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 Subjects With Active Nonradiographic Axial Spondyloarthritis

Protocol CNTO1275AKS3003; Phase 3

STELARA® (ustekinumab)

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Assessment in SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	aspartate aminotransferase
AxSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional 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
HCQ	Hydroxychloroquine
hs-CRP	high sensitivity C-reactive protein
IWRS	interactive web response system
LSMeans	Least-Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SSZ	Sulfasalazine
TEAEs	Treatment emergent adverse events
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VAS	visual analog scale

1. INTRODUCTION

CNTO1275AKS3003 was terminated by the sponsor on May 22, 2017 after reviewing the results of the statistically controlled endpoints for CNTO1275AKS3001 at the Week 24 database lock, which showed that the primary and major secondary endpoints were not met for either of the two active doses 45 or 90 mgs.

As a result of the early termination of the study, the originally planned efficacy analyses specified in the protocol based on intent-to-treat population would not be useful because about 30% of enrolled subjects had to discontinue study agent administration prior to Week 24 due to "Study terminated by sponsor", which makes missing data imputation rules specified in the protocol inappropriate. With these considerations, only selected efficacy analyses through Week 24 including primary and major secondary endpoints will be performed based on the subjects who were randomized by November 29, 2016 (approximately 25 weeks prior to the study was terminated) and received at least 1 administration of study treatment. No data analysis of imaging data, serum ustekinumab concentrations or antibodies to ustekinumab will be provided. However, all other data, such as, baseline demographics and disease characteristics, prior and concomitant medications, study agent discontinuations and study participation status, treatment compliance and protocol deviations, and all safety data including adverse events, vital signs and laboratory parameters will be summarized.

1.1. Trial Design

This was a Phase 3 multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of ustekinumab compared with placebo in adult subjects with active nr-AxSpA with an inadequate response or intolerance to nonsteroidal anti-inflammatory drugs (NSAID). They may have had exposure to no more than 1 anti-tumor necrosis factor alpha (TNFα) agent. Approximately 390 subjects were to be randomized at approximately 85 investigational sites. Subjects were randomly assigned to receive SC ustekinumab 45 mg or 90 mg or placebo administrations at Weeks 0, 4, and 16. At Week 16, subjects in the placebo group who qualify for early escape (subjects with <10% improvement from baseline in both total back pain and morning stiffness measures at both Week 12 and Week 16), began receiving randomly assigned SC ustekinumab 45 mg or 90 mg administrations at Weeks 16, 20, and 28 and q12w thereafter through Week 52 in a blinded fashion. At Week 24, all remaining subjects in the placebo group who did not meet early escape criteria were rerandomized to receive ustekinumab 45 mg or 90 mg at Weeks 24 and 28 followed by q12w therapy through Week 52. Subjects in the ustekinumab treatment groups received a placebo administration at Weeks 20 and 24 to maintain the blind and continue to receive SC ustekinumab 45 mg or 90 mg at Week 28 and q12w thereafter through Week 52. At Week 52, all subjects who achieve inactive disease (Ankylosing Spondylitis Disease Activity Score [ASDAS] erythrocyte sedimentation rate [ESR] <1.3) at both Week 40 and Week 52 visits were to undergo rerandomization to either remain on ustekinumab or receive placebo.

Subjects who did not achieve inactive disease (ASDAS [ESR] <1.3) at either the Week 40 or Week 52 visit were to receive their previously assigned ustekinumab dose at their scheduled visits.

All subjects who experienced a flare after Week 52 defined as ASDAS (ESR) >2.1 were given the option to discontinue study injections and utilize an alternative therapy per the physicians' discretion or to continue study injections in a blinded fashion. Subjects who elected to continue and were rerandomized to placebo at Week 52 were to have ustekinumab injections reinstituted at their next scheduled visit. Subjects who elected to continue and were rerandomized to ustekinumab at Week 52 were to continue with ustekinumab dose at their scheduled visits.

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

Subjects were to be followed for adverse events (AEs) and SAEs at least 12 weeks following the last study treatment administration.

1.2. Randomization and Blinding

1.2.1. Randomization

A central randomization was implemented in this study using an interactive web response system (IWRS). When a subject was eligible for randomization at a study site, the randomization requestor at that study site contacted the IWRS using the requester's own user identification and personal identification number and provided 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 assigned a unique treatment code, which dictated the treatment assignment and matching study agent kit for that subject. Randomization at Week 0 and the re-randomization at Weeks 16, 24, and 52 were conducted using permuted block method by the IWRS.

At Week 0, approximately 390 subjects were to be randomized in a blinded fashion in a 1:1:1 ratio to 1 of the 3 treatment groups. The Randomization was stratified by MRI/hsCRP status (MRI+/hsCRP+; MRI+/hsCRP-; MRI-/hsCRP+) and by the status of previous exposure to anti-TNFα (naïve, TNF-IR, or other).

To maintain the blind, all randomized subjects were to 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.

1.2.2. Maintenance of the Blind

The study blind was maintained for the duration of the study until after the final database lock (DBL).

However, if it was necessary for a subject's safety, the study blind may have been broken and the identity of the study agent ascertained. The study agent number was entered in the case report form when the study agent was administered. The study agents were identical in appearance and packaged in identical containers.

The investigator was not provided with randomization codes. The codes were to be maintained within the IWRS, which had 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 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 have been unblinded to a given subject's treatment allocation when specific emergency treatment would have been dictated by knowing the treatment status of the subject. In such cases, the investigator may have determined the identity of the treatment by contacting the IWRS provider. It was 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 was to be available 24 hours per day, 7 days per week. In the event that the investigator was unable to contact the Sponsor, or emergency unblinding was considered medically necessary, the investigator may have determined the identity of the treatment via IWRS. However, the Sponsor should have been informed as soon as possible. The date, time, and reason for the unblinding should have been documented in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break should have been 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 was 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 were expected to continue to return for scheduled evaluations. Further study agent administrations should have been discussed with the study responsible physician.

A given subject's treatment assignment may have been 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 was to 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 remained blinded through the end of the study to subject level treatment assignment and dosing regimen. Investigative sites and subjects were to remain blinded to treatment assignment for the duration of the study, until after the final DBL.

An independent, external DMC monitored the safety of the study in an unblinded fashion on a regular basis and whenever it was deemed necessary. The DMC's roles and responsibilities, the safety data for DMC review, and other related information (such as, the general procedures, communications, etc.) were 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.

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. Full Analysis 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.

2.3.2. Efficacy Analysis Set (Modified Full Analysis Set)

The efficacy analysis data set (Modified Full Analysis Set) includes subjects who were randomized by November 29, 2016 (approximately 25 weeks prior to the study was terminated on May 22, 2017) and received at least 1 administration of study treatment.

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

2.3.3. Safety Analysis Set

The safety analysis set through the end of the study (beyond week 24) 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.

2.4. Definition of Subgroups

To evaluate the consistency in the primary efficacy endpoint (proportion of subjects who achieve ASAS 20 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 (Asia Pacific, Europe, Latin America)

d) Age (< 30 years, ≥ 30 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])

2. Subgroups defined by baseline characteristics:

a) HLA-B27 (positive, negative)

b) Years since inflammatory back pain first appeared (≤ 10 years, >10 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

h) Laboratory CRP at baseline (<1.0 mg/dL, >=1.0 mg/dL)

g) MRI-CRP entry criteria

- Met only CRP criteria
- Met only MRI criteria
- Met both CRP and MRI criteria
- All who met CRP criteria
- All who met MRI criteria

h) Anti-TNF experience

a. Anti-TNF naïve

b. Anti-TNF-IR

c. Anti-TNF stopped due to other reason

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. DATA MONITORING COMMITTEE REVIEW

3.1. Data Monitoring Committee

The independent DMC monitored data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee were to meet periodically to review interim data. After the review, the DMC made recommendations regarding the continuation of the study. Any safety concerns were to be communicated to the Sponsor.

The content of the safety summaries, the DMC role and responsibilities and the general procedures (including communications) and their recommendations on the study conduct were 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 at or before the first study agent administration (Week 0) unless otherwise stated.

Demographic and baseline characteristics will be summarized based on the Full Analysis Set by the randomized treatment group. In addition, selected baseline summaries will be performed based on the Modified Full Analysis Set.

Subjects' demographic data including age, race, sex, height, weight and BMI at baseline will be summarized. Baseline disease characteristics 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 Week 24, and through the end of the study, 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.

See Section 4.5 Protocol Deviations for the summary related to incorrect study agent or dose received and administrations missed.

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. AxSpA disease criteria, medication criteria, laboratory criteria, and medical history criteria) will be summarized and listed by randomized treatment group.

Major protocol deviations will be identified in a blinded fashion prior to database lock. Subjects with major protocol deviations will be tabulated separately and presented by treatment group for the following categories including 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. 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.

5.1.1. 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 AxSpA.
- Increase SSZ, MTX, or hydroxychloroquine dose above baseline dose for AxSpA.

- Initiate treatment with oral, IV, or IM, corticosteroids for AxSpA.
- Increase the dose of oral corticosteroids above baseline dose for AxSpA.
- 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. 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.

5.1.3. Early Escape

For all subjects regardless of the treatment groups who met early escape criteria based on ePRO data from CRF Health, 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 20 responders at Week 24.

5.2.1. Definition

A 20% improvement in response according to the criteria of the ASAS (ASAS 20) 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.

Following are the definitions of each of the forgoing disease assessment criteria (components) that are used in the determination of ASAS 20 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.[1] An increase along the scale indicates a worsening condition. (Section 5.3.2 for details)

d) Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness) (See Section 5.3.3 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 20% improvement from baseline for that component since there is no room for improvement.

5.2.2. Analyses

1. The proportion of ASAS 20 responders at Week 24 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by the combined MRI/hsCRP status and the status of previous exposure to anti TNFα agents to summarize the difference between each ustekinumab group and the placebo group. A 95% confidence interval for the treatment difference will be calculated. Treatment Failure, Missing Data Imputation, and Early Escape rules will be applied.

2. The proportion of ASAS 20 responders at Week 24 based on the observed data will also be analyzed similarly (retrieved dropout analysis). No Treatment Failure, Missing Data Imputation, or Early Escape rules will be applied in this analysis.

3. Each component of the ASAS 20 endpoint will be summarized by treatment group with Treatment Failure and Early Escape rules applied. No missing data imputation rule will be applied.

5.2.3. Subgroup Analysis

ASAS 20 at Week 24, over demographic, baseline characteristics, and prior or baseline medication use, will be summarized using 95% CI for the treatment differences.

The subgroups are described in Section 2.4. If needed, some of the cut-off points may be changed to increase sample sizes within categories.

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 40 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 40 Response at Week 24

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.

The proportion of ASAS 40 responders at Week 24 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by the combined MRI/hsCRP status and the status of previous exposure to anti TNFα agents to summarize the difference between each ustekinumab group and the placebo group. A 95% confidence interval for the treatment difference will be calculated. Treatment Failure, Missing Data Imputation, and Early Escape rules will be applied.

ASAS 40 response status at Week 24 will also 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

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:[2]

A. Fatigue
B. Spinal pain
C. Joint pain
D. Enthesitis
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.

The proportion of subjects with at least 50% improvement from baseline in BASDAI at Week 24 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by the combined MRI/hsCRP status and the status of previous exposure to anti TNFα agents to summarize the difference between each ustekinumab group and the placebo group. A 95% confidence interval for the treatment difference will be calculated. Treatment Failure, Missing Data Imputation, and Early Escape rules will be applied.

The 50% improvement from baseline at Week 24 will also 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

The Bath Ankylosing Spondylitis Functional Index (BASFI) is calculated as the mean of 10 VAS from the following questions (Table 1), 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.

Table 1: 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.

The analysis for BASFI at Week 24 will be performed using a Mixed Model for Repeated Measures (MMRM) based on data with early escape rule applied only. The independent variables for this model are treatment group, MRI/hsCRP status and the status of previous exposure to anti-TNFα, 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. A 95% confidence interval for the difference in LSMeans and nominal p-value will be calculated.

An ANCOVA model will also be used to summarize 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 MRI/hsCRP status and the status of previous exposure to anti-TNFα as independent variables. A 95% confidence interval for the difference in LSMeans and nominal p-value will be calculated based on contrast. 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.

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

The ASAS has developed a disease activity score (DAS) for use in AS, the Ankylosing Spondylitis Disease Activity Score (ASDAS). 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. For non-ASDAS summaries of CRP, if the value is <LLOQ, then half of the value of LLOQ will be used for numerical calculations.

The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24 will be analyzed using CMH test stratified by the combined MRI/hsCRP status and the status of previous exposure to anti TNFα agents to summarize the difference between each ustekinumab group and the placebo group. A 95% confidence interval for the treatment difference will be calculated.

The proportion of subjects who achieve ASDAS (CRP) inactive disease (<1.3) at Week 24 based on the observed data will also be analyzed similarly (retrieved dropout analysis). No Treatment Failure, Missing Data Imputation, or Early Escape rules will be applied in this analysis.

5.3.5. Other Secondary Analyses

1. The numbers of subjects who achieved ASAS 40 response, ASAS 20 response, at least a 50% improvement from baseline in BASDAI, and ASDAS (CRP) inactive disease status will be summarized through Week 24. Both ASAS 40 and ASAS 20 response over time will also be presented in separate figures.

2. The change from baseline in BASFI and the change from baseline in hsCRP (mg/dL) will be summarized through Week 24.

6. SAFETY

Safety will be assessed by summarizing the occurrences and types of AEs, vital signs (pulse, blood pressure, weight and height) and the laboratory parameters at Week 16, Week 24, and through the end of the study.

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 treatment they were 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, and the end of study.

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

6.1.1. Summaries through Week 16

The safety tables will have the column headings below:

	Ustekinumab		
Placebo	45 mg	90 mg	Combined

6.1.2. Summaries through Week 24

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 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:

	Ustekinumab				
Placebo[a]	Placebo → 45 mg[b]	Placebo → 90 mg[b]	45 mg	90 mg	Combined

[a] Excludes adverse events that occurred following early escape to ustekinumab.
[b] Only includes adverse events that occurred following early escape to ustekinumab.

6.1.3. Summaries through the End of Study

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 the end of study 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		Ustekinumab Combined		
45 mg	90 mg	45 mg	90 mg	45 mg	90 mg	All Ustekinumab

[a] Only includes adverse events that occurred following early escape or crossover to ustekinumab. Adverse events are counted from the first dose of ustekinumab to the end of the study.

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, 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

Tests of hematologic function and clinical chemistry consisted of laboratory measurements of:

Hematology: hemoglobin, neutrophils, lymphocytes, platelets, and Leukocytes.

Chemistry: creatinine, bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, sodium, potassium, albumin, and glucose

NCI-CTCAE grades will be used in the summary of laboratory data (Grade 1 – 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, >5 to <8xULN, and ≥8xULN.

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

6.4. Vital Signs

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

REFERENCE

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2. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol.1994; 21(12):2286-2291.