this study is the proportion of subjects achieving an ASAS 40 response at Week 24. This endpoint was chosen because it is well accepted by regulatory authorities and the clinical AS community.

The null hypothesis is that there is no difference between either of the ustekinumab groups and the placebo group with respect to reduction in signs and symptoms of radiographic AxSpA as measured by ASAS 40 response at Week 24.

1.4. Sample Size Justification

The sample size of 327 subjects was chosen to achieve 90% power to detect a treatment difference between either ustekinumab group 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 (the ASAS 40 response rate is 16% in placebo and 48% in active).[9]

Table 1 shows the results of the power estimates for detecting a significant difference in the ASAS 40 response rates between the ustekinumab treatment group and the placebo treatment group.

Table 1: 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	109 109	20% 35%	0.7011
2	**Placebo** **Ustekinumab**	**109** **109**	**20%** **40%**	**0.9020**
3	Placebo Ustekinumab	109 109	20% 45%	0.9801
4	Placebo Ustekinumab	109 109	20% 50%	0.9976

1.5. Randomization and Blinding

1.5.1. Randomization

A central randomization is to be implemented in this study using an interactive web response system (IWRS). When a subject is eligible for randomization at a study site, the randomization requestor at that study site will contact the IWRS using the requester's own user identification and personal identification number and provide the relevant subject details to uniquely identify that subject. Based on computer-generated randomization schedules prepared before the study under the supervision of the Sponsor, the IWRS will then assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for that subject. Randomization at Week 0 and the re-randomization at Week 24 for placebo subjects will be conducted using permuted block method by the IWRS.

At Week 0, approximately 327 subjects will be randomized in a blinded fashion in a 1:1:1 ratio to 1 of the 3 treatment groups. The Randomization will be stratified by region (North America, Latin America, Europe, and Asia Pacific).

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.

1.5.2. Maintenance of the Blind

The study blind will be maintained for the duration of the study until after the final Week 112 database lock (DBL).

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.

An investigator may be unblinded to a given subject's treatment allocation when specific emergency treatment would be dictated by knowing the treatment status of the subject. In such cases, the investigator may determine the identity of the treatment by contacting the IWRS provider. It is strongly recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation prior to unblinding via IWRS. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event that the investigator is unable to contact the Sponsor, or emergency unblinding is considered medically necessary, the investigator may determine the identity of the treatment via IWRS. However, the Sponsor must be informed as soon as possible. The date, time, and reason for the 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 (e.g., sealed envelope) so as to not unblind the treatment assignment to the subject, the study site, or Sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the subject, the study site, or Sponsor personnel. Subjects who have had their treatment assignment unblinded are expected to continue to return for scheduled evaluations. Further study agent administrations should be discussed with the study responsible physician.

A given subject's treatment assignment may be unblinded to the Sponsor, Institutional Review Board/Independent Ethics Committee (IRB/IEC), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs). A separate code break procedure will be available for use by Janssen Global Medical Safety (GMS) to allow for unblinding of individual subjects to comply with specific requests from regulatory or health authorities.

The study responsible physician will remain blinded through the end of the study to subject level treatment assignment and dosing regimen. 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. Identification of Sponsor personnel who will have access to the unblinded subject level data will be documented prior to unblinding. Investigative sites and subjects will remain blinded to treatment assignment for the duration of the study, till after the final Week 112 DBL.

An independent, external DMC will monitor the safety of the study in unblinded fashion on a regular basis and whenever deemed necessary. In addition, the Sponsor Medical Monitor will review safety data in a blinded manner as the study is ongoing. The DMC's roles and responsibilities, the safety data for DMC review, and other related information (such as, the general procedures, communications, etc.) was defined and documented in the DMC charter.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Unless otherwise specified, nominal visits will be used for the summaries and listings over time with no visit windows applied.

Slotting for images taken outside of protocol-specified visit windows:

For subjects who are in MRI substudy, all MRIs have to be taken within a protocol-specified window of within 3 months prior to the first administration of study agent for the baseline, within 1 week before scheduled Week 24 visit, and within ±2 weeks of scheduled Week 100 visit. Nominal visits will still be used as the analytical window if the images are taken within -12 weeks of first administration of study agent for the baseline; -2 weeks of the Week 24 scheduled visit date; and ± 6 weeks of the Week 100 scheduled visit date. The images that are taken outside of the analytical window will be considered out-of-window, and the data will be set to missing for that scheduled visit.

As specified in the protocol, lateral view x-rays of the cervical and lumbar spine are to be obtained at baseline and at Week 100. The baseline x-rays will be performed within 8 weeks before randomization (Week 0); existing x-rays with acceptable quality obtained within six months prior to randomization may be sent for central reading in lieu of baseline x rays. Subjects without acceptable baseline x-rays will not have spinal x-rays performed at Week 100. For subjects enrolled after approval and implementation of Protocol CNTO1275AKS3001 Amendment 2, if the x-rays are not of adequate quality, new baseline x-rays must be submitted. Radiographs can be performed ±2 weeks of the scheduled Week 100 visits to allow time to address any potential issues with radiograph quality. Nominal visits will be used as the analytical window if the spine x-ray is taken within -24 weeks to +8 weeks of first administration of study agent for the baseline; ± 12 weeks of the Week 100 scheduled visit date. The x-rays that are taken outside of the analytical window will be set to missing for that scheduled visit. The subjects who had non-missing spine x-ray scores at both baseline and at Week 100 will be included in the analysis.

For PK analyses, if a subject has an administration more than +/- 7 days of the scheduled dosing date, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For the Week 24 visit, if the PK sampling time deviates more than +/- 3 days of the scheduled date, the PK concentration at this visit will be excluded from the by-visit data analyses.

2.2. Pooling Algorithm for Analysis Centers

Unless otherwise specified, data from all investigational centers/sites will be pooled by region for analyses.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set

The efficacy analysis data set (Full Analysis Set) includes all subjects who were randomized and received at least one administration of study agent, i.e., the modified Intent-to-Treat (mITT) Population.

Approximately 100 subjects will enroll in the MRI substudy and undergo MRI evaluations of the spine. The MRI analysis subset includes these subjects who have both baseline and post baseline MRI assessments.

X-ray analysis data set includes all subjects who have x-ray assessments at both baseline and Week 100.

In the efficacy analyses, subjects will be analyzed according to their assigned treatment group regardless of their actual treatment received.

2.3.2. Safety Analysis Set

The safety analysis set includes all subjects who received at least 1 (partial or complete) administration of study agent, i.e., the treated population.

In the safety analyses, subjects will be analyzed according to the treatment they actually received, regardless of their randomized treatments.

2.3.3. Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis set includes all subjects who received at least 1 complete administration of ustekinumab and had at least 1 valid blood sample drawn for PK analysis.

In the PK analyses, subjects will be analyzed according to the treatment they actually received, regardless of their randomized treatments.

2.3.4. Immunogenicity Analysis Set

The immunogenicity analysis set includes all subjects who received at least 1 (partial or complete) administration of uetekinumab and who have appropriate samples for detection of antibodies to ustekinumab (ie, subjects with at least 1 appropriate sample obtained after their first dose of ustekinumab).

In the immunogenicity analyses, subjects will be analyzed according to the treatment they actually received, regardless of their randomized treatments.

2.4. Definition of Subgroups

To evaluate the consistency in the primary efficacy endpoint (proportion of subjects who achieve ASAS 40 response at Week 24) over demographics, baseline characteristics, prior and baseline medication use, subgroup analyses will be performed when the number of subjects in the subgroups permits (eg, at least 15 subjects per treatment group for a given subgroup). The subgroups for subgroup analyses may include, but are not limited to, the following:

1. **Subgroups defined by demographics:**

   a) Gender (male, female)
   b) Race (White, Black or African American, Asian, Other)
   c) Geographic region (North America, Latin America, Europe, and Asia Pacific)
   d) Age (< 65 years, ≥ 65 years)
   e) Body mass index: (Normal [<25 kg/m^2], Overweight [≥ 25 kg/m^2 to <30 kg/m^2], Obese [≥ 30 kg/m^2])
   f) Body weight: as quartiles

2. **Subgroups defined by baseline characteristics:**

   a) Years since inflammatory back pain first appeared (<= 10 years, > 10 years)
   b) AS duration (<= 5 years, > 5 years)
   c) BASDAI (<= 6, > 6)
   d) BASFI (<= 5, > 5)
   e) BASMI (<= median, > median)
   f) Total back pain VAS (<= 7, > 7) in a 0 to 10 scale
   g) HLA-B27 (positive, negative)
   h) Laboratory CRP at baseline (<1.0 mg/dL, >=1.0 mg/dL)
   i) Complete ankylosis (yes, no)

3. Subgroups defined by medication (baseline or prior) use:

a) Use of NSAIDs at baseline (yes, no)

b) Use of oral corticosteroids at baseline (yes, no)

c) Use of DMARDs (SSZ/MTX/HCQ) at baseline (yes, no)

d) Number of DMARDs used in the past (none, 1, at least 2)

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

An interim analysis was planned to be performed when approximately 50% of the subjects completed the Week 24 visit or ended study participation before the Week 24 visit. The objective of the interim analysis was to determine whether the probability of meeting the primary endpoint at the end of the study was sufficiently low to consider terminating the study based on the data accrued up to the interim analysis. However, due to the rapid enrollment, it was determined that the planned interim analysis will not be performed.

3.2. 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. 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 consists of 2 medical experts in a relevant therapeutic area and 1 statistician. The members of the committee were specified prior to study initiation. The major function of this committee is 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.

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 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 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.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

The baseline measurement is defined as the closest measurement taken prior to the first study agent administration (Week 0) unless otherwise stated.

Demographic and baseline characteristic will be summarized for all subjects randomized into the study by the randomized treatment group.

Subjects' demographic data including age, race, sex, height, weight and BMI at baseline will be summarized. Baseline disease characteristics including duration of disease and baseline disease activity assessments will be summarized. Baseline concomitant medication usage will also be summarized. The number of subjects will also be summarized by geographic region, country, and investigational site.

4.2. Disposition Information

The number of subjects screened, randomized and treated will be summarized by treatment group. Subjects who discontinued study agent through Weeks 24, 52, and 100, and the reasons for discontinuing will also be summarized by randomized treatment group. Likewise, subjects who terminated study participation and the reasons for termination will also be summarized.

4.3. Treatment Compliance

Subjects will be summarized by the study agent lot(s) received. Subjects will also be summarized by the treatment group to which the subjects were randomized versus the actual treatment received during the study.

4.4. Extent of Exposure

The cumulative dose of ustekinumab (mg) received will be summarized by treatment group. The number of administrations will be summarized by treatment group. The average follow-up time will also be provided by treatment group in the safety tables.

4.5. Protocol Deviations

Subjects who did not meet study selection criteria (e.g. AS disease criteria, medication criteria, laboratory criteria, and medical history criteria) will be summarized and listed by randomized treatment group.

Subjects with major protocol deviations will be identified in the blind fashion prior to database lock. Major protocol deviations will be tabulated separately and presented by treatment group for the following categories: subjects who entered the study but did not meet entry criteria, subjects who received the wrong medication or incorrect dose, subjects who received disallowed medication, and "other".

4.6. Prior and Concomitant Medications

Medications taken by subjects prior to starting the study and concomitant medications will be summarized by medication and randomized treatment group.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Unless otherwise specified, all treatment group comparisons will be performed at a 2-sided α-level of 0.05.

5.1.1.1. Multiplicity Adjustment for Testing Procedures

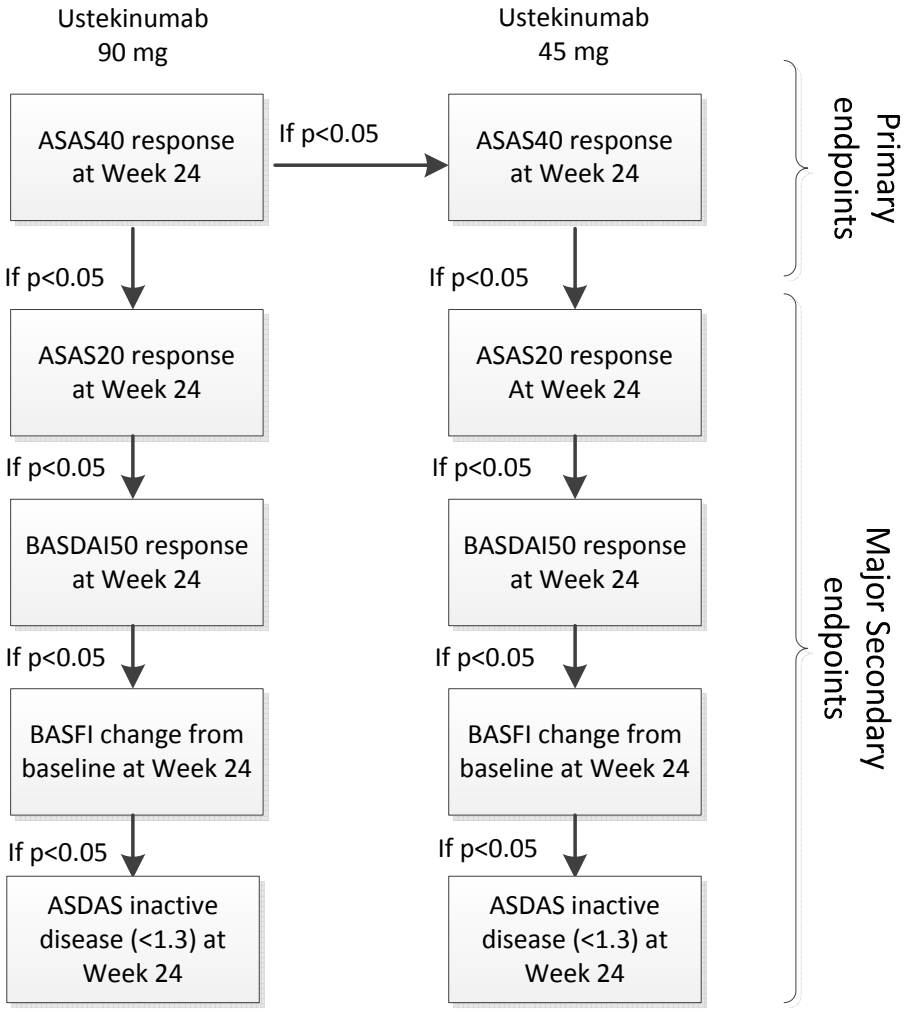
The primary endpoint of this study is the proportion of subjects who achieve an ASAS 40 response at Week 24.

There are 4 major secondary endpoints in this study:

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

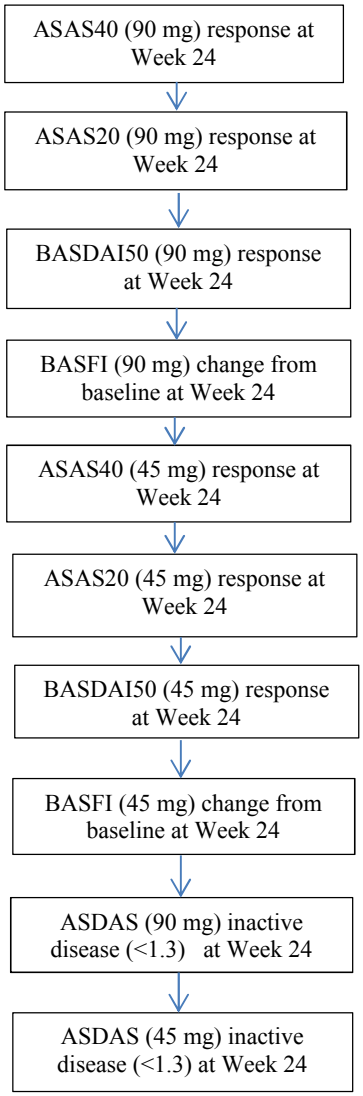
Global multiplicity adjustment (countries outside the United States): For an ustekinumab dose treatment group, the hypotheses for the major secondary endpoints will be tested only if the primary endpoint is significant for that ustekinumab dose treatment group. For each ustekinumab dose treatment group, the hypotheses of the major secondary endpoints will be tested in a fixed sequence as shown in Figure 2. If a given comparison is not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons in the sequence will be considered as supportive analyses.

Figure 2: Global Multiplicity Control



US-specific multiplicity adjustment: Because of regional differences in the regulatory requirement for controlling the type I error for the primary and secondary endpoints, a different multiple comparison procedure (Figure 3) is also pre-specified to address the FDA requirement for the family-wise control of the primary and secondary endpoints across doses. This testing procedure tests the primary and major secondary endpoints, for the two doses of ustekinumab, in a fixed sequence and each endpoint is tested at the two sided 0.05 level of significance. In this testing procedure the primary endpoint for the 90 mg ustekinumab dose is tested first followed by the 3 major secondary endpoints for the 90 mg dose of ustekinumab, then the primary for the 45 mg ustekinumab dose is tested followed by the 3 major secondary endpoints for the 45 mg dose of ustekinumab. They will be followed by the last major secondary endpoint for the 90 mg and 45 mg doses of ustekinumab, respectively. The fixed sequence testing method tests an endpoint only if the null hypothesis of no difference between the ustekinumab dose and placebo was rejected at the 0.05 level for all the endpoints above it in the sequence.

Figure 3: US Specific Multiplicity Adjustment



5.1.2. Data Handling Rules

Data handling rules discussed in this section will be applied to efficacy analyses through Week 24 when it is appropriate. In addition, selected data may also be reported using observed data without applying these data handling rules. **No data imputation rules will be applied for the analyses after Week 24.**

5.1.2.1. Treatment Failure

A subject who meets any one of the following treatment failure criteria will be considered a treatment failure from that point onward.

Treatment failure criteria:

- Initiate new DMARDs, biologics or systemic immunosuppressives for AS.
- Increase SSZ, MTX, or hydroxychloroquine dose above baseline dose for AS.
- Initiate treatment with oral, IV, or IM, corticosteroids for AS.
- Increase the dose of oral corticosteroids above baseline dose for AS.
- Discontinue study treatment due to lack of efficacy.

For dichotomous responder-type endpoints, subjects will be considered non-responders at the visit at and after treatment failure regardless of the actual measurements. Treatment failure rules will not be applied to continuous endpoints.

5.1.2.2. Missing Data Imputation

For dichotomous responder-type endpoints, missing responses at a post baseline visit will be imputed as a non-responder (NRI). For a composite dichotomous endpoint with missing response status due to missing data in any of its components, the endpoint will be set to a non-responder status (NRI).

For continuous endpoints, no missing data imputation rules will be applied, unless otherwise stated.

5.1.2.3. Early Escape

For a subject who enters early escape at Week 16 based on IWRS, the following adjustments will be made to subsequent data through Week 24:

- The subject will be considered a non-responder for response endpoints at Week 20 and Week 24;
- The measurement value at Week 20 and Week 24 will be set as missing for a continuous endpoint.

5.2. Primary Efficacy Endpoint

The primary endpoint is proportion of ASAS 40 responders at Week 24.

5.2.1. Definition

ASAS response is a composite measurement of change in AS signs and symptoms.

A 40% improvement in response according to the criteria of the ASAS International Working Group (ASAS 40)[1,12,15] is defined as:

1. An improvement of ≥ 40% from baseline and absolute improvement from baseline of at least 2 on a 0 to 10 cm scale in at least 3 of the following 4 domains:

   i. Patient global
   ii. Total back pain
   iii. Function (BASFI)
   iv. Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness)

2. No worsening at all in the remaining domain.

Following are the definitions of each of the forgoing disease assessment criteria (components) that are used in the determination of ASAS40 response:

a) Patient's Global Assessment: a measure from 0 (very well) to 10 (very poor) on a 0 to 10 cm VAS scale.

b) Total back pain: the average total back pain over the past week on a VAS (0 to 10 cm; 0 = no pain, 10 = most severe pain).

c) The BASFI is a subject's self-assessment represented as a mean (VAS; 0 to 10 cm) 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.[3] An increase along the scale indicates a worsening condition. (Section 5.3.3.1 for details)

d) Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness) (See Section 5.3.2.1 for BASDAI definition).

If a subject's baseline value for a component is zero (ie, no disease activity as measured by that component), the subject should be considered as not achieving 40% improvement from baseline for that component since there is no room for improvement.

5.2.2. Analysis Methods

Analyses

To address the primary hypothesis, a Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Latin America, Europe, and Asia Pacific) will be used to test the difference between the ustekinumab group and the placebo group for the proportion of ASAS 40 responders at Week 24. A 95% confidence interval for the treatment difference will be calculated based on the Wald statistic[18].

The adjusted proportion difference will be estimated as $d_{adj} = \sum_{j=1}^{4} w_j d_j$,

where $w_j = \frac{\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)}{\sum_{j=1}^{4}\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)}$, n_{ij} is the number of subjects who are in the i[th] treatment and the j[th] stratum; $d_j = \frac{x_{1j}}{n_{1j}} - \frac{x_{2j}}{n_{2j}}$, x_{ij}/n_{ij} is the estimated proportion of responders in the i[th] treatment and the j[th] stratum, where i=1,2 for treatments and j=1,2,3,4 for regions.

Let $r_{ij} = x_{ij}/n_{ij}$, the Wald-type 95% confidence interval is defined as

$$d_{adj} \pm 1.96\sqrt{\sum_{j=1}^{4} w_j^2\left(\frac{r_{1j}(1-r_{1j})}{n_{1j}} + \frac{r_{2j}(1-r_{2j})}{n_{2j}}\right)}$$

Data handling rules

The data handling rules in Section 5.1.2.1 Treatment Failure, Section 5.1.2.2 Missing Data Imputation, and Section 5.1.2.3 Early Escape will be applied.

5.2.3. Sensitivity Analyses

To test the robustness of the primary endpoint analysis, the following sensitivity analysis will be performed.

1. An analysis similar to that described in Section 5.2.2 will be performed with Treatment Failure, Missing Data Imputation, and Early Escape rules applied. However, subjects who discontinued study agent for any reason prior to Week 24 will be considered as ASAS 40 non-responders at Week 24.

2. An analysis similar to that described in Section 5.2.2 will be performed with Treatment Failure and Early Escape rules applied. However, Missing Data Imputation rule will not be applied.

3. ASAS 40 response status at Week 24 will be determined based on the observed data at Week 24 (retrieved dropout analysis). That is, no Treatment Failure, Missing Data Imputation, or Early Escape rules will be applied.

4. An analysis similar to that described in Section 5.2.2 will be performed with Missing Data Imputation and Early Escape rules applied. However, if at any one of the pre-week 24 visits (i.e., Weeks 4, 8, 12, 16, and 20) a subject meets any one of the treatment failure criteria and is an ASAS 40 non-responder at that visit, this subject should be considered a non-responder. Otherwise, the subject should be considered a responder for the primary efficacy analysis at Week 24 unless the subject's ASAS 40 result at Week 24 is a non-responder.

5. An analysis similar to that described in Section 5.2.2 will be performed with Missing Data Imputation and Early escape rules applied. However, Treatment Failure rule will not be applied.

6. "Tipping Point analysis via exhaustive scenarios" will be performed to evaluate various deviations from the assumption of non-response. For subjects with missing response data at Week 24, responder status will be imputed in an increasing manner by subject level for each treatment group. Specifically, for each subject, a responder / non-responder status will be imputed starting with the scenario where all subjects being non-responders up to the scenario where all subjects are responders. This would include all possible scenarios of responder status for all missing data, including scenarios where subjects on ustekinumab have worse outcomes than subjects on placebo. For each scenario, an analysis similar to that described in Section 5.2.2 will be performed.

7. The following "Tipping Point" analysis based on multiple imputations will be performed to evaluate various deviations from the assumption of non-response.
   For the tipping point analysis, a ρ will be assumed for each treatment group's response rate to the imputed value for missing values based on a Bernoulli distribution. This will be repeated N (N=100) times to generate N multiple imputations.
   For a given value of ρ, the analysis similar to Section 5.2.2 based on the multiple imputation approach will be carried out and the corresponding 95% CIs will be constructed to compare the difference in proportions in ASAS 40 responders between the placebo and each of ustekinumab groups. The analysis will be repeated for a range of values for ρ (i.e. 0% to 100% in increments of 10% independently, for both the placebo and the ustekinumab group); and thus will include scenarios where subjects on ustekinumab have worse outcomes than subjects on placebo. If the number of missing subjects is less than 10 in both placebo and ustekinumab groups, then the range of values for ρ would be 0% to 100% in increments of 25%. It should be noted that when the amount of missing data is small then this analysis should be interpreted with extra caution.

5.2.4. Analysis Methods

To evaluate the consistency in the primary efficacy endpoint, ASAS 40 at Week 24, over demographic, baseline characteristics, and prior or baseline medication use, subgroup analyses will be performed. If needed, some of the cut-off points may be changed to increase sample sizes within categories.

Proportion difference and the respective 95% CIs will be used for all subgroup mentioned in this section. In addition, the nominal p-values based on CMH test controlling region for the subgroups will also be provided. The 95% CI for the treatment differences will also be calculated based on the Wald statistics. .

The subgroups are described in Section 2.4.

5.2.5. Supportive Analyses

To evaluate the consistency of the primary endpoint, a supportive summary of each component of the composite endpoint will be summarized by treatment group with Treatment Failure and Early Escape rules applied. No missing data imputation rule will be applied.

5.3. Major Secondary Endpoints

This section outlines the definition and analyses of the major secondary endpoints.

The major secondary endpoints are listed below:

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

5.3.1. Proportion of Subjects who Achieve an ASAS 20 Response at Week 24

5.3.1.1. Definition

ASAS 20 is defined as a ≥20% improvement in 3 of the 4 ASAS response domains (Section 5.2.1), with an absolute improvement of at least 1 on a 0 to 10 cm scale, and absence of deterioration from baseline (≥ 20% and worsening of at least 1 on a 0 to 10 cm scale) in the potential remaining domain.

5.3.1.2. Analysis Methods

A Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Latin America, Europe, and Asia Pacific) will be used to test the difference between the ustekinumab group and the placebo group for the proportion of ASAS 20 responders at Week 24. A 95% confidence interval for the treatment difference will be calculated based on the Wald statistic.

Data handling rules

Similarly, to the primary endpoint, Treatment Failure, Missing Data Imputation, and Early Escape rules will be applied.

5.3.1.3. Sensitivity Analyses

ASAS 20 response status at Week 24 will be determined based on the observed data at Week 24 (retrieved dropout analysis). That is, no Treatment Failure, Missing Data Imputation, or Early Escape rules will be applied.

5.3.2. Proportion of Subjects who Achieve at Least a 50% Improvement from Baseline in BASDAI at Week 24

5.3.2.1. Definition

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a summary of six self-assessments using a VAS (0 to 10 cm) based on the following criteria**:**[6]

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

The BASDAI is a continuous parameter and is defined as follows:

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

The index will be calculated if at least 3 of the 5 components are present. Otherwise BASDAI is missing. Percent improvement from baseline is calculated as baseline value minus post-baseline value divided by baseline value.

5.3.2.2. Analysis Methods

A Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Latin America, Europe, and Asia Pacific) will be used to test the difference between the ustekinumab group and the placebo group for the proportion of subjects with at least 50% improvement from baseline in BASDAI at Week 24. A 95% confidence interval for the treatment difference will be calculated based on the Wald statistic.

Data handling rules

Similarly, to the primary endpoint, Treatment Failure, Missing Data Imputation, and Early Escape rules will be applied.

5.3.2.3. Sensitivity Analyses

The 50% improvement from baseline at Week 24 will be determined based on the observed data at Week 24 (retrieved dropout analysis). That is, no Treatment Failure, Missing Data Imputation, or Early Escape rules will be applied.

5.3.3. Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 24

5.3.3.1. Definition

The Bath Ankylosing Spondylitis Functional Index (BASFI) is calculated as the mean of 10 VAS from the following questions (Table 2), each of length 10 cm (0 – 10). Eight of the scales relate to functional capacity of subjects while the other 2 relate to a subject's ability to cope with everyday life. An increase along the scale indicates a worsening condition.[3]

Table 2: The Bath Ankylosing Spondylitis Functional Index
1. Putting on your socks or panty hose without help or aids (a sock aid, for example).
2. Bending forward from the waist to pick up a pen from the floor without an aid.
3. Reaching up to a high shelf without help or aids (a helping hand, for example).
4. Getting up out of an armless dining room chair without using your hands or any other help.
5. Getting up off the floor without help from lying on your back.
6. Standing unsupported for 10 minutes without discomfort.
7. Climbing 12-15 steps without using a handrail or walking aid, one foot on each step.
8. Looking over your shoulder without turning your body.
9. Doing physically demanding activities (for example, physical therapy exercises, gardening or sports).
10. Doing a full day's activities, whether it be at home or at work.

In case of missing responses, the mean score will be based on the available data from a minimum of 5 questions. Otherwise, BASFI is considered missing.

5.3.3.2. Analysis Methods

The analysis will be performed using a Mixed Model Repeated Measurements (MMRM) based on data using early escape rule only.

The independent variables for this model are treatment group, region (North America, Latin America, Europe, and Asia Pacific), baseline BASFI score, visit week, and an interaction of treatment and visit week. An unstructured (UN) variance-covariance matrix for repeated measures within a subject will be used unless there are issues related to convergence.

5.3.3.3. Sensitivity Analyses

1. An ANCOVA model will be used to test the difference between the ustekinumab group and the placebo group, with change from baseline in the BASFI scores at Week 24 being the dependent variable, and treatment group, baseline BASFI and region (North America, Latin America, Europe, and Asia Pacific) as independent variables. A 95% confidence interval for the difference in LSMeans and p-value will be calculated based on contrast test statistics. Last observed value (including baseline value) will be used to replace missing values and Week 16 values will be used to replace Week 24 values for early escaped subjects.
2. Tipping point analysis based on multiple imputations will be performed only if the amount of missing data is not negligible.

5.3.4. Proportion of Subjects who Achieve ASDAS (CRP) inactive disease (<1.3) at Week 24

5.3.4.1. Definition

The ASAS has developed a disease activity score (DAS) for use in AS, the Ankylosing Spondylitis Disease Activity Score (ASDAS).[2,10,14] 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 (CRP (mg/L) +1).

Where:

Total back pain is BASDAI question 2 (VAS 0-10 cm);

Duration of morning stiffness is BASDAI question 6 (VAS 0-10 cm);

Patient global assessment is patient global activity (VAS 0-10 cm);

Peripheral pain/swelling is BASDAI question 3 (VAS 0-10 cm);

CRP: C-reactive protein the natural log in mg/L + 1.

When the hsCRP level is <2 mg/L, a value of 2 mg/L should be used to calculate the ASDAS score.[11] For non-ASDAS summaries of CRP, if the value is <LLOQ, then half of the value of LLOQ will be used for numerical calculations.

5.3.4.2. Analysis Methods

A Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Latin America, Europe, and Asia Pacific) will be used to test the difference between the ustekinumab group and the placebo group for the proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24. A 95% confidence interval for the treatment difference will be calculated based on the Wald statistic.

Data handling rules

Similarly to the primary endpoint, Treatment Failure, Missing Data Imputation, and Early Escape rules will be applied.

5.3.4.3. Sensitivity Analyses

ASDAS (CRP) inactive disease status at Week 24 will be determined based on the observed data at Week 24 (retrieved dropout analysis). That is, no Treatment Failure, Missing Data Imputation, or Early Escape rules will be applied.

5.4. Estimands of Primary and Major Secondary Endpoints

The following Table 3 outlines the targeted estimands of primary and major secondary efficacy endpoints including related sensitivity analyses.

Table 3: Estimands of Primary and Major Secondary Endpoints

Variable	Analysis	Estimand/change in assumption(s)
Primary endpoint: proportion of ASAS 40 responders at Week 24	Primary analysis	Difference in the probability of ASAS40 response and remaining on study treatment and not adding/modifying ancillary therapies.
	Sensitivity analysis 1	Same estimand as for the primary analysis but consider subjects with study agent discontinuation prior to Week 24 for any reason as non-responder.
	Sensitivity analysis 2	Same estimand as for the primary analysis but exclude subjects with missing data (ie, ASAS40 response cannot be determined due to missing components).
	Sensitivity analysis 3	Difference in probability of ASAS40 response regardless of adherence or use of ancillary therapies (i.e., de facto estimand based on the observed data).
	Sensitivity analysis 4	Same estimand as for the primary analysis but consider only the cases with non-response status and meeting treatment failure criteria as treatment failure.
	Sensitivity analysis 5	Same estimand as for the primary analysis but no treatment failure rule is applied in this analysis.
	Sensitivity analysis 6 (Tipping point analysis via exhaustive scenarios)	Same estimand as for the primary analysis but the response for missing data will be varied to evaluate various deviations from the assumption of non-response.
	Sensitivity analysis 7 (Tipping point analysis based on multiple imputations)	Same estimand as for the primary analysis but the response for missing data will be varied to evaluate various deviations from the assumption of non-response.
1st Major secondary endpoint: proportion of subjects who achieve an ASAS 20 response at Week 24	Main analysis	Difference in the probability of ASAS20 response and remaining on study treatment and not adding/modifying ancillary therapies.
	Sensitivity analysis 2	Difference in probability of ASAS20 response regardless of adherence or use of ancillary therapies (i.e., de facto estimand based on observed data).

Table 3: Estimands of Primary and Major Secondary Endpoints		
2nd Major secondary endpoint: proportion of subjects who achieve at least a 50% improvement from baseline in BASDAI at Week 24	Main analysis	Difference in the probability of BASDAI50 response and remaining on study treatment and not adding/modifying ancillary therapies.
	Sensitivity analysis 1	Difference in probability of BASDAI50 response regardless of adherence or use of ancillary therapies (i.e., de facto estimand based on the observed data).
3rd Major secondary endpoint: change from baseline in BASFI at Week 24	Main analysis	Difference in change from baseline in BASFI and remaining on study treatment (values set missing after early escape). MMRM is used for the analysis.
	Sensitivity analysis 1	Same estimand as for the main analysis but assume the change from baseline in BASFI does not change after discontinuation or early escape. ANCOVA is used for the analysis.
	Sensitivity analysis 2 (Tipping point analysis based on multiple imputations) This analysis will be performed only if the amount of missing data is not negligible	Same estimand as for the main analysis but the value for missing data will be varied to evaluate various MNAR assumptions
4th Major secondary endpoint: proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24	Main analysis	Difference in the probability of achieving ASDAS (CRP) inactive disease status and remaining on study treatment and not adding/modifying ancillary therapies.
	Sensitivity analysis 1	Difference in probability of achieving ASDAS (CRP) inactive disease status regardless of adherence or use of ancillary therapies (i.e., de facto estimand based on the observed data).

5.5. Other Secondary Endpoints

In addition to the primary, major secondary endpoints, other secondary endpoints will be analyzed over time through Week 100 unless otherwise specified.

5.5.1. Definition of Other Secondary Endpoints

5.5.1.1. Low Disease Activity (ASAS Partial Remission)

Low level of disease activity will be measured by criteria for "ASAS partial remission," defined as a value below 2 on a scale of 0 to 10 cm in each of the 4 ASAS domains described above (Section 5.2.1).

5.5.1.2. ASAS 5/6 Response

ASAS 5/6 is defined as a ≥20% improvement in any 5 of the 6 domains of spinal pain (VAS 0 to 10 cm), patient global (VAS 0 to 10 cm), function (BASFI score), morning stiffness (from BASDAI), CRP, and spine mobility (lumbar side flexion). The spine mobility is based on the measured values of lumbar spine flexion, and not the converted values used to determine BASMI. Improvement is shown by an *increase* in lumbar spine flexion.

Any component with missing score at baseline will be excluded from the analyses. Except for spine mobility, if a subject's baseline value for a component is zero (ie, no disease activity as measured by that component), the subject should be considered as not achieving 20% improvement from baseline for that component since there is no room for improvement. In addition, all other 5 components should be >=20% improvement to be qualified as a responder.

5.5.1.3. A ≥20%, ≥50%, ≥70%, ≥90% Improvement from baseline in BASDAI

The definition of the improvement from baseline in BASDAI is defined in Section 5.3.2.1.

5.5.1.4. ASDAS (CRP)

The definition of the ASDAS (CRP) is defined in Section 5.3.4.1.

5.5.1.5. ASDAS (CRP) Inactive Disease (<1.3)

The definition of the ASDAS (CRP) is defined in Section 5.3.4.1.

5.5.1.6. ASDAS (CRP) Major Improvement (Decrease ≥2.0)

The definition of the ASDAS (CRP) is defined in Section 5.3.4.1.

Major improvement in ASDAS is defined as a decrease from baseline ≥2.0.

5.5.1.7. ASDAS (CRP) Clinically Important Improvement (Decrease≥1.1)

The definition of the ASDAS (CRP) is defined in Section 5.3.4.1.

Clinically important improvement in ASDAS is defined as a decrease from baseline ≥1.1.

5.5.1.8. Bath Ankylosing Spondylitis Metrology Index (BASMI)

The 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[13] as shown in Table 4: Equations proposed for the conversion of the assessments (A) into scores (S) for the five components of the BASMIlin Table 4.

Table 4: Equations proposed for the conversion of the assessments (A) into scores (S) for the five components of the BASMIlin

	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 and the scores (S) will be calculated programmatically based on assessments when analysis is performed.

5.5.1.9. 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.

5.5.1.10. MASES Enthesitis Scores

Enthesitis will be assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index in this study.[7]

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.

Entheses are scored as either 0 (nontender) or 1 (tender). The enthesitis index is a total score of 13 evaluated sites as listed above with a range from 0 to 13.

5.5.1.11. MRI Scores of the Spine

For approximately 100 subjects from selected sites, a magnetic resonance imaging (MRI) assessment of the cervical, thoracic and lumbar spine will be performed. These subjects will have MRI evaluations performed at 3 imaging timepoints (Screening/Baseline, 24, and 100). The subjects who had MRI scores at both baseline and postbaseline will be included in the analyses.

The Scoring of Spine MRI is based on the Berlin MRI Score, a modification of the ASspiMRI-a criteria assessed on MRI scans of the total spine. A total of 23 discovertebral units (DVU) C2 -S1 including the intervertebral space and the discs will be scored using a four-point scale from 0 to 3 as follows:

0 = Normal, no lesions
1 = Mild bone marrow edema, covering ≤25% of a DVU
2 = Moderate bone marrow edema, covering ≤50% of a DVU
3 = Severe bone marrow edema, covering >50% of a DVU

A score of 'NA' will be assigned in the case that the DVU is non-evaluable due to poor anatomical depiction, fat saturation failure or other artifacts.

The maximum possible Berlin MRI score for activity (acute changes) is 69.

The following review campaigns will be used for central efficacy reading of total spine MRI scans:

- MRI Campaign 1: Screening/Baseline and Week 24
- MRI Campaign 2: Screening/Baseline, Week 24, and Week 100

The images from all visits for a subject will be displayed in random time order with blinding of the chronological sequence. Two qualified, trained primary readers and one adjudicator will independently perform the assessment of MRIs for a given subject.

Adjusted score rules:

For a given subject and timepoint, the following rules will be applied to determine the reader score in case of incomplete set of evaluable DVU. If total number of DVU evaluable at the given time point is ≥ 12 (ie, 50% of 23), then the score for that subject, reader and timepoint will be obtained by calculating the average score for all non-missing DVU and multiplying by 23. If the total number of DVU evaluable at the given time point is < 12, then the score for that subject, reader and timepoint will be set to missing.

Adjudication rules:

For each subject, if Δ1 and Δ2 are the change from baseline in MRI scores at Week 24 (or Week 100) of 2 primary readers 1 and 2 respectively, and either Δ1 or Δ2 is missing or unreadable (but not both Δ1 and Δ2 missing/unreadable) or the absolute difference between Δ1 and Δ2 with different directions (ie, $\Delta1*\Delta2<0$) is greater or equal to 4 (ie, $|\Delta1 - \Delta2|\geq4$), or the absolute difference between Δ1 and Δ2 with the same directions (ie, $\Delta1*\Delta2\geq0$) is greater or equal to 9 (ie, $|\Delta1 - \Delta2|\geq9$), the change score in MRI from an adjudicator (third reader) will be involved.

The change from baseline in MRI spine score will be calculated as the average of each change score in MRI provided by the 2 independent readers, either 2 primary readers or 1 primary reader and 1 adjudicator.

5.5.1.12. mSASSS and New Formed Syndesmophytes

The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) will be used to assess the radiographic abnormalities in the cervical and lumbar vertebrae. The mSASSS is the sum of numerical scores, derived from radiological changes identified from the assessments of the lateral view of the cervical spine from the lower endplate of the second cervical vertebra (C2) to the upper endplate of the first thoracic vertebra (T1), and the lateral view of the lumbar spine from the lower endplate of the twelfth thoracic vertebra T12 to the upper endplate of the first sacral vertebra (S1).

Thus, 12 locations in the cervical spine and 12 locations in the lumbar spine will be assessed giving a total of 24 locations in the spine that will be scored. For each vertebral endplate, spinal changes will be scored according to the following grading scheme:

0 = normal
1 = erosion, sclerosis or squaring (C3 is not scored for squaring, but only erosion and sclerosis)
2 = syndesmophyte
3 = bridging syndesmophyte (when bridged, both endplate locations are scored as 3)

Based on 24 scoring locations and a maximum score of 3, the maximum total mSASSS score is therefore 72.

A score of 'NA' will be assigned in the case that the location is non-evaluable due to poor radiographic depiction, poor quality of the exposure or an interfering condition such as osteoarthritis.

Detailed information on the acquisition of x-rays will be provided in the Imaging Manual.

If a subject had mSASSS score of 0 at baseline and had mSASSS score ≥2 at Week 100, this subject is counted as having new formed syndesmophytes at Week 100.

5.5.1.13. Inflammation

Inflammation is defined as average of the last 2 questions of the BASDAI concerning morning stiffness). It is one of the components of ASAS 40. One question measures overall level of morning stiffness from the time you wake up in the last 7 days on a VAS (0 to 10 cm; 0 = no stiffness, 10 = very severe stiffness). The other question measures duration of morning stiffness from the time you wake up on a VAS (0 to 10 cm; 0 = 0 hours, 10 = 2 or more hours).

5.5.1.14. Total Back Pain

The total back pain is one of the components of ASAS 40. It is measured on a VAS (0 to 10 cm; 0 = no pain, 10 = most severe pain).

40% improvement in Total Back Pain

If a subject's baseline value is zero (ie. no pain), the subject should be considered as not achieving 40% improvement from baseline since there is no room for improvement.

5.5.1.15. Night Back Pain

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

5.5.1.16. Patient Global Assessment

The Patient's Global Assessment of Disease Activity is one of the components of ASAS 40. It is measured on a VAS (0 to 10 cm; 0 = very well, 10 = very poor).

40% improvement in Patient Global Assessment

If a subject's baseline value is zero (ie. no pain), the subject should be considered as not achieving 40% improvement from baseline since there is no room for improvement.

5.5.1.17. 36-Item Short-form Health Survey

The SF-36 is a health-related quality of life instrument with 36 questions. Version 2 will be used. This instrument yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. The 8 multi-item scales of SF-36 instrument are as follows:

- 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. The 2 aggregate summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), are based on the 8 subscales. The PCS, MCS, and the 8 subscales 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. 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[16,17]. High scores indicate better health for both summary scores (PCS and MCS) and all 8 subscales.

For partially answered questionnaires, if more than 50% of the items within each scale are left unanswered, that scale score for the subject will be assigned as missing. If at least 50% of the items within each scale are answered, the missing item scores will be imputed with the average score for the subject across completed items in the same scale.

5.5.1.18. Medical Outcomes Study Sleep Scale (MOS-SS)

The extent of sleep problems will be assessed using the Medical Outcomes Study Sleep Scale (MOS-SS).[8] The MOS Sleep Scale is a generic health measure, assessing a health-related quality of life (HRQOL) concept- sleep that is relevant to everyone's health status and well-being and known to be directly affected by disease and treatment. 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). A composite sleep problems index score can also be generated.

The scale uses predominantly Likert-type questions to evaluate sleep. Scales range from 1 (meaning "all of the time") to 6 ("none of the time"), and require respondents to indicate how frequently during the previous 4 weeks they have experienced certain sleep-related issues.

Several of these items are reverse scored. Another Likert-type item queries sleep latency (1 = "0–15 min" and 5 = "more than 60 min"). Finally, a fill-in-the blank question asks participants to estimate the average number of hours they have slept each night in the past month – a response of 8 h or greater receives a 1, while answers below 8 h receive 0.

5.5.1.19. Ankylosing Spondylitis Quality of Life (ASQoL) Questionnaire

Ankylosing spondylitis quality of life questionnaire is a self-administered patient-reported outcomes instrument.[4] 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 0–18. Higher scores indicate worse health related quality of life. Subjects can complete the instrument in less than four minutes.

5.5.1.20. EuroQol 5 Dimension Questionnaire (EQ-5D)

The EQ-5D is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal.[5] Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical economic evaluation of health care. The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There are 3 response options: no problems, some problems, severe problems. The EQ VAS records the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labeled "Best imaginable health state" and "Worst imaginable health state." The EQ VAS is used as a quantitative measure of health outcome as judged by the individual respondent. The US model will be used for analyses.

5.5.1.21. Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire (FACIT-Fatigue)

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.

5.5.2. Analysis Methods for Other Secondary Endpoints

Unless otherwise specified, the analysis population will be the FAS defined in Section 2.3.1. The following endpoints will be summarized by treatment groups.

Summaries over time will be for all visits data collected through Week 100. Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

Nominal p-values will be provided at each visit through Week 24.

1. For dichotomous endpoints, Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Latin America, Europe, and Asia Pacific) will be used. A 95% confidence interval for the treatment difference will be calculated based on the Wald statistic.
2. For continuous endpoints, a Mixed Model Repeated Measurements (MMRM) will be used.

The independent variables for this model are treatment group, region (North America, Latin America, Europe, and Asia Pacific), baseline value, visit week, and an interaction of treatment and visit week. An unstructured (UN) variance-covariance matrix for repeated measures within a subject will be used unless there are issues related to convergence.

The following Table 5 outlines the efficacy endpoints, type of the analyses, and the data handling rules used through Week 24. After Week 24, no treatment failure rule and no missing data imputation rules will be applied. All early escaped subjects will be excluded in the analyses after Week 24.

Table 5: Analyses and data handling rules for other secondary endpoints through Week 24

	Endpoints	**Data handling rules**		
		Treatment Failure	**Missing data imputation**	**Early escape**
1	The proportion of subjects who achieve an ASAS 40 response	√	√	√
2	The proportion of subjects who achieve an ASAS 20 response	√	√	√
3	The proportion of subjects who achieve low disease activity (ASAS partial remission)	√	√	√
4	The proportion of subjects who achieve an ASAS 5/6 response	√	√	√
5	The change from baseline in BASFI			√
6	The proportion of subjects who achieve a ≥20%, ≥50%, ≥70%, ≥90% improvement from baseline in BASDAI	√	√	√
7	The change from baseline in BASDAI			√
8	The change from baseline in ASDAS (CRP)			√
9	The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3)	√	√	√
10	The proportion of subjects who achieve ASDAS (CRP) major improvement (decrease ≥2.0)	√	√	√
11	The proportion of subjects who achieve ASDAS (CRP) clinically important improvement (decrease ≥1.1)	√	√	√
12	The change from baseline in BASMI			√
13	The change from baseline in each component of BASMI			√
14	The change from baseline in the PCS and MCS scores of SF-36			√
15	The proportion of Subjects Who Achieved at Least a 5 Unit Improvement From Baseline in the PCS and MCS scores of SF-36	√	√	√
16	The change from baseline in SF-36 subscales			√
17	The change from baseline in hsCRP			√
18	The change from baseline in chest expansion			√
19	The change from baseline in night back pain			√
20	The change from baseline in MASES enthesitis scores in subjects with enthesitis at baseline			√
21	The change from baseline in the Patient's Global Assessment of Disease Activity			√
22	The change from baseline in the Patient's Assessment of Total Back Pain			√
23	The change from baseline in inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness)			√
24	The proportion of subjects who achieve a ≥40% improvement from baseline in the Patient's Global	√	√	√

Table 5: Analyses and data handling rules for other secondary endpoints through Week 24				
	Assessment of Disease Activity			
25	The proportion of subjects who achieve a ≥40% improvement from baseline in the Patient's Assessment of Total Back Pain.	√	√	√
26	The proportion of subjects who achieve a ≥40% improvement from baseline in BASFI	√	√	√
27	The proportion of subjects who achieve a ≥40% improvement from baseline in the Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness)	√	√	√
28	The change from baseline in composite scores of MOS-SS			√
29	The change from baseline in ASQoL scores			√
30	The change from baseline in EQ-5D VAS and in EQ-5D index			√
31	The change from baseline in FACIT-Fatigue			√
32	The proportion of Subjects Who Achieved at Least a 4-Unit Improvement From Baseline in FACIT-Fatigue	√	√	√
33	The change from baseline in MRI spine score			√

For X-ray data, the change from baseline in mSASSS at Week 100 and the proportion of subjects who have new formed syndesmophytes at Week 100 will be summarized based on observed data.

In addition, the change from baseline in BASDAI after Week 24 through Week 52 will be summarized based on observed data for early escape subjects only.

6. SAFETY

Safety will be assessed by summarizing the occurrences and types of AEs, vital signs (pulse, blood pressure, weight and height) and the changes in the laboratory parameters.

Subjects who received at least 1 study agent administration will be included in the analysis (Safety analysis set) according to the treatment they actually received, regardless of the treatments they are randomized to.

6.1. Safety Table Presentation

If a subject discontinues study participation, the follow-up time will stop at the day of study participation discontinuation. The safety summary tables will be presented through the following periods: through Week 16, Week 24, Week 64, and Week 112.

The treatment group descriptions for all study periods are also outlined below.

6.1.1. Summaries through Week 16

1. **Placebo**: Subjects received placebo only through Week 16.

2. **Ustekinumab 45 mg**: Subjects who received at least one dose of 45 mg ustekinumab and never received 90 mg through Week 16. Subjects may have inadvertently received placebo prior to Week 16. Subjects may have missed one or more ustekinumab 45 doses.

3. **Ustekinumab 90 mg**: Subjects who received at least one dose of 90 mg ustekinumab through Week 16. Subjects may have inadvertently received placebo or ustekinumab 45 mg prior to Week 16. Subjects may have missed one or more ustekinumab 90 mg doses.

4. **Ustekinumab Combined**: Combined 2 and 3 above.

The treatment groups above are mutually exclusive for 1, 2, and 3. The safety tables will have the column headings below:

	Ustekinumab		
Placebo	45 mg	90 mg	Combined

6.1.2. Summaries through Week 24

Based on the protocol, subjects who qualified for early escape begin to receive golimumab at Week 16. Please note after Week 16, AE rates across treatment groups are no longer based upon subjects' initial randomized treatment assignments and/or initially assigned treatment (due to early escape and/or crossover), and the number of subjects and/or the lengths of follow-up may differ among the groups.

See the column headings below for the safety tables through Week 24:

Placebo/ Early Escape		Ustekinumab 45 mg/ Early Escape		Ustekinumab 90 mg/ Early Escape		
Placebo[a]	(Placebo→ Golimumab)[b]	45 mg Only[a]	(45 mg → Golimumab)[b]	90 mg Only[a]	(90 mg → Golimumab)[b]	Ustekinumab Only Combined[a]

[a] Includes all subjects, but adverse events for subjects who early escaped at Week 16 are only counted up to Week 16.
[b] Only includes subjects who early escaped at Week 16. Adverse events are counted from early escape onward.

6.1.3. Summaries through Week 64

Subjects who were randomized to placebo and did not qualify for early escape are re-randomized at Week 24 to receive either ustekinumab 45 mg or ustekinumab 90 mg. These summaries through Week 64 will be based on subjects who have been treated with ustekinumab and will exclude subjects who only received placebo.

See below for a sample layout.

Placebo->Ustekinumab[a]		Ustekinumab Only[b]		Ustekinumab Combined		
Placebo→ 45 mg	Placebo→ 90 mg	45 mg	90 mg	45 mg	90 mg	All Ustekinumab

[a] Placebo subjects who crossed over at Week 24.
[b] Adverse events for subjects who early escaped at Week 16 are only counted up to Week 16.

Selected safety summaries and listings will also be performed through Week 64 for subjects who early escaped to golimumab.

6.1.4. Summaries through Week 112

Subjects remain on the same treatment through Week 112 as they were taking at Week 64. The safety tables will have column headings below:

Ustekinumab		
45 mg[a]	90 mg[a]	Combined

[a] Include placebo subjects who crossed over to ustekinumab. Exclude adverse events that occurred following early escape to golimumab.

6.2. Adverse Events

Treatment-emergent AEs will be summarized by system organ class and preferred term defined by MedDRA.

The following treatment-emergent AE summary tables will be provided for this study:

- Any AEs
- SAEs
- AEs with severe intensity
- AEs and SAEs that are reasonably related to study agent
- AEs leading to discontinuation of study agent
- Injection site reactions
- Infections and infections requiring oral or parenteral anti-microbial treatment
- Serious infections

In addition to the summary tables, the incidence per 100 subject-years for select events including but not limited to serious infection and malignancies will be provided, and a listing of subjects who died and listings of subjects with the following AEs will be presented: SAEs, AEs leading to discontinuation of study agent, anaphylactic reactions, serum sickness reactions, malignancy, active tuberculosis, opportunistic infections, injection site reactions, and hepatobiliary events (defined as ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN).

Injection site reactions and infection:

- An injection site reaction is defined as any adverse reaction at a SC study agent injection site and is captured in the eCRF.
- An infection is identified as any AE that was recorded as an infection by the investigator on the eCRF.

Since safety should be assessed relative to exposure, the following summaries will be presented:

- Proportion of subjects receiving scheduled study agent administrations at each study agent administration visit by treatment group
- Summary of cumulative ustekinumab dose by treatment group

In addition, all AE summary tables will include average weeks of follow-up and average number of administrations for each treatment group.

6.3. Clinical Laboratory Tests

The laboratory parameters include but are not limited to the following:

Hematology: RBC, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, platelets, and WBC count.

Chemistry: BUN/urea, creatinine, total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bicarbonate, sodium, potassium, calcium, albumin, chloride, phosphate, glucose, and total protein.

NCI-CTCAE grades will be used in the summary of laboratory data (Grade 0 – 4). The proportion of subjects for each laboratory parameter with maximum Grades will be presented. Proportion of subjects with maximum ALT/AST will be provided for the categories: >1 to <2xULN, ≥2 to ≤3xULN, >3 to ≤5xULN, and >5 to <8xULN. These will also be provided by TB prophylaxis status.

A listing of subjects with post-baseline abnormal laboratory results based on CTCAE grades >=3 will also be provided.

6.4. Vital Signs

Vital signs are collected at every study visit, Week 0, 4, 8, 12, 16, 20, 24, 28, 40, 52, 64, 76, 88, 100 and 112. Markedly abnormal vital signs will be summarized by treatment group and listed.

Markedly Abnormal Criteria for Vital Signs in Adults		
Parameter	**Low**	**High**
Systolic BP	Absolute value ≤ 90 mmHg and a decrease from baseline ≥ 20 mmHg	Absolute value ≥ 180 mmHg and an increase from baseline ≥ 20 mmHg
Diastolic BP	Absolute value ≤ 50 mmHg and a decrease from baseline ≥ 15 mmHg	Absolute value ≥ 105 mmHg and an increase from baseline ≥ 15 mmHg
Pulse	Absolute value ≤ 50 bpm and a decrease from baseline ≥ 15 bpm	Absolute value ≥ 120 bpm and an increase from baseline ≥ 15 bpm

6.5. Electrocardiogram

This section does not apply to this study.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Pharmacokinetics (PK) samples for measuring serum ustekinumab concentrations will be collected from all subjects at the specified visits as shown in the schedule of events of the protocol. Samples will be collected at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 40, 52, 76, 100, and 112. All PK evaluations will be based on the subjects who receive at least 1 injection of ustekinumab (PK analysis set). No imputation for missing concentration data will be performed.

The data analysis of serum ustekinumab concentrations includes the following:

- Summary of serum ustekinumab concentrations at each visit by treatment group
- Summary of serum ustekinumab concentrations at each visit by treatment group and body weight quartiles
- Summary of serum ustekinumab concentrations at each visit by treatment group and baseline MTX (Yes, No)
- Summary of serum ustekinumab concentrations by CRP levels at baseline
- Proportion of subjects without detectable serum ustekinumab concentration at each visit by treatment group
- Median serum ustekinumab concentrations plotted over time by treatment group.

In addition, the relationship between serum ustekinumab concentrations, and antibody to ustekinumab status, safety and efficacy may be explored. Median trough serum ustekinumab concentrations will be plotted. Box plots of serum ustekinumab concentrations will be plotted by percentage subjects who achieved ASAS 20 and ASAS 40 responses.

For summary statistics of serum ustekinumab concentrations, concentration values below the lower limit of quantification will be treated as zero. Once a subject meets one of the following dosing deviation criteria, the subject's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

- Discontinue study agent administrations
- Skipped an administration
- Received an incorrect dose
- Received an incorrect study agent
- Received an additional dose

In addition, if a subject has an administration more than 7 days earlier or later than the scheduled dosing date, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For the Week 24 visit, if the PK sampling time deviates more than 3 days earlier or later than the scheduled date, the PK concentration at this visit will be excluded from the by-visit data analysis. Additional exclusions for incongruous PK data to be implemented based on Janssen TV-SOP-11008v3.0.

Population PK analyses will be performed to characterize the population PK parameters based on the available ustekinumab concentration data obtained through the Week 24 visit. The population pharmacokinetic approach will also be used to identify and quantify any significant covariates such as demographic characteristics (including but not limited to body weight, ethnic origin, sex, and age) and concomitant medications that have substantial impact on the population pharmacokinetics of ustekinumab in subjects with AS. A detailed analysis plan for population PK analysis will be developed separately, and a stand-alone technical report will be written to summarize the results of the population PK analysis.

PK analyses presentation

PK analyses will be summarized through the following time periods:

- Through Week 24
- Through Week 52
- Through Week 112

For the analyses, a subject is included in one and only one treatment group on the basis of the treatment regimen followed. The descriptions of treatment groups for all reporting periods are as follows.

7.1.1. PK Treatment Groups Through Week 24

1. **Ustekinumab 45 mg**: Subjects randomized to ustekinumab 45 mg and received 45 mg ustekinumab through Week 24.

2. **Ustekinumab 90 mg**: Subjects randomized to ustekinumab 90 mg and received 90 mg ustekinumab through Week 24.

7.1.2. PK Treatment Groups Through Week 52

1. **Placebo → Ustekinumab 45 mg**: Subjects randomized to placebo and were switched over to ustekinumab 45 mg at Week 24 and continue to receive ustekinumab 45 mg through Week 52.

2. **Ustekinumab 45 mg**: Subjects randomized to ustekinumab 45 mg and received 45 mg ustekinumab through Week 52.

3. **Placebo → Ustekinumab 90 mg**: Subjects randomized to placebo and were switched over to ustekinumab 90 mg at Week 24 and continue to receive ustekinumab 90 mg through Week 52.

4. **Ustekinumab 90 mg**: Subjects randomized to ustekinumab 90 mg and received 90 mg ustekinumab through Week 52.

7.1.3. PK Treatment Groups Through Week 112

1. **Placebo → Ustekinumab 45 mg**: Subjects randomized to placebo and were switched over to ustekinumab 45 mg at Week 24 and continue to receive ustekinumab 45 mg through the end of the study.

2. **Ustekinumab 45 mg**: Subjects randomized to ustekinumab 45 mg and received 45 mg ustekinumab through the end of the study.

3. **Placebo → Ustekinumab 90 mg**: Subjects randomized to placebo and were switched over to ustekinumab 90 mg at Week 24 and continue to receive ustekinumab 90 mg through the end of the study.

4. **Ustekinumab 90 mg**: Subjects randomized to ustekinumab 90 mg and received 90 mg ustekinumab through the end of the study.

7.2. Immune Response

Blood samples will be collected to examine the formation of antibodies to ustekinumab at the specified visits as shown in the schedule of events of the protocol (Weeks 0, 4, 8, 12, 24, 40, 52, 76, 100, and 112). For subjects who discontinue study agent administrations, samples will be collected at their final safety visit, 12 weeks after the last study agent administration.

The data analysis of antibodies to ustekinumab includes the following will be provided:

- The summary of subjects' antibody status (positive, negative) by ustekinumab treatment groups
- A listing of subjects who are positive for antibodies to ustekinumab.
- A summary of subject's neutralizing antibody status (positive, negative) by ustekinumab treatment groups.

- For subjects who discontinue study agent administrations, a listing of their antibody status will be presented.
- The relationship between antibody to ustekinumab status and efficacy and safety at major assessment time points (Week 24, 52, 100); ASAS 20 and ASAS 40 responses by antibody to ustekinumab status and treatment group (additionally at Week 16 which is the trough concentration for ustekinumab with Week 24 ASAS 20/ASAS 40 responses); injection-site reactions by antibody to ustekinumab status and treatment group; hypersensitivity by antibody to ustekinumab status and treatment group
- The relationship between antibody to ustekinumab status at Week 24 and antibody to ustekinumab status at Week 52 will be explored. The same analysis between Week 52 to Week 100 will be explored.
- The summary of onset and duration of antibody formation
- Figure of serum ustekinumab concentrations by treatment group and by antibody to ustekinumab status and summary of PK concentration by treatment group and by antibody to ustekinumab status

The descriptions of treatment groups for all reporting periods are as follows.

7.2.1. Immunogenicity Treatment Groups Through Week 24

1. **Ustekinumab 45 mg**: Subjects randomized to ustekinumab 45 mg and received 45 mg ustekinumab through Week 24.

2. **Ustekinumab 90 mg**: Subjects randomized to ustekinumab 90 mg and received 90 mg ustekinumab through Week 24.

3. **Total**: subjects are in one of above groups 1and 2.

7.2.2. Immunogenicity Treatment Groups Through Week 52

1. **Placebo → Ustekinumab 45 mg**: Subjects randomized to placebo and were switched over to ustekinumab 45 mg at Week 24 and continue to receive ustekinumab 45 mg through Week 52.

2. **Ustekinumab 45 mg**: Subjects randomized to ustekinumab 45 mg and received 45 mg ustekinumab through Week 52.

3. **Combined Ustekinumab 45 mg**: Subjects are in one of above groups 1 and 2.

4. **Placebo → Ustekinumab 90 mg**: Subjects randomized to placebo and were switched over to ustekinumab 90 mg at Week 24 and continue to receive ustekinumab 90 mg through Week 52.

5. **Ustekinumab 90 mg**: Subjects randomized to ustekinumab 90 mg and received 90 mg ustekinumab through Week 52.

6. **Combined Ustekinumab 90 mg**: Subjects are in one of above groups 4 and 5.

7. **Total**: Subjects are in one of above groups 1,2, 4, and 5.

7.2.3. Immunogenicity Treatment Groups Through Week 100

1. **Placebo → Ustekinumab 45 mg**: Subjects randomized to placebo and were switched over to ustekinumab 45 mg at Week 24 and continue to receive ustekinumab 45 mg through Week 100.

2. **Ustekinumab 45 mg**: Subjects randomized to ustekinumab 45 mg and received 45 mg ustekinumab through Week 100.

3. **Combined Ustekinumab 45 mg**: Subjects are in one of above groups 1 and 2.

4. **Placebo → Ustekinumab 90 mg**: Subjects randomized to placebo and were switched over to ustekinumab 90 mg at Week 24 and continue to receive ustekinumab 90 mg through Week 100.

5. **Ustekinumab 90 mg**: Subjects randomized to ustekinumab 90 mg and received 90 mg ustekinumab through Week 100.

6. **Combined Ustekinumab 90 mg**: Subjects are in one of above groups 4 and 5.

7. **Total**: Subjects are in one of above groups 1,2, 4, and 5.

7.3. Pharmacodynamics

Pharmacodynamics biomarkers are collected at Weeks 0, 24, 52, and 100. The analyses results will be provided in an independent technical report.

7.4. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between serum ustekinumab concentrations and pharmacodynamics markers may be explored and results will be reported in an independent technical report.

7.5. Microbiome Substudy

Approximately 100 subjects will be asked to provide stool samples for a fecal microbiome substudy. The samples will be collected at baseline, Weeks 4, 24, 52 and 100, and analyses results will be provided in an independent technical report.

7.6. Pharmacogenomics

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 in consenting subjects only. The analyses results will be provided in an independent technical report.

8. HEALTH ECONOMICS

8.1. Definition

8.1.1. 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. 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.

8.2. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS defined in Section 2.3.1. The change from baseline in 4 WPAI scores will be summarized over time by treatment groups. The 4 WPAI scores are:

1. Percent work time missed due to AS. This score is defined by $[Q2/(Q2+Q4)]x100$;
2. Percent Impairment while Working due to AS. This score is defined by $(Q5/10)x100$;
3. Percent overall Work Impairment due to AS. This score is defined by $\{Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]\}x100$;
4. Percent activity impairment due to AS. This score is defined by $(Q6/10)x100$.

Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum will be provided.

Nominal p-values will be provided at Week 16 and at Week 24.

A Mixed Model Repeated Measurements (MMRM) will be used.

The independent variables for this model are treatment group, region (North America, Latin America, Europe, and Asia Pacific), baseline score, visit week, and an interaction of treatment and visit week. An unstructured (UN) variance-covariance matrix for repeated measures within a subject will be used unless there are issues related to convergence.

Data handling rule:

Subjects with no observed data at all will be excluded from the analysis. Subjects with no value at baseline are excluded from the analysis. Early escape rules will be applied on Week 24 data. After Week 24, no treatment failure rule and no missing data imputation rules will be applied. All early escaped subjects will be excluded in the analyses after Week 24 through Week 100.

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