Janssen Research & Development

Statistical Analysis Plan

A Phase-IV, Multicenter, Noncomparative, Open-Label Study Evaluating the Safety and Efficacy of Golimumab (a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously) in the Treatment of Indian Patients with Active Spondyloarthropathy of Ankylosing Spondylitis or Psoriatic Arthritis

Protocol CNTO148SPD4001; Phase 4

SIMPONI **(**Golimumab**)**

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

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AMENDMENT HISTORY

The SAP is being amended to update the adverse event section. AE listings and tables for subjects with at least one major protocol deviations related to COVID-19 has been removed due to no infection cases reported.

SAP Version	**Approval Date**
Original SAP Version 1.0	23 September 2021
Amendment 1 SAP Version 2.0	21 January 2022

ABBREVIATIONS

ACR20	American College of Rheumatology 20% Improvement Criteria
AE	adverse event
ASAS20	Assessment in SpondyloArthritis International Society 20% Improvement Criteria
BASDI	Bath AS Disease Activity Index
BASFI	Bath AS Functional Index
BMI	body mass index
CI	confidence interval
ECG	electrocardiogram
eCRF	electronic case report form
HAQ	Health Assessment Questionnaire
HBV	HBV Hepatitis B Virus
HCV	HCV Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen-B27
ICH	International Conference on Harmonization
ITT	Intention-to-Treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
PGA	Patient Global Assessment
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
VAS	Visual Analogue Scale (Score)

1. INTRODUCTION

This statistical analysis plan (SAP) contains statistical methods for all planned analyses and definitions of analysis population for the study.

1.1. Trial Objectives

1.1.1 Primary Objective

- To assess the safety of subcutaneous (SC) golimumab in patients with active AS or PsA over 24 weeks.

1.1.2 Secondary Objective

- To assess the efficacy of SC golimumab in patients with active AS or PsA as measured by reduction in signs and symptoms of arthritis in active AS or PsA at Week 14.

- To assess achievement of sustained arthritis response in patients with active AS or PsA at Week 24.

1.2. Trial Design

This is an open-label, multicenter, interventional, noncomparative, single-arm, Phase IV study to evaluate safety and efficacy of golimumab (a fully human anti-TNFα mAb, administered subcutaneously) in the treatment of Indian patients with active spondyloarthropathy of AS or PsA. A total of 100 patients will be enrolled in this study. Approximately, 50% patients would be enrolled for each indication-50 patients with active AS, and another 50 with active PsA.

The study consists of three phases- Screening phase (Day -7 to Day -1), Treatment phase (Week 0 to Week 24) and Follow-up phase (Week 25 to Week 32).

Patients will receive golimumab 50 mg SC injections at Week 0 and every 4 weeks thereafter through Week 24. End of treatment (EOT) is defined as the time the last subject completes the week 24 visit. End of study (EOS) visit (in-person or telephonic as per convenience of the patient) will be conducted 8 weeks after the EOT Visit or after the last dose of golimumab (whichever is earlier), to inquire about any AEs experienced by the patient.

A diagram of the study design is provided below in Figure 1.

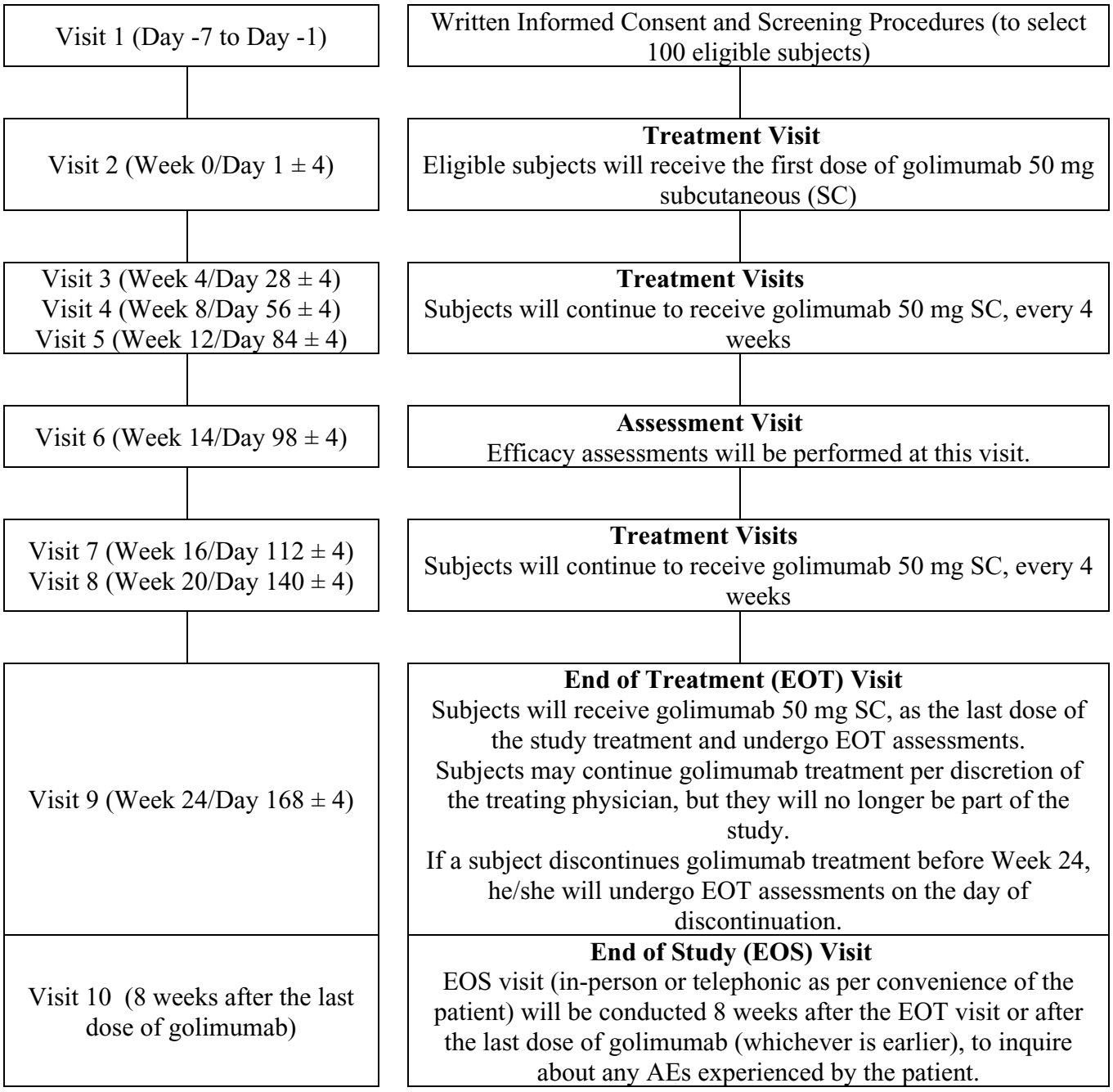

Figure 1: Schematic Overview of the Phase IV clinical study for a single subject

1.3. Statistical Hypotheses for Trial Objectives

No formal hypothesis testing will be tested.

1.4. Sample Size Justification

Approximately 100 patients with spondyloarthropathy (50 patients of AS and 50 patients of PsA) will be enrolled in this Phase IV non-comparative open-label study as per Indian Health Regulatory Authority (DCGI office, n=100) requirement. After enrollment of all 50 participants with one of the disease condition (AS or PsA) the recruitment of participants for that particular disease condition should be stopped, while recruitment for the other disease condition should continue until 50 participants are recruited.

Based on available literature, prevalence rate of AS is approximately 0.25% and prevalence rate of PsA is approximately 0.22% in India. So considering this, close to 50% subjects would be enrolled for each indication.

1.5. Randomization and Blinding

As this is an open and single-arm study, randomization and blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

To allow for variation in scheduling, the following set of visit windows (Table 1, Table 2) will be used to assign evaluations to a most appropriate visit for analysis. Furthermore, there will be no gaps between visit windows in order to include as many data points as possible for summarization.

Regardless of the width of the visit window, if more than 1 visit falls in the defined window, the result from the visit closest to the target day will be used. If 2 evaluations are equidistant from the target day, the result from the later visit will be used. Results not included for analysis will be included in the listings.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point.

Listed below (Table 1, table 2) are the visit windows and the target days for each visit defined in the protocol.

Table 1– Visit Windows for Vital signs and Urine Pregnancy Tests

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
1	Screening	-7 to -1	<= -1
2	Week 0	<= 1	1
3	Week 4	2 to 42	28
4	Week 8	43 to 70	56
5	Week 12	71 to 91	84
6	Week 14	92 to 105	98
7	Week 16	106 to 126	112
8	Week 20	127 to 154	140
9	Week 24	155 to 182	168
10	End of Study	183 to 228	224

Table 2- Visit Window for ASAS20 (BASDAI Evaluation (NRS), BASFI Evaluation (NRS), Total and Night Spinal Pain Assessment (NRS), Patient Global Assessment (NRS)), ACR20

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
1	Screening	-7 to -1	<= -1
2	Week 0	<= 1	1
3	Week 4	2 to 63	28
6	Week 14	64 to 133	98
9	Week 24	134 to 203	168

*Relative to Study Day 1

If subject discontinues the study at any point of time then the visit will be considered as “End of Study” visit.

2.2. Analysis Sets

The analysis sets used in this study are Safety and Intent to Treat (ITT) analysis sets. The efficacy endpoints will be assessed by using ITT analysis set and Efficacy Analysis Set, and safety endpoints by Safety Analysis set.

Safety Analysis Set: The Safety Analysis set includes all subjects who were enrolled and received at least one dose of the study drug.

Intent to Treat (ITT) Analysis Set: The ITT population will include all subjects who were enrolled and received at least one dose of the study drug and have completed Week 24 visit

Efficacy Analysis Set for AS subjects: Efficacy analysis set for AS subjects includes all AS subjects who were enrolled and received at least one dose of the study drug and having at least one non-missing post-baseline ASAS20 score for AS indication.

Efficacy Analysis Set for PsA subjects: Efficacy analysis set for PsA subjects includes all PsA subjects who were enrolled and received at least one dose of the study drug and having at least one non-missing post-baseline ACR20 score for PsA indication.

2.3. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study drug administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

2.4. Baseline

Baseline is defined as the last observation prior to the start of the first study drug administration.

2.5. General Analysis Rules

- Continuous data will be summarized by descriptive statistics, including number of subjects (N), mean, standard deviation (SD), median, and range (minimum; maximum).
- The minimum and maximum will be presented to the same number of decimal places as the original data. The mean and median will be rounded to one additional decimal place than the original data, while SD will be approximated to two additional decimal places.
- If a count is 0, the percentage (0%) should not be displayed. The 0 count will be displayed, but the corresponding percentage should be omitted.
- The percentages (%) in tables will be presented to 1 decimal place If the percentage is 100% then we display it as 100% and not 100.0%.
- For continuous parameters, descriptive statistics will be presented when n ≥2
- All safety analysis will be provided for each indication (AS and PsA indications) and overall population separately.

2.6. Handling Missing Data

For subjects who discontinue treatment but continue to be followed up and for whom some end-point component data are missing, the last observation carried forward will be followed to Week 14 or Week 24 as applicable.

For a composite endpoint, if all its components are missing, no imputation will be done; if not all its components are missing, LOCF will be used to impute the missing components.

3. SUBJECT INFORMATION

The number of subjects in Safety analysis set will be summarized by disease indication group and overall population, separately.

The number of subjects in Safety analysis set will be listed by disease indication group.

3.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables that will be summarized separately for each indication and overall population, for the Safety analysis set.

Descriptive statistics (mean, SD, median, minimum and maximum) will be presented for continuous data. Frequency and percentage will be presented for all categorical data. Subject-wise data listing will be provided.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of subjects in each category.
Race (Indian, Non-Indian)	

Baseline Disease Characteristics:

The table 4 presents the list of disease characteristics that will be summarized for Ankylosing Spondylitis (AS).

Table 4: Disease Characteristics Variables (For AS)

Continuous Variables:	**Summary Type**
Patient Global Assessment (PGA) Score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Total and Night Spinal Pain Score	
Bath Ankylosing Spondylitis Functional Index (BASFI) Score	
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score	
HLA B-27 Result	Counts and Percentage will be presented.
Chest X-Ray Interpretation (categories like Normal, Abnormal, Not Evaluable, Latent TB, Active TB will be presented).	

Table 5 presents the list of disease characteristics that will be summarized for Psoriasis Arthritis (PsA).

Table 5: Disease Characteristics Variables (For PsA)

Continuous Variables:	**Summary Type**
Tender joint count	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Swollen joint count	
Patient's Assessment of pain	
Patient's Global Assessment of Disease Activity	
Physician’s Global Assessment of Disease Activity	
Health Assessment Questionnaire (HAQ)	
Erythrocyte Sedimentation Rate (ESR)	
C-reactive Protein (CRP)	

Listings will be provided for disease characteristic.

3.2. Disposition Information

Disposition will be summarized for each indication and overall population, separately.

If the patient has completed the EOS assessments (in person or telephonically) then the disposition event of that patient will be considered as "Completed".

The summary for the treatment disposition will be as follows:

- Number of subjects enrolled
- Number of subjects discontinued the study drug

The Summary for the study disposition will be as follows:

- Number of subjects enrolled
- Number of subjects receiving study drug
- Number of subjects completed the study
- Number of subjects terminated study participation prematurely

The following primary reason for discontinuation will be summarized throughout the study under the following categories:

- Adverse Event
- Death
- Disease Relapse
- Lack of Efficacy
- Lost to Follow-Up
- Non-Compliance with Study Drug
- Received a Disallowed Concomitant Treatment
- Physician Decision
- Protocol Violation
- Study Terminated by Sponsor
- Withdrawal by Subject
- Screen Failure (Failure to Meet Eligibility Criterion)
- Pregnancy
- Progressive Disease
- Other

A listing of subjects will be provided along with the dates, study days and reason for discontinuation/ termination for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely

The summary tables and listings will be provided separately for each indication and overall population separately.

3.3. Protocol Deviations

In general, major protocol deviations may impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study.

Listing will be provided for major protocol deviations. Covid19-related Major deviations will be listed separately.

3.4. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the latest World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study drug. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study drug, including those that started before and continue on after the first dose of study drug. If start date and end date of medication is missing then this medication will be considered as prior and concomitant medication. If start date is after the date of first dose of study drug and end date is missing then decision of ongoing flag will be depend on the "Concomitant Medication End Relative to Reference Period".

Concomitant medications and prior medications will be listed separately.

4. EFFICACY

4.1. Efficacy Endpoint(s)

- Proportion of AS patients achieving ASAS20 criteria at Week 14.
- Proportion of PsA patients meeting the ACR20 criteria at Week 14.
- Proportion of AS patients achieving ASAS20 criteria at Week 24.
- Proportion of PsA patients meeting the ACR20 criteria at Week 24.

4.1.1. Definition of Endpoints

The ASAS Response Criteria (**ASAS 20**) is defined as:

- An improvement from baseline of >20% and >1 unit in at least 3 of the 4 ASAS domains on a scale of 0 to 10 units, and
- No worsening from baseline of >20% and >1 unit in the remaining ASAS domain on a scale of 0 to 10 units

The four ASAS domains are the following:

a) ***Patient Global Assessment of Disease (0 to 10 unit NRS):*** Patient's assessment of how active their spondylitis was on average during the last week and last six months. The patient will be asked to mark the box with an X on a 0 to 10 unit NRS (Numerical Rating Scale) on which the left-hand box (0) represents '*not active'* and the right-hand box (10) represents '*very active*'.

b) ***Total and Night Spinal Pain (NRS):*** Pain assessment represented by the average of total and nocturnal pain scores, both are assessed by two questions rated on a 0 to 10 NRS, where 0='*no pain*' and 10='*most severe pain*'. Total spine pain is assessed by '*How much pain in your spine due to spondyloarthritis do you have?*', and nocturnal spine pain by '*How much pain in your spine due to spondyloarthritis do you have at night?'*

c) ***Bath AS Functional Index (BASFI):*** A composite score based on a patient self-administered survey of 10 questions using a 0 to 10 unit NRS that assesses a patient's degree of mobility and functional ability. The questionnaire consists of eight questions regarding function in AS and the two last questions reflecting the patient's ability to cope with everyday life. The patient will be asked to mark the box with an X on a 0 to 10 unit NRS for each of the 10 questions, on which the left-hand box (0) represents '*easy*' and the right-hand box (10) represents '*impossible*'. The resulting 0 to 100 score is divided by 10 to give a final 0 to 10 BASFI score. A higher BASFI score correlates to reduced functional ability.

d) ***Bath AS Disease Activity Index (BASDAI):*** A composite score based on a patient self-administered survey of six questions using a 0 to 10 unit NRS that assesses the patient's five major symptoms of AS: 1) *fatigue*; 2) *spinal pain*; 3) *peripheral joint pain/swelling*; 4) *areas of localized tenderness*; 5) *morning stiffness severity upon wakening*; 6) *morning stiffness duration upon wakening*. The patient will be asked to mark the box with an X on a 0 to 10 unit NRS for each of the 6 questions. To give each of the five symptoms equal

weighting, the mean of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. A BASDAI score of 4 or greater is considered to be indicative of active AS disease.

The ACR response criteria (**ACR20)** is defined as

- **≥ 20% improvement in swollen joint count** – ACR swollen joint count, an assessment of 28 or more joints, which includes the shoulders, elbows, wrists, metacarpophalangeal (MCP) 1-5, proximal interphalangeal (PIP) 1-5 and the knees, bilaterally. Joints are classified as either *swollen* or *not swollen*.
- **≥20% improvement in tender joint count** –ACR tender joint count, an assessment of 28 or more joints, which includes the shoulders, elbows, wrists, MCPs 1-5, PIPs 1-5 and the knees, bilaterally. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single *tender*-versus-*nontender* dichotomy.
- **≥ 20% improvement in 3 of the following 5 assessments**:
    a) ***Patient's assessment of pain*** - A horizontal visual analogue scale (VAS) (usually 10 cm) assessment of the patient's current level of pain. The patient will be asked for severity of pain and he/she should be marked on the scale as per severity. The left side of VAS is of '*No Pain*' and right side is of '*Most Severe Pain*'.
    b) ***Patient's global assessment of disease activity*** – A simple patient-reported VAS which assesses the patient's general health and the effect of their arthritis at that point in time. The VAS is scored by measuring from 0 to where the patient marks on the line.
    c) ***Physician's global assessment of disease activity*** **-** A physician's global assessments of disease activity will be recorded on a VAS Scale.
    d) ***Patient's assessment of physical function as measured by the Health Assessment Questionnaire*** **-** The functional status of the patient will be assessed by means of the Disability Index of the HAQ. This 20- question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (*dressing, arising, eating, walking, hygiene, reaching, gripping*, and *activities of daily living*). Responses in each functional area are scored from 0, indicating '*no difficulty*', to 3, indicating '*inability to perform a task in that area*'.
    e) ***Acute-phase reactant-*** (A Westergren Erythrocyte Sedimentation Rate and a C-reactive Protein level).

4.1.2. Analysis Methods

Intent-to-treat population will be used for efficacy endpoints. Analysis for efficacy endpoints will be repeated on the efficacy analysis set.

The ASAS20 and ACR20 response evaluations will be performed on week 0, week 4, week 14 and week 24. The scores obtained from the respective domains will decide the responder for

ASAS20 or ACR20 criteria. Proportion of patients who achieve ASAS20 or ACR20 criteria at week 24 will be calculated, along with a 95% confidence interval.

For ASAS20, if data for percent improvement from baseline is missing at a particular assessment visit, then the response for the subject at that visit will be considered as missing.

If a subject's baseline value is zero (i.e. for ACR no disease activity for one assessment,) or missing, the subject should be considered as non-responder.

If all its components for a composite endpoint (i.e. score for subdomain as captured in CRF) are missing, the response for the endpoint at the particular visit will be set as missing; if not all its components are missing, LOCF will be used to impute the missing components and the value of the composite endpoint will be derived based on the imputed components.
If subject discontinues due to lack of efficacy, subject should be considered as non-responder.
If there is an Increase in the dose of MTX subject should be considered as non-responder.

The analysis will be done separately for each indication.

The scores for individual domains for both the ASAS20 and ACR20 will be descriptively summarized at all analysis visits.

The individual domain scores will be listed for each criteria.

5. SAFETY

The summary tables and listings will be provided separately for each indication and overall population, separately.

5.1. Clinical Laboratory Tests

Change from baseline summaries will be presented for chemistry and hematology laboratory tests at scheduled time points.
Number and percentage of subjects with markedly abnormal laboratory values for hematology and chemistry will be presented over time. Listings of markedly abnormal laboratory findings will be provided.
Shift tables will be provided summarizing the shift in laboratory values from baseline to week 14 and week 24 with respect to abnormality criteria (low, normal, high).

5.2. Adverse Events

All Adverse Events will be coded by system organ class and preferred term using the latest Medical Dictionary for Regulatory Activities version (MedDRA 24.0).

Any AE occurring at or after the initial administration of study drug through the day of last dose plus 8 weeks is considered to be treatment emergent. If the event occurs on the day of the initial administration of study drug, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study drug based on partial onset date or resolution date.

All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- TEAEs leading to discontinuation of study agent
- TEAEs by severity
- TEAEs by relationship to study drug
- TEAEs of special Interest by SOC and PT
- TEAEs by SOC and PT

In addition to the summary tables, listings will be provided for subjects who had:

- Any AE
- SAEs
- AEs leading to discontinuation of study drug
- Deaths due to AE.

5.3. Medical History

The listing will be provided for medical history.

5.4. Physical Examination

Abnormal physical examination findings will be listed.

5.5. Vital Signs

Vital signs parameters include temperature, respiratory rate, pulse and blood pressure (systolic and diastolic. These parameters will be descriptively summarized. A listing of all vital sign measurements will be presented. Abnormal vital signs records will be listed.

5.6. Electrocardiogram

ECG assessment will be performed at the screening visit using 12 Lead ECG method.

Overall interpretation of ECG data will be listed for all subjects. A separate listing will be provided for clinically significant results.

5.7. Other Safety Parameters

Listings will be provided for the following assessments, as collected:

- Smoking and Substance Use

- Pregnancy Test (Serum/Urine)
- TB Suspicion & Evaluation
- HLA B-27 Status
- Serology tests (HIV, HBV, HCV)
- Chest x-ray

Incidence (N, %) of study drug injection site reactions will be provided for subjects with injection site reaction.

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