Johnson & Johnson Private Limited

Clinical Protocol

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

AMENDMENT 1
SIMPONI (Golimumab)

This compound is approved for marketing in India for the following indications in adults:

- Moderately to severely active rheumatoid arthritis in combination with methotrexate
- Active psoriatic arthritis alone
- Active ankylosing spondylitis

Status: Approved
Date: 2 July 2018
Prepared by: Johnson & Johnson Private Limited
EDMS number: EDMS-ERI-155893782; 3.0

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

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PROTOCOL AMMENDMENTS

Protocol Version	Issue Date
Original Protocol	17-Jan-2018
Amendment 1	02-Jul-2018

Amendment_1 (02-Jul-2018)

The overall reason for the amendment: the overall reason for this amendment was to provide clarification to the existing inclusion criteria with definition of Inadequate response, dose, duration of partial responder and time period of assessment for patients with Ankylosing Spondylitis and Psoriatic Arthritis as suggested by DCGI.

Applicable Section(s)	Description of Change(s)
Rationale: As requested by the DCGI, definition of inadequate response, dose, duration of partial responder and time period of assessment for patients with Ankylosing Spondylitis was provided as a clarification to the existing inclusion criteria for Ankylosing Spondylitis.	
Synopsis; 4.1 Inclusion Criteria	Patients with Ankylosing Spondylitis, having an Inadequate response (defined as BASDAI ≥4) to current or past therapies (including biologics naïve patients). Patients who were receiving NSAIDs or DMARDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID or DMARD therapy because of intolerance, toxicity, or contraindications. Maximum recommended dosages for DMARDs if used, would be: methotrexate 25 mg/week, oral corticosteroids (≤10 mg/day of prednisone or equivalent) or sulfasalazine 3 g/day.
Rationale: As requested by the DCGI, definition of inadequate response, dose, duration of partial responder and time period of assessment for patients with Psoriatic Arthritis was provided as a clarification to the existing inclusion criteria for Psoriatic Arthritis.	
Synopsis; 4.1 Inclusion Criteria	Patients with Psoriatic Arthritis, having an inadequate response (defined by presence of active arthritis [presence of any swollen or any tender joint]) despite current or previous therapies (including biologics naïve patients). Patients who were receiving NSAIDs or DMARDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID or DMARD therapy because of intolerance, toxicity, or contraindications. Maximum recommended dosages for DMARDs, if used would be: methotrexate 25 mg/week, oral corticosteroids (≤10 mg/day of prednisone or equivalent), sulfasalazine 3 g/day or leflunomide 20 mg/day.

STUDY SYNOPSIS

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

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

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human tumour necrosis factor α (TNFα, a cytokine protein). This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. Golimumab antibody does not bind to other TNF superfamily ligands, including human lymphotoxin. Golimumab does not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells. Elevated TNFα levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Post-marketing Phase IV clinical trial is useful in identifying new safety issues and trends, which were not observed in previously conducted controlled clinical studies. The data obtained from the present study will help to understand the safety and efficacy profile of golimumab in a real-world Indian scenario compared with that obtained in a controlled clinical environment.

The objective of the present study is to address the mandatory regulatory requirement of Indian Health Regulatory Authority (Drugs Controller General of India [DCGI]) regarding conduct of study in Indian population to monitor the adverse events (AEs) with SIMPONI® (golimumab 50 mg) in patients of AS or PsA with active disease. The study will assess the safety of SIMPONI® prescribed as per locally approved prescribing information in Indian patients with active AS or PsA.

OBJECTIVES

Primary Objective

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

Secondary Objectives

- 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.

HYPOTHESIS

No formal hypothesis testing will be conducted.

OVERVIEW OF STUDY DESIGN

This is an open-label, multicentre, interventional, noncomparative, single-arm, Phase IV study to assess the safety and efficacy of golimumab in Indian patients with active spondyloarthropathy of AS or PsA. Approximately, 100 patients (50 patients of AS and 50 patients of PsA) selected by investigators and determined to be eligible for golimumab treatment per protocol eligibility criteria will be enrolled in the study, after obtaining written informed consent. Patients will be monitored for AEs during 24 weeks of treatment with golimumab and till end of study (EOS) visit (8 weeks after the last dose of golimumab). Participating investigator will be trained on the locally approved prescribing information of golimumab by the sponsor designee before the enrolment of first patient. Commercial stocks of SIMPONI® will be used

for the patients enrolled in the study with appropriate labelling and will be provided free of cost to the patient enrolled for 24 weeks treatment. Patients will procure SIMPONI® from the existing distribution channel (regular supply chain) as obtained by routine patients but the drug will be free of cost for clinical trial patients as per the mentioned duration in the study protocol. Study drug will be administered at the investigator study site by the investigator or an appropriately licensed and authorized health professional (under the supervision of the investigator).

Screening Visit (Visit 1 / Day [-7 to -1]):

After obtaining the signed informed consent, data will be collected at this visit including demographics, medical history, disease-related history, concomitant medications, and laboratory investigations.

Treatment Visits:

Patients who qualify will be enrolled in the study and will receive the study drug on confirmation of their enrolment status. Patients will receive golimumab 50 mg SC injections at Week 0 and every 4 weeks thereafter through Week 24 (ie Week 0, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24).

Assessment Visit:

This visit will be an additional visit conducted at Week 14. In this visit, all the assessments will be performed for evaluating efficacy endpoints at Week 14.

End of treatment (EOT) Visit:

The EOT visit will be conducted after the completion of 24 weeks SIMPONI® treatment (at Week 24) or on the day at which the patient discontinues the SIMPONI® treatment or study.

End of Study (EOS) Visit:

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

All the study-related activities or procedures of each and every visit of this Phase IV clinical trial are summarized in the TIME AND EVENTS SCHEDULE**Error! Reference source not found.**, presented after the synopsis.

SUBJECT POPULATION

Patients eligible for the study will be men or women (excluding pregnant or nursing women; men and women planning a pregnancy) aged 18 years or older who have had a definite diagnosis of AS or PsA prior to first study drug administration.

Key criteria for AS patients:

Adult patients who have definite diagnosis of AS (according to the Modified New York Criteria) and either have an inadequate response (defined as BASDAI ≥4) to current or past therapies (including biologics naïve patients). Patients who were receiving NSAIDs or DMARDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID or DMARD therapy because of intolerance, toxicity, or contraindications. Maximum

recommended dosages for DMARDs if used, would be: methotrexate 25 mg/week, oral corticosteroids (≤10 mg/day of prednisone or equivalent) or sulfasalazine 3 g/day.

Key criteria for PsA patients:

Patients who have definite diagnosis of active PsA (according to the ClASsification criteria for Psoriatic ARthritis [CASPAR]) prior to the first administration of study drug and have at least 1 of the PsA subsets: distal interphalangeal joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis; patients who are negative for rheumatoid factors according to the reference range of the local laboratory conducting the test and have inadequate response (defined by presence of active arthritis [presence of any swollen or any tender joint]) despite current or previous therapies (including biologics naïve patients). Patients who were receiving NSAIDs or DMARDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID or DMARD therapy because of intolerance, toxicity, or contraindications. Maximum recommended dosages for DMARDs, if used would be: methotrexate 25 mg/week, oral corticosteroids (≤10 mg/day of prednisone or equivalent), sulfasalazine 3 g/day or leflunomide 20 mg/day.

Further screening as per inclusion and exclusion criteria will apply.

DOSAGE AND ADMINISTRATION

Golimumab will be prescribed to the patients as per locally approved prescribing information. The recommended dose of SIMPONI® is 50 mg administered by SC injection once a month for both AS and PsA.

ENDPOINTS:

Safety Endpoint

- Occurrence of an AE/ serious adverse event (SAE) (clinical or laboratory safety event).

Efficacy Endpoints

- Proportion of AS patients achieving at least 20% improvement in the Assessment of Spondyloarthritis International Society criteria (ASAS20) at Week 14.
- Proportion of PsA patients meeting the American College of Rheumatology 20% improvement criteria (ACR20) at Week 14.
- Proportion of AS patients achieving ASAS20 criteria at Week 24.
- Proportion of PsA patients meeting the ACR20 criteria at Week 24.

SAFETY EVALUATIONS

Routine safety evaluations will be performed for AEs and SAEs and will be summarized. Safety will be assessed by evaluating the incidence and type of AEs, including SAEs, causality, or clinically significant AEs (as per principal investigator's discretion), and discontinuations due to AEs and routine clinical laboratory values. Frequency of serious infections, including tuberculosis, demyelinating disorders, new onset of autoimmune diseases, and malignancies will be summarized. The incidence of study drug injection-site reactions will be noted. The laboratory (haematology and chemistry) parameters and change from baseline in laboratory parameters will be assessed. The incidence of markedly abnormal laboratory (haematology and chemistry) parameters will also be evaluated.

STATISTICAL METHODS

Sample Size Determination:

Approximately 100 patients with spondyloarthropathy (50 patients of AS and 50 patients of PsA) will be enrolled in this Phase IV post-marketing noncomparative open-label study as per Indian Health Regulatory Authority (DCGI office, n=100) requirements. Enrollment of participants with the diagnosis of AS and PsA will start simultaneously. 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% patients would be enrolled for each indication.

Statistical analysis:

The safety endpoint of the trial is to demonstrate the safety profile of golimumab in routine clinical practice as assessed by the frequency and proportion of AEs (serious and non-serious AEs) observed during 24 weeks. Efficacy endpoint analyses will include ASAS20 response (for AS patients) or ACR20 response (for PsA patients) at Week 14 and Week 24.

Statistical analysis will be performed separately for each indication.

All statistical analysis will performed using SAS® software version 9.4 or later. Descriptive statistics will be computed and reported for safety and efficacy variables. A statistical analysis plan will be issued as a separate document providing detailed methods for analysis. For this study, the intent-to-treat population will be analysed. The intention-to-treat population will include all enrolled patients who have received at least 1 study drug administration.

No interim analysis is planned for this study.

Screening	**Treatment**				**Assessment**	**Treatment**			**End of Study**
Day (-7) *(±4 days)*	Week 0 Day 1 *(±4 days)*	End of Week 4 Day 28 *(±4 days)*	End of Week 8 Day 56 *(±4 days)*	End of Week 12 Day 84 *(±4 days)*	End of Week 14 Day 98 *(±4 days)*	End of Week 16 Day 112 *(±4 days)*	End of Week 20 Day 140 *(±4 days)*	End of Week 24 Day 168 *(±4 days)*	End of Week 32 Day 224 *(±4 days)*
	Approximately start of Month 1	Approximately start of Month 2	Approximately start of Month 3	Approximately start of Month 4		Approximately start of Month 5	Approximately start of Month 6	Approximately end of Month 6	Approximately end of Month 8
Screening Visit 1	Dose 1 Visit 2	Dose 2 Visit 3	Dose 3 Visit 4 (Dose only)	Dose 4 Visit 5 (Dose only)	(No Dose) Visit 6	Dose 5 Visit 7 (Dose only)	Dose 6 Visit 8 (Dose only)	Dose 7 Visit 9	(No Dose) Visit 9
Assessment 1 (Screening)	**Assessment 2 Enrolment (Baseline)**	**Assessment 3**			**Assessment 4 (Efficacy Endpoints)**			**Assessment 5 (End-of-Treatment)**	

Note: End of study visit (in-person or telephonic as per convenience of the patient) will be conducted 8 weeks after the end of treatment visit or after the last dose of golimumab (whichever is earlier), to inquire about any adverse events experienced by the patient.

Table 1: TIME AND EVENTS SCHEDULE

	Schedule of events									
	Screening	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 32[k]**
Visit Day	Visit 1 Day (-7 to -1) (±4 days)	Visit 2 Day 1 (±4 days)	Visit 3 Day 28 (±4 days)	Visit 4 Day 56 (±4 days)	Visit 5 Day 84 (±4 days)	Visit 6 Day 98 (±4 days)	Visit 7 Day 112 (±4 days)	Visit 8 Day 140 (±4 days)	Visit 9 Day 168 (±4 days)	Visit 10 Day 224 (±4 days)
		Approximately start of Month 1	Approximately start of Month 2	Approximately start of Month 3	Approximately start of Month 4		Approximately start of Month 5	Approximately start of Month 6	Approximately end of Month 6	Approximately end of Month 8
Assessment/Study Procedure[a]										
Informed Consent	X									
Demographics	X									
Medical History	X									
Physical Examination	X									
Vital Signs	X	X	X	X	X	X	X	X	X	
Height and Weight	X									
Chest X-ray[b]	X									
Serum Pregnancy Test	X									
Urine Pregnancy Test		X	X	X	X	X	X	X	X	
HLA B-27 Status[c]	X									
HIV, HBV and HCV test[d]	X									
ECG	X									
TB Suspicion & Evaluation[e]	X	X	X	X	X	X	X	X	X	
QuantiFeron - TB Gold Test	X									
Tuberculin Skin Test	X									
Review of Eligibility Criteria	X	X								
Study Drug Injection		X	X	X	X		X	X	X	

Study Drug Injection-site Evaluation[f]		X	X	X	X		X	X	X	
ASAS20 Response Evaluation[g]		X	X			X			X	
BASDAI Evaluation (NRS)	X	X	X			X			X	
BASFI Evaluation (NRS)		X	X			X			X	
Total and Night Spinal Pain Assessment (NRS)	X	X	X			X			X	
Patient Global Assessment (NRS)		X	X			X			X	
ACR20 Response Evaluation[h]		X	X			X			X	
HAQ		X	X			X			X	
CRP (quantitative mg/L)	X	X	X			X			X	
ESR	X	X	X			X			X	
Routine Laboratory Analyses[i]	X								X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
AE/SAE Review[j]	X	X	X	X	X	X	X	X	X	X

a. All assessments are to be completed prior to study drug injection, except at Week 14 (no study drug injection), unless otherwise specified.
b. May be taken within 3 months prior to Week 0.
c. This test should be performed if previous results are not available (for AS subjects).
d. ELISA test for HIV, HBsAg test for HBV, and Anti-HCV test for HCV will be performed.
e. If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold test, and tuberculin skin test should be performed.
f. Subjects should be monitored for the occurrence of AEs for 30 minutes after study drug administration.
g. For AS subjects, evaluations include BASDAI, BASFI, patient's global assessment, total back pain, and night back pain assessments.
h. For PsA subjects, evaluations include tender and swollen joint count assessment, Patient's assessment of pain, Patient's global assessment of disease activity, Physician's global assessment of disease activity, HAQ and Acute-phase reactant (ESR and CRP).
i. Routine Labs: Samples for routine laboratory analyses (haemoglobin, haematocrit, platelet count, total and differential white blood cell count, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, blood glucose, albumin and total protein) will be collected.
j. If there is any ongoing AE at last visit, it will be followed up till resolution or considered stable as per investigator

k. 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.

Abbreviations: ACR20=American College of Rheumatology 20% improvement criteria; AE=Adverse event; ASAS20=Assessment in SpondyloArthritis International Society 20% improvement criteria; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=The Bath Ankylosing Spondylitis Functional Index; CRP=C-reactive protein; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; HAQ=Health Assessment Questionnaire; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen-B27; NRS=numerical rating scale; SAE=Serious Adverse Event; TB=Tuberculosis

ABBREVIATIONS

ACR20	American College of Rheumatology 20% Improvement Criteria
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AS	Ankylosing Spondylitis
ASAS20	Assessment in SpondyloArthritis International Society 20% Improvement Criteria
AST	Aspartate Aminotransferase
BASDAI	Bath AS Disease Activity Index
BASFI	Bath AS Functional Index
BCG	Bacille Calmette-Guérin
BUN	Blood Urea Nitrogen
CASPAR	The ClASsification criteria for Psoriatic ARthritis
CHF	Congestive Heart Failure
CRP	C-reactive Protein
DCGI	Drugs Controller General of India
DIP	Distal Interphalangeal
DMARD	Disease Modifying Antirheumatic Drugs
ECG	Electrocardiogram
eCRF	Electronic Case Report Form(s)
eDC	Electronic Data Capture
EOS	End of study
EOT	End of treatment
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen-B27
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-Treat
IV	Intravenous
LAR	Legally Acceptable Representative
mAb	Monoclonal Antibodies
MCP	Metacarpophalangeal
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRS	Numerical Rating Scale
PGA	Patient Global Assessment
PIP	Proximal Interphalangeal
PQC	Product Quality Complaint
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis

SAE(s)	Serious Adverse Event(s)
SC	Subcutaneous
SD	Standard Deviation
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TNF	Tumour Necrosis Factor
VAS	Visual Analogue Scale (Score)
WBC	White Blood Cell

1. INTRODUCTION

Golimumab is a human monoclonal antibody (mAb) that binds to both the soluble and transmembrane bioactive forms of human tumour necrosis factor α (TNFα, a cytokine protein). This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. Golimumab antibody does not bind to other TNF superfamily ligands, including human lymphotoxin. Golimumab does not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells. Elevated TNFα levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). TNFα is an important mediator of the articular inflammation that is characteristic of these diseases. Treatment with golimumab has been shown to decrease the levels of C-reactive protein (CRP), interleukin 6, matrix metalloproteinase 3, intercellular adhesion molecule 1 and vascular endothelial growth factor in patients with RA, PsA, and AS.[1]

Golimumab is indicated for the treatment of adult patients with active PsA. It is also indicated for the treatment of adult patients with active AS.[1]

For the most comprehensive nonclinical and clinical information regarding golimumab, refer to the latest version of the prescribing information of SIMPONI®.[1]

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

1.1. Background

1.1.1. Ankylosing spondylitis

Ankylosing spondylitis is a chronic inflammatory disease of unknown etiology that involves the sacroiliac joints, axial skeleton, entheses, and peripheral joints. Chronic inflammation of entheses leads to new bone formation, syndesmophytes, and ankylosis of joints, primarily in the axial skeleton, that may lead to dramatic loss of range of motion and to disability. The disease may also have nonskeletal manifestations, including uveitis, carditis, pulmonary fibrosis, bowel inflammation, and cardiac conduction abnormalities. Considered a subset of the spondyloarthropathies, AS is strongly associated with the presence of the human leukocyte antigen-B27 (HLA-B27).[2]

The mean AS prevalence per 10,000 (from 36 eligible studies) was 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa. The prevalence of AS is generally believed to be between 0.1% and 1.4% globally.[3] AS is traditionally considered as a predominantly male disease, with a commonly reported male:female ratio around 3:1. Moreover, a slower progression rate for spinal ankylosis was found in female patients, although they reported significantly more pain and need for drug therapy.[4]

Although patients may experience a variety of musculoskeletal symptoms (proximal arthralgias, chest pain, and tenderness around peripheral joints from enthesitis), the most common presenting symptom is chronic low-back pain. The low-back pain usually begins before the age of 40 years, is

insidious in onset, associated with morning stiffness, and eventually, is symmetrical. These musculoskeletal symptoms may be associated with constitutional symptoms, such as fatigue, fever, and weight loss.[5]

Until recently, treatment has been limited to nonsteroidal anti-inflammatory drugs and physiotherapy, but the development of cytokine inhibitors that inhibit the activity of TNFα has been an important advance in treatment.[6] The current management approach to AS requires a combination of nonpharmacologic and pharmacologic treatment modalities. Appropriate and timely use of TNFα antagonists is an additional option for patients with active AS who are inadequately controlled with conventional treatment. TNF-α inhibitor therapies have demonstrated rapid and consistent effectiveness in reducing the axial and peripheral symptoms of AS, and improving patient function and quality of life.

1.1.2. Psoriatic Arthritis

Psoriatic arthritis is a chronic, inflammatory, usually rheumatoid factor negative arthritis that is associated with psoriasis. Psoriasis affects 2% to 3% of the population. Psoriatic arthritis develops in approximately 30% of psoriatics. The reported prevalence of PsA varies from 7% to 42%.[7] The prevalence of psoriasis in the general Caucasian population is approximately 2%. Psoriatic arthritis affects men and women equally and peaks between the ages of 30 and 55 years.[8]

Psoriatic arthritis involves peripheral joints, axial skeleton, sacroiliac joints, nails, and entheses, and is associated with psoriatic skin lesions.[8,9] The presentation of PsA can be categorized into 5 overlapping clinical patterns, which include oligoarthritis in approximately 22% to 37% of patients; polyarthritis in 36% to 41% of patients; arthritis of distal interphalangeal (DIP) joints in up to 20% of patients; spondylitis affecting approximately 7% to 23% of patients; and arthritis mutilans in approximately 4% of patients.[9,10] Over one-third of patients with PsA also develop dactylitis and enthesitis.[9,11] More than one-half of the patients with PsA may have evidence of erosions on x-rays, and up to 40% of the patients develop severe, erosive arthropathy.[9,10] Psoriatic arthritis leads to functional impairment, reduced quality of life, and increased mortality.[10,11,12,13]

Most of the treatments currently used for PsA were adapted from experience in the RA patient population. Despite the progressive and potentially disabling nature of PsA, and in contrast with RA, only a few, randomized, controlled trials have examined the role of traditional disease modifying antirheumatic drugs (DMARDs) in the treatment of PsA.[14,15,16,17] In these studies, methotrexate (MTX), cyclosporine, sulfasalazine (SSZ), and leflunomide demonstrated efficacy in the treatment of this condition, although the treatments were associated with a time lag of several weeks between treatment initiation and a clinically significant response in either arthritis or psoriasis (MTX, cyclosporine), or only had modest efficacy on the skin (SSZ, leflunomide). Corticosteroids are rarely used to treat PsA since they are known to cause severe psoriasis flares upon withdrawal.

Until recently the main classification criteria for psoriatic arthritis were those of Moll and Wright. These are not suitable to diagnose early PsA (sensitivity 80 to 85%). Now ClASsification criteria for Psoriatic ARthritis [CASPAR] with high sensitivity and specificity have been developed.[7]

New biologic treatments targeting TNF, including the recombinant soluble TNF receptor etanercept and the monoclonal anti-TNFα antibodies infliximab and adalimumab, were recently shown to induce rapid and significant improvement of arthritis and psoriasis in subjects with active PsA while maintaining an acceptable safety profile.[18,19,20]

Etanercept and adalimumab are administered either twice weekly, weekly, or every 2 weeks by subcutaneous (SC) injection, while infliximab is administered as an intravenous (IV) infusion in an office based setting at Week 0, 2, 6, and every 8 weeks thereafter. Golimumab, a fully human monoclonal anti-TNFα antibody, administered every 4 weeks by SC injection, may optimize convenience of use and provide efficacy comparable to infliximab.

1.1.3. Rationale for Golimumab in Ankylosing Spondylitis and Psoriatic Arthritis

The safety and efficacy profile of anti-TNFα therapy for a variety of rheumatological indications, including AS & PsA, has been well characterized. Although therapy with anti-TNFα agents has been used successfully in the treatment of AS, anti-TNFα agents have limitations with respect to safety, dosing regimen, cost, and immunogenicity. To address some of these limitations, the sponsor has developed a fully human anti-TNFα mAb, designated golimumab (also known as CNTO 148 and rTNV148B). Like REMICADE® (infliximab), a human/murine chimeric anti-TNFα mAb, golimumab binds with high affinity to human TNFα and inhibits TNFα bioactivity. The constant regions of both the heavy and light chains of golimumab have amino acid sequences identical to the corresponding constant regions of infliximab. Golimumab contains human variable regions (fully human mAb), whereas infliximab contains mouse variable regions (mouse/human chimeric mA). Preclinical in vitro studies have demonstrated that golimumab has high affinity for soluble TNFα and inhibits TNFα binding to the TNFα receptor with a 2- to 4-fold greater potency than infliximab. In addition, golimumab inhibits TNFα-mediated cell cytotoxicity and TNFα mediated endothelial cell activation. Golimumab also induces activation of complement-mediated cell lysis and reduces the development of arthritis in mice that over-express human TNFα.

SIMPONI® (golimumab) was approved in USA and Europe for treatment of active AS and PsA since 2009. Refer to the latest prescribing information of SIMPONI® for updated information regarding premarketing safety and efficacy of golimumab in AS and PsA.

1.2. Overall Rationale for the Study

Post-marketing Phase IV clinical trial is useful in identifying new safety issues and trends, which were not observed in previously conducted controlled clinical studies. The data obtained from the present study will help to understand the safety and efficacy profile of golimumab in a real-world Indian scenario compared with that obtained in a controlled clinical environment. The objective of the present study is to address the mandatory regulatory requirement of Indian Health Regulatory Authority (Drugs Controller General of India [DCGI]) regarding conduct of study in Indian population to monitor the adverse events (AEs) with SIMPONI® (golimumab 50 mg) in patients of AS or PsA with active disease. The study will assess the safety of SIMPONI® prescribed as per locally approved prescribing information in Indian patients with active AS or PsA.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives

Primary Objective

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

Secondary Objectives

- 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.

2.2. Endpoints

Safety Endpoint

- Occurrence of an AE/SAE (clinical or laboratory safety event).

Efficacy Endpoints

- Proportion of AS patients achieving at least 20% improvement in the Assessment of Spondyloarthritis International Society criteria (ASAS20) at Week 14.
- Proportion of PsA patients meeting the American College of Rheumatology 20% Improvement Criteria (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.

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.3. Hypothesis

No formal hypothesis testing will be conducted.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label, multicentre, 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. Enrollment of participants with the diagnosis of AS and PsA will start simultaneously. 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. Patients will receive golimumab 50 mg SC injections at Week 0 and every 4 weeks thereafter through Week 24. The end of treatment (EOT) visit 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

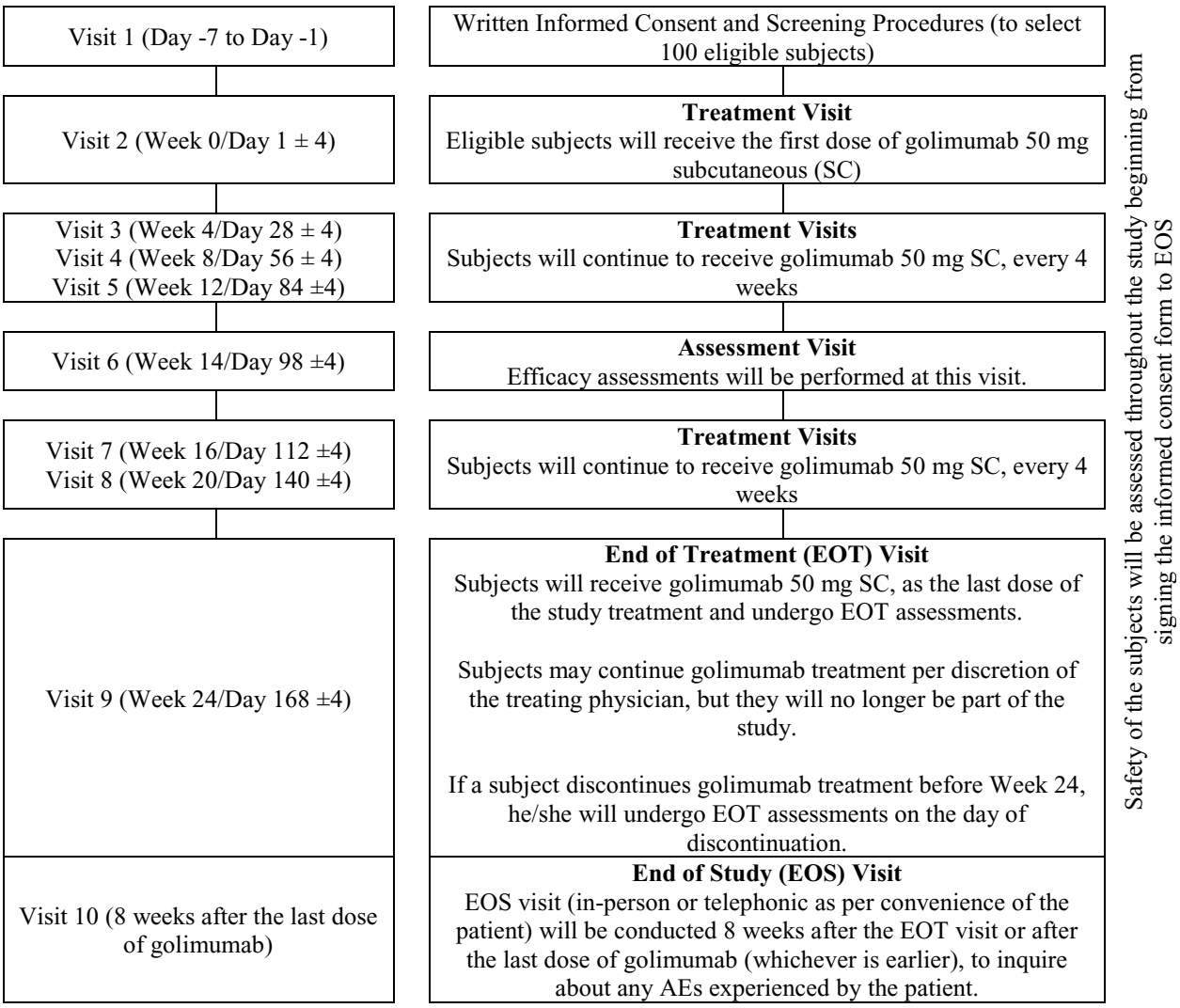

Figure 1: Schematic Overview of the Phase IV clinical study for a single subject

3.2. Study Design Rationale

This is an open-label, multicentre, interventional, noncomparative, single-arm, Phase IV study to assess the safety and efficacy of golimumab in Indian patients with active spondyloarthropathy of AS or PsA. Approximately, 100 patients (50 patients of AS and 50 patients with PsA) selected by investigators and determined to be eligible for golimumab treatment per protocol eligibility criteria will be enrolled in the study, after obtaining written informed consent. Patients will be monitored for AEs during 24 weeks of treatment with golimumab and till EOS visit. Participating investigator will be trained on the locally approved prescribing information of golimumab by the sponsor designee before the enrolment of first patient. Commercial stocks of SIMPONI® will be used for the patients enrolled in the study with appropriate labelling and will be provided free of cost to the subject enrolled for 24 weeks treatment. Patients will procure SIMPONI® from the existing distribution channel (regular supply chain) as obtained by routine patients but the drug will be free of cost for clinical trial patients as per the mentioned duration in the study protocol.

4. SUBJECT POPULATION

Screening for eligible patients will be performed within 7 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling patients in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a patient in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

All potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Are man or woman 18 years of age or older.
2. Women of childbearing potential or men capable of fathering children must be using adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization) during the study and must be willing to use such birth control measures for 6 months after receiving the last administration of study drug. Female subjects of childbearing potential must test negative for pregnancy.
3. Are considered eligible per the following tuberculosis (TB) screening criteria:
    a. Have no history of TB prior to screening.
    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    c. Have had no recent close contact with a person with active TB, or if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study drug.
    d. Within 6 weeks prior to the first administration of study drug, have a negative QuantiFERON-TB Gold and a negative tuberculin skin test result, or have a newly identified positive QuantiFERON-TB Gold or tuberculin skin test result during screening in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study drug.
    e. Have a chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to the first administration of study drug and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.
4. Have screening laboratory test results as follows:
    a. Haemoglobin more than or equal to 8.5 g/dL
    b. White blood cells (WBC) count more than or equal to 3.5×10^3 cells/micro-litre
    c. Platelets more than or equal to 100×10^3 cells/micro-litre

d. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level not exceeding 1.5 times the upper limits of normal for the laboratory conducting the test.

e. Serum creatinine not exceeding 1.5 mg/dL

5. Are willing and able to adhere to the study visit schedule and other protocol requirements.
6. Are capable of giving informed consent, which must be obtained prior to any study-related procedures.

For Patients with AS:

1. Have a diagnosis of definite AS (according to the Modified New York Criteria).[21]
2. Have symptoms of active disease at screening and at baseline, as determined by the treating physician.
3. Either has an inadequate response (defined as BASDAI ≥4) to current or past therapies (including biologics naïve patients). Patients who were receiving NSAIDs or DMARDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID or DMARD therapy because of intolerance, toxicity, or contraindications. Maximum recommended dosages for DMARDs if used, would be: methotrexate 25 mg/week, oral corticosteroids (≤10 mg/day of prednisone or equivalent) or sulfasalazine 3 g/day.

For Patients with PsA:

1. Have PsA that was diagnosed at least 6 months prior to the first administration of study drug (according to the CASPAR).[22]
2. Have active PsA at the time of screening and at baseline, as determined by the treating physician.
3. Have at least 1 of the PsA subsets: DIP joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.
4. Are negative for rheumatoid factors according to the reference range of the local laboratory conducting the test.
5. Have inadequate response (defined by presence of active arthritis [presence of any swollen or any tender joint]) despite current or previous therapies (including biologics naïve patients). Patients who were receiving NSAIDs or DMARDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID or DMARD therapy because of intolerance, toxicity, or contraindications. Maximum recommended dosages for DMARDs, if used would be: methotrexate 25 mg/week, oral corticosteroids (≤10 mg/day of prednisone or equivalent), sulfasalazine 3 g/day or leflunomide 20 mg/day.

4.2. Exclusion Criteria

1. Are pregnant, nursing, or planning a pregnancy or fathering a child during the study or within 6 months after receiving the last administration of study drug.

2. Have a known hypersensitivity to human immunoglobulin proteins or other components of golimumab.
3. Have been treated with any investigational drug within 5 half-lives of that drug prior to the first administration of study drug.
4. Have a history of latent or active granulomatous infection, including histoplasmosis, or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.
5. Have a chest radiograph within 3 months prior to the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.
6. Have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening.
7. Have received, or are expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug, during the study, or within 6 months after the last administration of study drug.
8. Have a history of an infected joint prosthesis, or have received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
9. Have had a serious infection (including but not limited to, hepatitis, pneumonia, sepsis, or pyelonephritis), or have been hospitalized for an infection, or have been treated with IV antibiotics for an infection within 2 months prior to first administration of study drug. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.
10. Have a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis, chronic non-remitting cystitis), an open, draining, or infected skin wound, or an ulcer.
11. Are currently infected (including carriers) with Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).
12. Have a history of known demyelinating diseases such as multiple sclerosis or optic neuritis.
13. Have current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease.
14. Have a history of, or concurrent congestive heart failure (CHF), including medically controlled, asymptomatic CHF.
15. Have a history of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location, or clinically significant splenomegaly.
16. Have any known malignancy or have a history of malignancy within the previous 5 years (except for a nonmelanoma skin cancer that has been treated with no evidence of recurrence).
17. Have a transplanted organ (except for a corneal transplant performed >3 months prior to first administration of study drug).

18. Have or have had a substance abuse (drug or alcohol) problem within the previous 3 years.
19. Are unwilling or unable to undergo multiple venipunctures.
20. Are participating in another study with an investigational drug or procedure.

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

4.3. Prohibitions and Restrictions

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

1. Prohibitions and restrictions regarding concomitant therapy during the study (refer to Section 8 Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study).
2. Agree to follow all requirements that must be met during the study as noted in Section 4.1 and 4.2 the Inclusion and Exclusion Criteria, respectively (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

This, being a single-arm study, eligible patients will be sequentially enrolled in the study and will receive golimumab 50 mg SC injections starting at Week 0 and every 4 weeks thereafter, up to Week 24. Randomization is not applicable to this study design.

Blinding

As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Golimumab will be prescribed to the patients as per locally approved prescribing information. The recommended dose of SIMPONI® is 50 mg administered by SC injection once a month for both AS and PsA with or without MTX or other nonbiologic DMARDs (as long as the patient eligibility criteria are adhered to when the subject is administered golimumab as part of this study).

Golimumab will be available as a sterile, liquid for SC injection at a volume of 0.5 mL in prefilled single-use syringes (as pen-device Simponi Smartject®). Each prefilled Smartject® will contain 50 mg golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5. No preservatives are present.

The needle cover may contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Study drug will be administered at the investigator study site by the investigator or an appropriately licensed and authorized health professional (under the supervision of the investigator). All administrations through the Week 24 database lock will be given as a single SC injection, containing 0.5 mL of study drug. Patients will procure study drug from the existing distribution channel (regular supply chain) as obtained by routine patients but the drug will be provided free of cost for patients enrolled in clinical trial till Week 24.

7. TREATMENT COMPLIANCE

The appropriate doses of golimumab (50 mg) will be administered as SC injections by designated study personnel at the study sites and the details of each administration will be recorded in the electronic case report forms (eCRF).

Injections will be administered at Week 0, 4, 8, 12, 16, 20 and 24 (last dose of golimumab). A window period of ±4 days will be allowed for each treatment visit.

Treatments that are administered outside of the scheduled windows, as well as missed injections or visits, will be recorded on the eCRFs. A site monitor designated by the sponsor will monitor all eCRFs and Drug Accountability Logs. During these monitoring visits, all procedures will be evaluated for compliance with the protocol.

8. PRESTUDY AND CONCOMITANT THERAPY

Patients should not initiate any new treatment for AS or PsA during the 24-week study period.

Prestudy therapies administered up to 30 days before first dose of study drug must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug until the last dose of study drug. Every effort should be made to keep subject's concomitant medications stable through Week 24 or as specified in the following sections.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug, dosing regimen, route of administration, and its indication.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, and safety measurements applicable to this study.

Written informed consent will be obtained from all patients by the principal investigator or his/her designee prior to the performance of any protocol-specific procedure. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the patient's participation in the study.

Once patient is considered eligible to be enrolled in the study, patient will receive golimumab treatment for a period of 24 weeks (6 months), which will be provided free of cost. During the study period, safety data will be collected at 4-week intervals until 24 weeks and efficacy data will be collected at Week 0, Week 4, Week 14 and Week 24. Study visits through and including Week 32 may occur at the week indicated with an allowed window period of ±4 days. If the recommended acceptable window cannot be observed, the sponsor must be contacted before scheduling a visit and a deviation in process must be noted in study documents.

9.1.2. Screening Visit: Visit 1 / Day (-7 to -1)

After informed consent has been obtained at screening, each patient will be assigned a unique number for the duration of the trial.

Indian patients who are eligible to receive SIMPONI® will be considered in the present study. Prior to data collection, all patients and/or their legally acceptable representative (LAR) where applicable will sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local regulations.

The below mentioned procedure and measurements will be performed at screening visit:

- Obtaining written informed consent
- Confirming eligibility criteria check
- Collection of demographic data
- Measurement of height and weight
- Physical examination
- Examination of vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Confirmation of diagnosis of AS or PsA and history of the disease
- Other medical history
- Electrocardiogram
- Serum Pregnancy test
- HIV (ELISA test), HBV (HBsAg test), and HCV (Anti-HCV test)
- Routine laboratory tests: haemoglobin, haematocrit, platelet count, total and differential WBC count, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, blood glucose, albumin and total protein
- Qualitative urinalysis (dipstick) of protein, glucose, ketones, blood, leucocyte esterase or nitrate. If dipstick urine analysis is positive for blood, WBC (eg, leucocyte esterase or nitrates), or protein, then complete urinalysis (dipstick and microscopy) will be performed.
- Chest x-ray
- QuantiFeron-TB Gold test and tuberculin skin test

- Documentation of HLA B-27 status
- Erythrocyte sedimentation rate (ESR)
- CRP
- Bath AS Disease Activity Index (BASDAI) evaluation,
- Spinal Pain (Numerical Rating Scale [NRS]) assessment
- Concomitant medications review
- AE/SAE review (the collection of AE information will start from the time of provision of written informed consent)

9.1.3. Treatment and Assessment Visits

Week 0 (Visit 2/Day 1)

Patients who qualify will be enrolled in the study and will receive the study drug on confirmation of their enrolment status. Before the first administrations of the study drug (Week 0, Day 1), assessments/procedures should be performed as indicated in TIME AND EVENTS SCHEDULE. Patients must meet all of the inclusion and none of the exclusion criteria that are assessable in the clinic at the time of the baseline visit before enrolment in the study.

The below mentioned procedure and measurements will be performed at this visit:

- Eligibility Criteria
- AE/SAE review
- Concomitant medications review
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Urine pregnancy test
- TB suspicion & evaluation (If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold test, and tuberculin skin test should be performed)
- ASAS20 (for AS patient) response evaluation:
    - BASDAI evaluation
    - Bath AS Functional Index (BASFI) evaluation
    - Spinal Pain (NRS) assessment
    - Patient global assessment (PGA) (NRS)
- ACR20 (for PsA patient) response evaluation:
    - tender and swollen joint count assessment,
    - Patient’s assessment of pain,
    - Patient’s global assessment of disease activity,
    - Physician’s global assessment of disease activity,
    - Health Assessment Questionnaire (HAQ)
    - ESR
    - CRP
- Study drug administration
- Study drug injection-site evaluation

Week 4 (Visit 3/Day 28)

The below mentioned procedure and measurements will be performed at this visit:

- AE/SAE review
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Urine pregnancy test
- TB suspicion & evaluation (If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold test, and tuberculin skin test should be performed)
- Concomitant medications review
- ASAS20 (for AS patient) response evaluation:
    - BASDAI evaluation
    - BASFI evaluation
    - Spinal Pain (NRS) assessment
    - PGA (NRS)
- ACR20 (for PsA patient) response evaluation:
    - tender and swollen joint count assessment,
    - Patient's assessment of pain,
    - Patient's global assessment of disease activity,
    - Physician's global assessment of disease activity,
    - HAQ
    - ESR
    - CRP
- Study drug administration
- Study drug injection-site evaluation

Week 8 (Visit 4/Day 56) and Week 12 (Visit 5/Day 84)

The below mentioned procedure and measurements will be performed at these visits:

- AE/SAE review
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Urine pregnancy test
- TB suspicion & evaluation (If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold test, and tuberculin skin test should be performed)
- Concomitant medications review
- Study drug administration
- Study drug injection-site evaluation

Week 14 (Visit 5/Day 98) - Efficacy Endpoint Assessment Visit

In this visit, all the assessments will be performed for evaluating the efficacy endpoint at Week 14. The below mentioned procedure and measurements will be performed this visit:

- AE/SAE review

- TB suspicion & evaluation (If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold test, and tuberculin skin test should be performed)
- Concomitant medications review
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Urine pregnancy test
- ASAS20 (for AS patient) response evaluation:
    - BASDAI evaluation
    - BASFI evaluation
    - Spinal Pain (NRS) assessment
    - PGA (NRS)
- ACR20 (for PsA patient) response evaluation:
    - tender and swollen joint count assessment,
    - Patient's assessment of pain,
    - Patient's global assessment of disease activity,
    - Physician's global assessment of disease activity,
    - HAQ
    - ESR
    - CRP

Week 16 (Visit 6/Day 112) and Week 20 (Visit 8/Day 140)

All procedures performed at Week 8 and Week 12 will also be performed at Week 16 and Week 20.

Week 24 (Visit 7/Day 168) – End of Treatment Visit

The EOT visit will be conducted after the completion of 24 weeks of golimumab treatment (at Visit 9) or on the day on which the patient discontinues the golimumab treatment or study. The below mentioned procedure and measurements will be performed at this visit:

- AE/SAE review
- TB suspicion & evaluation (If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold test, and tuberculin skin test should be performed)
- Concomitant medications review
- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Routine laboratory tests: haemoglobin, haematocrit, platelet count, total and differential WBC count, BUN, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, blood glucose, albumin and total protein
- Urine pregnancy test
- ASAS20 (for AS patient) response evaluation:
    - BASDAI evaluation
    - BASFI evaluation
    - Spinal Pain (NRS) assessment
    - PGA (NRS)
- ACR20 (for PsA patient) response evaluation:

  - tender and swollen joint count assessment,
  - Patient's assessment of pain,
  - Patient's global assessment of disease activity,
  - Physician's global assessment of disease activity,
  - HAQ
  - ESR
  - CRP
- Study drug administration
- Study drug injection-site evaluation

End of Study Visit

End of study 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). In this follow-up visit/call, enquiry about any AEs experienced or concomitant medications taken by the subject will be made and recorded in the CRF unless the patient has died, or is lost to follow-up, or has withdrawn consent. If the information on safety is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the patient has died, the date and cause of death will be collected and documented in the CRF.

9.2. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, and other safety evaluations at specified time points as described in the TIME AND EVENTS SCHEDULE. Safety will be assessed by evaluating the incidence and type of AEs including SAEs, causality, or clinically significant AEs (as per principal investigator's discretion), and discontinuations due to AEs and routine clinical laboratory values. Frequency of serious infections, including TB, demyelinating disorders, new onset of autoimmune diseases, and malignancies will be summarized. The incidence of study drug injection-site reactions will be noted. End of study 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). Any clinically significant abnormalities persisting at the EOS/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

Adverse Events

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

Clinical Laboratory Tests

Results of clinical laboratory tests from the local laboratory will be used at the screening visit to confirm eligibility of potential patients through the EOT visit (Week 24) for monitoring safety.

Blood samples for serum chemistry, haematology and pregnancy test will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. The laboratory (hematology and chemistry) parameters and change from baseline in laboratory parameters will be assessed. The incidence of markedly abnormal laboratory (hematology and chemistry) parameters will also be evaluated.

Vital Signs: temperature, pulse/heart rate, respiratory rate, blood pressure

Physical Examination: The extent of the physical examination will be conducted by the site per usual local standard-of-care.

9.3. Efficacy Evaluations for Ankylosing Spondylitis

The ASAS Response Criteria (ASAS 20) is defined as:[21,23]

- 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:

1. PGA of Disease (0 to 10 unit NRS): It is the 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 on which the left-hand box (0) represents "not active," and the right-hand box (10) represents "very active". (Appendix B)
2. 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: 'How much pain in your spine due to spondyloarthritis do you have at night? (Appendix C)
3. BASFI: The BASFI is 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. (Appendix D)

4. BASDAI: The BASDAI is 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 (Appendix E)

9.4. Efficacy Evaluations for PsA

The ACR20 response is defined as (Appendix G):[24]

- **≥ 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 dichotomv.
- **≥ 20% improvement in 3 of the following 5 assessments:**
    1. Patient's assessment of pain - A horizontal visual analogue scale (VAS) (usually 10 cm) assessment of the patient's current level of pain.
    2. Patient's global assessment of disease activity – The patient global assessment of disease activity is a simple 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.
    3. Physician's global assessment of disease activity - A physician's global assessments of disease activity will be recorded on a VAS Scale.
    4. Patient's assessment of physical function as measured by the HAQ - The functional status of the patient will be assessed by means of the Disability Index of the HAQ.[25] 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.
    5. Acute-phase reactant: (A Westergren ESR and a CRP level)

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

The study will be considered completed with the EOS within the study for the last subject participating in the study. A patient will be considered as having completed the study if he/she has completed the EOS assessments (in-person or telephonically) or has experienced a clinical endpoint that precludes further evaluation.

Last completed assessment of patients who prematurely discontinue study treatment for any reason before completion of this Phase IV study will be considered for analysis.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor. A participating site is considered closed when all required documents and study specific supplies have been collected and a site closure assessment has been performed.

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

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

- Failure of the participating physician to comply with the protocol, requirements of the IRB or local health authorities, or the sponsor's procedures, or Good Clinical Practice (GCP) guidelines;
- Inadequate recruitment of subjects by the participating physician.

10.2. Discontinuation of Treatment

If a patient must be discontinued from treatment before the EOT regimen, this will not result in automatic withdrawal of the patient from the study.

A patient should be discontinued from study treatment if:

- The investigator believes that for any safety reasons (ie, AE) as mentioned below, it is in the best interest of the patient to stop treatment:
  - opportunistic infection
  - malignancy, excluding nonmelanoma skin cancer
  - CHF
  - demyelinating disease
  - subject is deemed ineligible according to the TB screening criteria
- The patient becomes pregnant.
- The patient initiates the use of prohibited medications or treatments.

- The patient develops a severe or serious injection-site reaction or serious infection.
- Noncompliance defined as any missed visit which results to missed doses. The investigator should contact the medical monitor to discuss any unexplained study drug non-compliance.

If a patient discontinues treatment before the EOT, all Week 24 evaluations should be performed.

10.3. Withdrawal from the Study

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

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

If a patient withdraws from the study before the EOT visit, all EOT and post-treatment assessments should be obtained. If a patient is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Patients who withdraws will not be replaced.

11. STATISTICAL METHODS

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

Statistical Analysis Plan will be issued as a separate document, providing detailed methods for analysis planned in the study. All statistical analysis will performed using SAS® software version 9.4 or later. For study endpoints analysis, intention-to-treat (ITT) population will be considered.

Continuous data variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum and maximum). Change from baseline will be calculated where appropriate. Subject-wise data listing will be provided. All categorical data will be summarized using frequency counts and percentages. Statistical analysis will be performed separately for each indication.

Disposition, Demographics and Baseline Characteristics:

Disposition will be summarized for all subjects. Demographics and disease baseline characteristics will be summarized for ITT population.

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

Handling of 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.

No other imputation is planned for missing data assessments.

11.1. Analysis Population

11.1.1. Safety Population

The safety population will include all subjects who were enrolled and received at least one dose of the study drug.

11.1.2. Intent-to-Treat Population

The ITT population will include all subjects who were enrolled and received at least one dose of a study drug and have completed Week 24 visit.

11.2. Sample Size Determination

Approximately 100 patients with spondyloarthropathy (50 patients of AS and 50 patients of PsA) will be enrolled in this Phase IV noncomparative open-label study as per Indian Health Regulatory Authority (DCGI office, n=100) requirements. Enrollment of participants with the diagnosis of AS and PsA will start simultaneously. 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.[26,27] So considering this, close to 50% subjects would be enrolled for each indication.

11.3. Endpoints:

Safety Endpoint

- Occurrence of an AE/SAE (clinical or laboratory safety event)

Efficacy Endpoints

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

11.4. Safety Analyses

Safety will be recorded at time points specified in the TIME AND EVENTS SCHEDULE and the analysis will be summarized using safety population. Incidence of AEs will be tabulated. Laboratory abnormalities will be reported if clinically significant.

Adverse Events

All AEs will be coded by system organ class and preferred term using the latest Medical Dictionary for Regulatory Activities version. Summaries, listing, datasets or subjects narratives may be provided, as appropriate, for subjects who die, who discontinue treatment due to an AE, or who experience an SAE.

Clinical Laboratory Tests

Clinical laboratory evaluations will be performed and the results if considered clinically significant (as per principal investigator's discretion) and/or reported as AE/SAE will be reported and summarized.

11.5. Efficacy Analyses

For the efficacy endpoints, to assess the improvement in ASAS20 (for AS patients) or ACR20 (for PsA patients).

11.6. Interim Analysis

No interim analysis is planned for this study.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

The undesirable effects known to be associated with the use of golimumab are summarised in the current issue of the prescribing information of SIMPONI®.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal

(investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All AEs, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For golimumab, the expectedness of an AE will be determined by whether or not it is listed in the prescribing information.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Any adverse event or serious adverse event not listed in the NCI-CTCAE Version 4.03 will be graded according to investigator clinical judgment by

- Grade 1: (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Grade 2: (Moderate): Sufficient discomfort is present to cause interference with normal activity.
- Grade 3: (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
- Grade 4: Life-threatening of disabling adverse event
- Grade 5: Death related to the adverse event

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

12.2. Special Reporting Situations

Safety events of interest on golimumab that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug

- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding
- Drug exposure during pregnancy (maternal and paternal)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF and reported to the local sponsor within 24 hours of them becoming aware of the event.

12.3. Procedures

In this Phase IV clinical study, SIMPONI® (golimumab) is the Johnson & Johnson product under study.

The sponsor will provide appropriate pharmacovigilance training to the participating site personnel. The sponsor assumes responsibility for appropriate reporting of AEs/SAEs and significant safety information originating from the data collected for Johnson & Johnson medicinal products to the regulatory authorities. All collected AEs will be summarized in the final study report.

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

Sponsor's Contact Details:

Local Safety Officer
Johnson & Johnson Private Limited
501, Arena Space, 8th Floor,
Behind Majas Bus Depot,
Off. J.V. Link Road, Jogeshwari (East),
Mumbai 400060, India.
Telephone: +91 22 6664 6629
Fax: +91 22 6671 8204
Email: drugsafe@its.jnj.com

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety

information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee (IEC) /Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

12.3.2. Serious Adverse Events

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

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

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

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must promptly discontinue further study treatment. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labelling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labelling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The golimumab supplied for this study is a mAb with an immunoglobulin - IgG1 heavy chain isotype (G1m[z] allotype) and a kappa light chain isotype. The molecular weight of golimumab ranges from 149,802 to 151,064 daltons. Golimumab binds TNFα with high affinity. It will be manufactured and provided under the responsibility of the sponsor. Refer to the prescribing information for a list of excipients.

14.2. Packaging

Commercial stocks of SIMPONI® will be used for the patients enrolled in the study with appropriate labelling and will be provided free of cost to the patient enrolled for 24 weeks treatment. Patients will procure SIMPONI® from the existing distribution channel (regular supply chain) as obtained by

routine patients but the drug will be free of cost for clinical trial patients as per the mentioned duration in the study protocol.

14.3. Labelling

Commercial stocks of SIMPONI® supplied to the patients enrolled in the study with appropriate labelling.

14.4. Preparation, Handling, and Storage

Golimumab will be available as a sterile liquid for SC injection at a volume of 0.5 mL in prefilled single-use Smartject® device (a kind of prefilled pen-device for injection). Each Simponi Smartject® will contain 50 mg golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5. No preservatives are present. The needle cover may contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex. Aseptic procedures must be used during the preparation and administration of the study material. Exposure to direct sunlight should be avoided during administration. Prior to administration, the drug product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow colour), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

- Store in a refrigerator: 2 ºC to 8 ºC (36 ºF to 46 ºF)
- Store in original carton until time of use
- Do not freeze
- Do not shake

14.5. Drug Accountability

The investigator will be responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the patient must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers. Study drug must be handled in strict accordance with the protocol.

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Prescribing information for SIMPONI®
- Pharmacy manual/study site investigational product and procedures manual
- Study Laboratory Manual
- NCI-CTCAE Version 4.03

- Electronic data capture (eDC) manual
- Sample ICF
- CRF and CRF completion guidelines

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to patients
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the patients or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients
- Report of deaths of patients under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

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

16.2.3. Informed Consent

Each patient will have to give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the patient can read and understand. The informed

consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrolment in the study, the investigator or an authorized member of the study-site personnel must explain to potential patients the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the patient will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the patient is authorizing such access. It also denotes that the patient agrees to allow his or her study physician to recontact the patient for the purpose of obtaining consent for additional safety evaluations, if needed.

The patient will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the patient.

If the patient or LAR is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the patient or LAR is obtained.

16.2.4. Privacy of Personal Data

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

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

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

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

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable

laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrolment of the first patient:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Photocopy of the site signature log, describing delegation of roles and responsibilities at the start of the study
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Patient Identification, Enrolment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: patient identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the

protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of smoking (all nicotine use, eg, cigarettes or the equivalent of e-cigarettes, cigars, chewing tobacco, patch, gum), alcohol intake
- Vital Signs (blood pressure, heart rate, respiratory rate and temperature)
- Height and weight
- Details of physical examination
- The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:
  - Referral letter from treating physician or
  - Complete history of medical notes at the site
  - Discharge summaries

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms will be prepared and provided by the sponsor for each patient in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

The eCRF must be completed as soon as possible after a patient visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

17.7. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

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

17.9.2. Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

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

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study patient identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicentre) data and information without approval from the investigator. The investigator has the right to publish study

site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicentre study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicentre study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicentre study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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1. Prescribing Information of SIMPONI® (golimumab). Updated January 2017. Available from: https://www.accessdata fda.gov/drugsatfda_docs/label/2011/125289s0064lbl.pdf .
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APPENDIX A: EVALUATION OF ANKYLOSING SPONDYLITIS

Modified New York criteria for classification of ankylosing spondylitis*

Criteria	Description
Clinical criteria	(a) Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest (b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes (c) Limitation of chest expansion relative to normal values correlated for age and sex
Radiological criterion	Sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally – Grade 0 = normal – Grade 1 = suspicious – Grade 2 = sclerosis, some erosions – Grade 3 = severe erosions, widening of the joint space, some ankylosis – Grade 4 = complete ankylosis
Definite AS is present if the radiological criterion is associated with at least 1 clinical criterion	

The ASAS 20 is defined as achieving:

- 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:

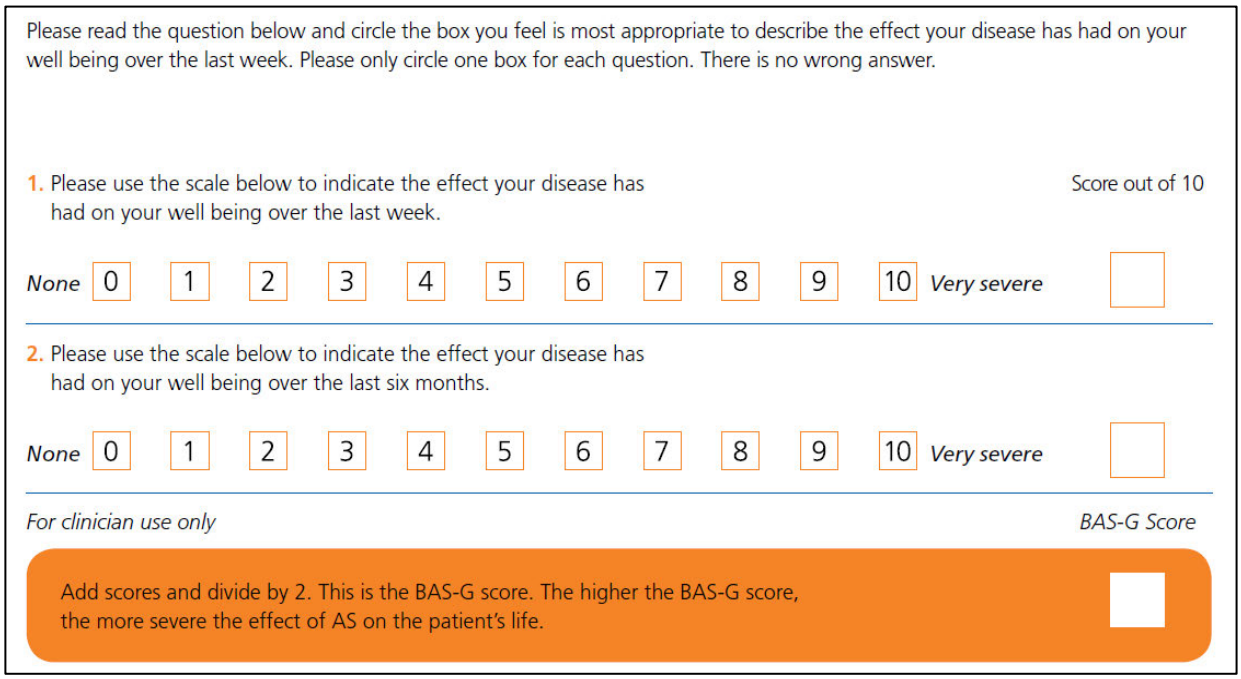
1. Patient Global Assessment of Disease (0 to 10 unit Numerical Rating Scale [NRS]);
2. Total Back Pain NRS;
3. Function Bath Ankylosing Spondylitis Functional Index (BASFI) score NRS;
4. Inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] NRS Question #5 and #6 for morning stiffness).

Reference:

- Dureza CJ. Approaches to Missing Data in the Analysis of SpondyloArthritis International Society (ASAS 20) Response and the Creation of the Related CDISC Compliant Analysis Data Sets. PharmaSUG China, 2015.
- Zochling J and Braun J. Assessment of ankylosing spondylitis. Clin Exp Rheumatol 2005; 23 (Suppl. 39): S133-S141.

APPENDIX B: PATIENT GLOBAL ASSESSMENT (PGA) - NRS:

The Patient Global Assessment of Disease Activity is the patient's assessment of how active their spondylitis was on average during the last week. The BAS-G consists of two questions which ask patients to indicate, the effect the disease has had on their well-being over the last week and last 6 months. The patient will be asked to mark the box with an X on a 0 to 10 unit NRS on which the left-hand box of 0 represents "none," and the right-hand box represents "very severe".


Please read the question below and circle the box you feel is most appropriate to describe the effect your disease has had on your well being over the last week. Please only circle one box for each question. There is no wrong answer.

1. Please use the scale below to indicate the effect your disease has had on your well being over the last week. Score out of 10

None 0 1 2 3 4 5 6 7 8 9 10 Very severe

2. Please use the scale below to indicate the effect your disease has had on your well being over the last six months.

None 0 1 2 3 4 5 6 7 8 9 10 Very severe

For clinician use only *BAS-G Score*

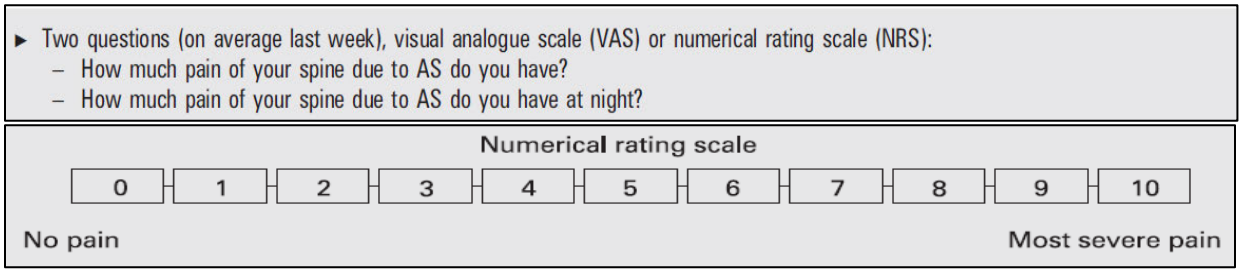
Add scores and divide by 2. This is the BAS-G score. The higher the BAS-G score, the more severe the effect of AS on the patient's life.

References:

- Irons K, Harrison H, Thomas A and Martindale J. An updated synopsis of the Bath Indices – outcome measures for use with Ankylosing Spondylitis patients and their broader application. 2016. Available from: https://nass.co.uk/download/5723760081867/
- Dureza CJ. Approaches to Missing Data in the Analysis of SpondyloArthritis International Society (ASAS 20) Response and the Creation of the Related CDISC Compliant Analysis Data Sets. PharmaSUG China, 2015.

APPENDIX C: TOTAL AND NIGHT SPINAL PAIN - NRS:

The total back pain NRS is the patient's assessment of, on average last week, how much pain they have in their spine due to AS and how much pain they have at night. The patient will be asked to mark the box with an X on a 0 to 10 unit NRS on which the left-hand box of 0 represents "no pain," and the right-hand box represents "most severe pain".

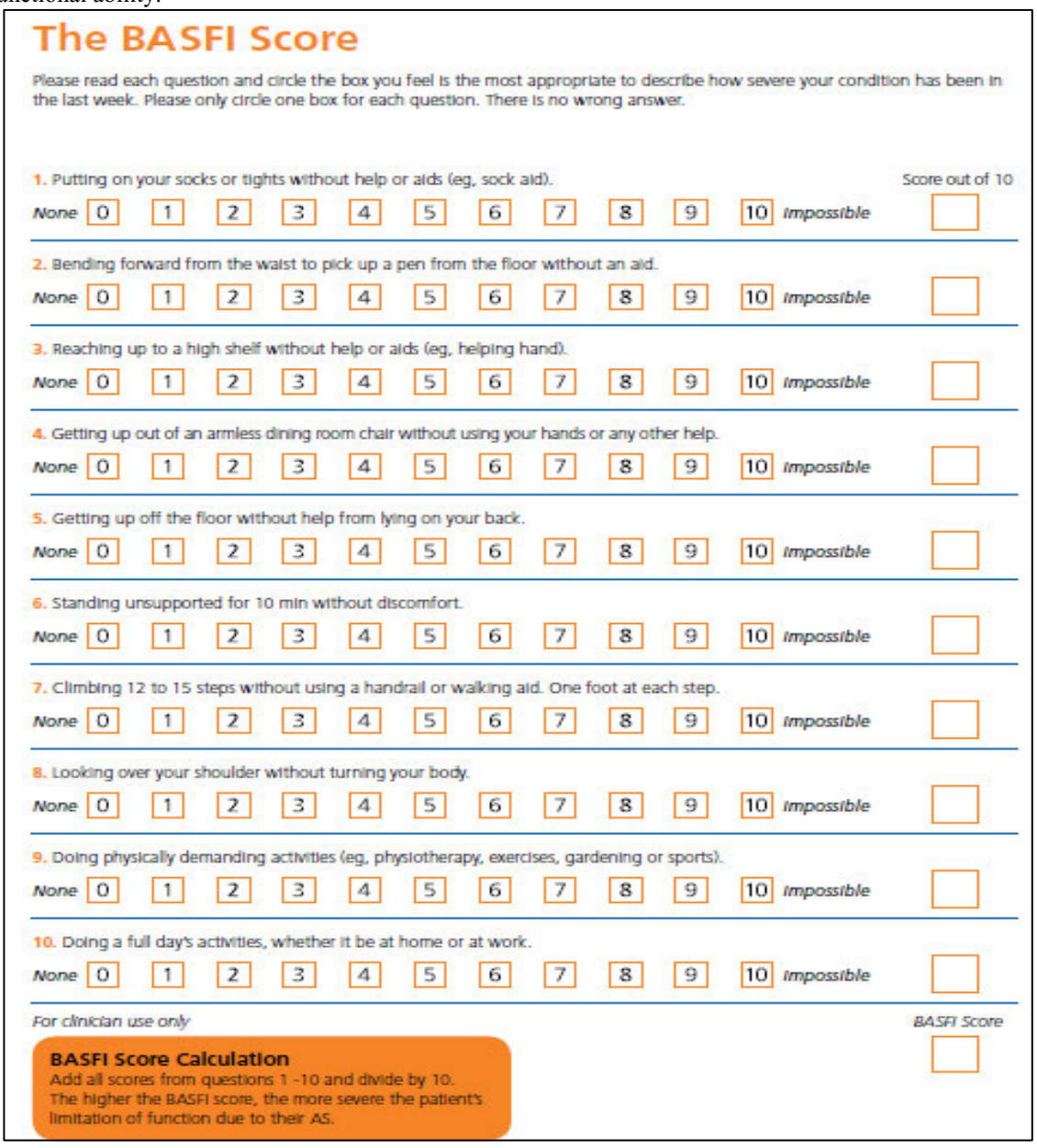


References:

- Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas et.al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68(Suppl II):ii1–ii44.

APPENDIX D: BATH ANKYLOSING SPONDYLITIS FUNCTIONAL INDEX (BASFI) ASSESSMENT

The BASFI is a composite score based on a patient self-administered survey of ten questions using a 0 to 10 unit numerical rating scale (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 of 0 represents "none," and the right-hand box 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.



The BASFI Score

Please read each question and circle the box you feel is the most appropriate to describe how severe your condition has been in the last week. Please only circle one box for each question. There is no wrong answer.

1. Putting on your socks or tights without help or aids (eg, sock aid). Score out of 10

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

2. Bending forward from the waist to pick up a pen from the floor without an aid.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

3. Reaching up to a high shelf without help or aids (eg, helping hand).

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

4. Getting up out of an armless dining room chair without using your hands or any other help.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

5. Getting up off the floor without help from lying on your back.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

6. Standing unsupported for 10 min without discomfort.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

7. Climbing 12 to 15 steps without using a handrail or walking aid. One foot at each step.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

8. Looking over your shoulder without turning your body.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

9. Doing physically demanding activities (eg, physiotherapy, exercises, gardening or sports).

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

10. Doing a full day's activities, whether it be at home or at work.

None 0 1 2 3 4 5 6 7 8 9 10 *Impossible* ☐

For clinician use only *BASFI Score* ☐

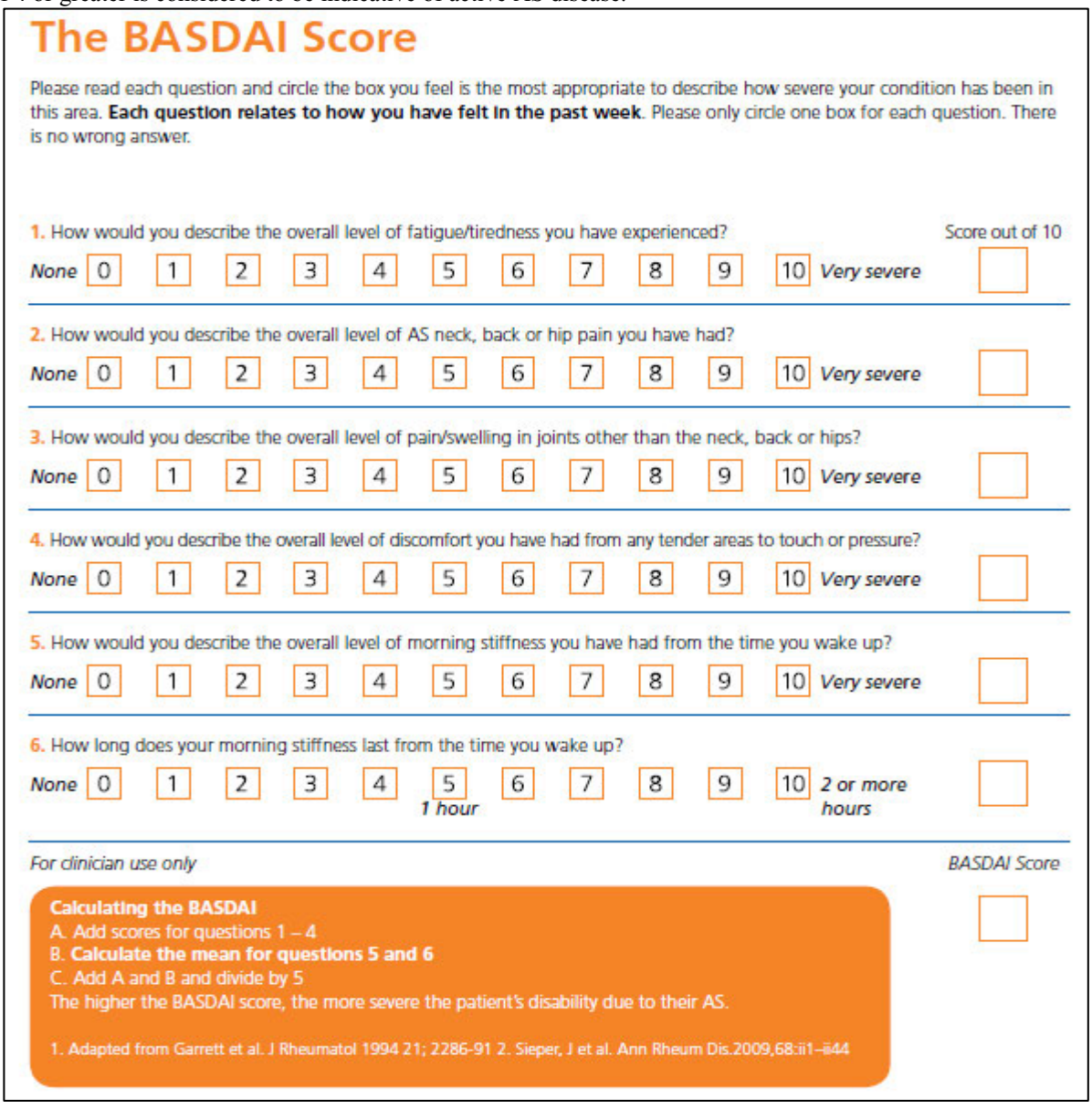
BASFI Score Calculation
Add all scores from questions 1 -10 and divide by 10.
The higher the BASFI score, the more severe the patient's limitation of function due to their AS.

References:

- Irons K, Harrison H, Thomas A and Martindale J. An updated synopsis of the Bath Indices – outcome measures for use with Ankylosing Spondylitis patients and their broader application. 2016. Available from: https://nass.co.uk/download/5723760081867/
- Dureza C. Approaches to Missing Data in the Analysis of SpondyloArthritis International Society (ASAS 20) Response and the Creation of the Related CDISC Compliant Analysis Data Sets. PharmaSUG China 2015 - Paper 067.

APPENDIX E: THE BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI) SCALE:

The BASDAI is a composite score based on a patient self-administered survey of six questions using a 0 to 10 unit numerical rating scale (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 BASDAI Score

Please read each question and circle the box you feel is the most appropriate to describe how severe your condition has been in this area. **Each question relates to how you have felt in the past week**. Please only circle one box for each question. There is no wrong answer.

1. How would you describe the overall level of fatigue/tiredness you have experienced? Score out of 10

None 0 1 2 3 4 5 6 7 8 9 10 *Very severe*

2. How would you describe the overall level of AS neck, back or hip pain you have had?

None 0 1 2 3 4 5 6 7 8 9 10 *Very severe*

3. How would you describe the overall level of pain/swelling in joints other than the neck, back or hips?

None 0 1 2 3 4 5 6 7 8 9 10 *Very severe*

4. How would you describe the overall level of discomfort you have had from any tender areas to touch or pressure?

None 0 1 2 3 4 5 6 7 8 9 10 *Very severe*

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

None 0 1 2 3 4 5 6 7 8 9 10 *Very severe*

6. How long does your morning stiffness last from the time you wake up?

None 0 1 2 3 4 5 *1 hour* 6 7 8 9 10 *2 or more hours*

For clinician use only *BASDAI Score*

Calculating the BASDAI
A. Add scores for questions 1 – 4
B. **Calculate the mean for questions 5 and 6**
C. Add A and B and divide by 5
The higher the BASDAI score, the more severe the patient's disability due to their AS.

1. Adapted from Garrett et al. J Rheumatol 1994 21; 2286-91 2. Sieper, J et al. Ann Rheum Dis.2009,68:ii1–ii44

References

- Irons K, Harrison H, Thomas A and Martindale J. An updated synopsis of the Bath Indices – outcome measures for use with Ankylosing Spondylitis patients and their broader application. 2016. Available from: https://nass.co.uk/download/5723760081867/
- Dureza C. Approaches to Missing Data in the Analysis of SpondyloArthritis International Society (ASAS 20) Response and the Creation of the Related CDISC Compliant Analysis Data Sets. PharmaSUG China 2015 - Paper 067.

APPENDIX F: THE CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS [CASPAR] CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS

To be classified as having PsA, a patient must have inflammatory articular disease (joint, spine, entheseal) with ≥ 3 of the following 5 points:

Criterion	Description
1. Evidence of psoriasis (one of a, b, c):	
(a) Current psoriasis[a]	Psoriatic skin or scalp disease currently present, as judged by a rheumatologist or a dermatologist
(b) Personal history of psoriasis	A history of psoriasis obtained from patient or family physician, dermatologist, rheumatologist, or other qualified health care professional
(c) Family history of psoriasis	A history of psoriasis in a first- or second-degree relative by patient report
2. Psoriatic nail dystrophy	Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. Negative test result for RF	By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis (one of a, b):	
(a) Current	Swelling of an entire digit
(b) History	A history of dactylitis recorded by a rheumatologist
5. Radiological evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (excluding osteophyte formation) on plain x-ray films of hand or foot

[a] Current psoriasis scores 2; all other items score 1.

References

- Philipose J and Deodhar A. Classification Criteria for Psoriatic Arthritis: CASPAR. The Journal of Musculoskeletal Medicine 2012. Available from: http://www rheumatologynetwork.com/psoriatic-arthritis/classification-criteria-psoriatic-arthritis-caspar

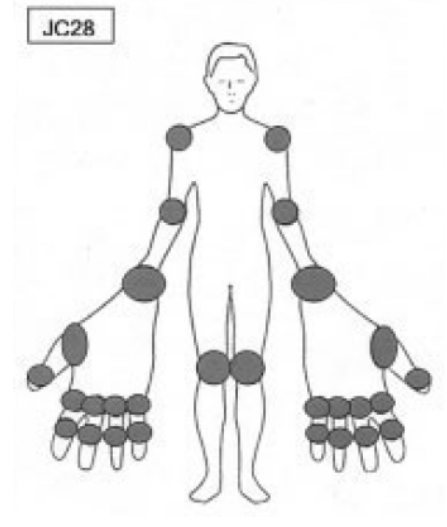
APPENDIX G: AMERICAN COLLEGE OF RHEUMATOLOGY PRELIMINARY DEFINITION OF IMPROVEMENT IN RHEUMATOID ARTHRITIS* (ACR20)

Required	≥20% improvement in tender joint count ≥20% improvement in swollen joint count ≥20% improvement in 3 of following 5: Patient pain assessment Patient global assessment Physician global assessment Patient self-assessed disability Acute-phase reactant (ESR or CRP)
Tender joint count	ACR tender joint count, an assessment of 28 or more joints. 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 dichotomv.
Swollen joint countt	ACR swollen joint count, an assessment of 28 or more joints. Joints are classified as either swollen or not swollen.
Patient's assessment of pain	A horizontal visual analog scale (usually 10 cm) or Likert scale assessment of the patient's current level of pain.
Patient's global assessment of disease activity	The patient's overall assessment of how the arthritis is doing. One acceptable method for determining this is the question from the AIMS instrument: "Considering all the ways your arthritis affects you, mark 'X' on the scale for how well you are doing." An anchored, horizontal, visual analog scale (usually 10 cm) should be provided. A Likert scale response is also acceptable.
Physician's global assessment of disease activity	A horizontal visual analog scale (usually 10 cm) or Likert scale measure of the physician's assessment of the patient's current disease activity.
Patient's assessment of physical function	Any patient self-assessment instrument which has been validated, has reliability, has been proven in RA trials to be sensitive to change, and which measures physical function in RA patients is acceptable. Instruments which have been demonstrated to be sensitive in RA trials include the AIMS, the HAQ, the Quality (or Index) of Well Being, the MHIQ, and the MACTAR.
Acute-phase reactant value	A Westergren ESR or a CRP level.

ACR = American College of Rheumatology; AIMS = Arthritis Impact Measurement Scales; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; MACTAR = McMaster Toronto Arthritis Patient Preference Disability Questionnaire; MHIQ = McMaster Health Index Questionnaire; RA = rheumatoid arthritis

1. TENDER JOINT COUNT ASSESSMENT (28 JOINT COUNT)

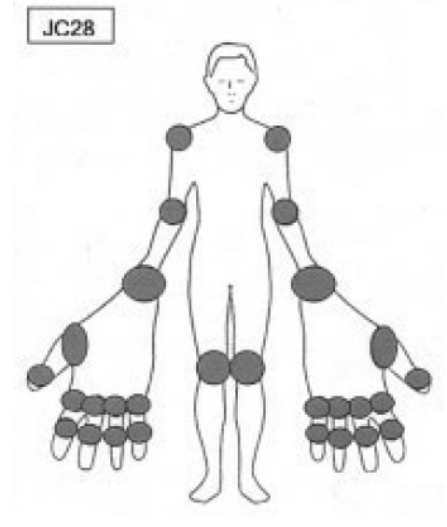
A 28 tender joint count, includes the shoulders, elbows, wrists, MCPs 1-5, PIPs 1-5 and the knees, bilaterally. Although the 28 joint count excludes some joints characteristically involved in PsA, such as the DIP joints, it has been shown to perform acceptably in PsA.



Right	Left
Shoulder	Shoulder
Elbow	Elbow
Wrist	Wrist
Metacarpophalangeal First Second Third Fourth Fifth	Metacarpophalangeal First Second Third Fourth Fifth
Proximal interphalangeal First Second Third Fourth Fifth	Proximal interphalangeal First Second Third Fourth Fifth
Knee	Knee

2. SWOLLEN JOINT COUNT ASSESSMENT (28 JOINT COUNT)

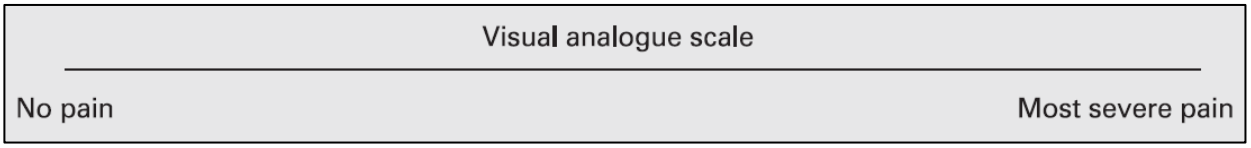
A 28 swollen joint count, includes the shoulders, elbows, wrists, MCPs 1-5, PIPs 1-5 and the knees, bilaterally. Although the 28 joint count excludes some joints characteristically involved in PsA, such as the DIP joints, it has been shown to perform acceptably in PsA.



Right	Left
Shoulder	Shoulder
Elbow	Elbow
Wrist	Wrist
Metacarpophalangeal First Second Third Fourth Fifth	Metacarpophalangeal First Second Third Fourth Fifth
Proximal interphalangeal First Second Third Fourth Fifth	Proximal interphalangeal First Second Third Fourth Fifth
Knee	Knee

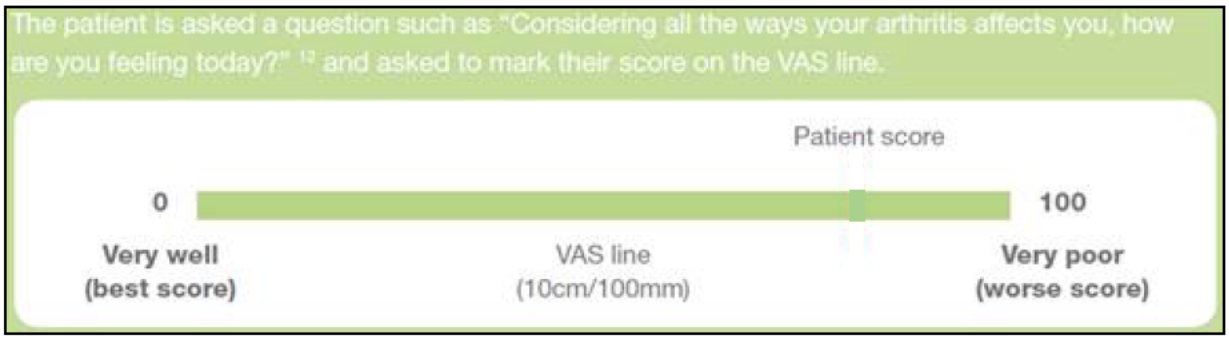
3. PATIENT'S ASSESSMENT OF PAIN

The patient will be asked – "How severe was the pain you have experienced in the last 24 hours?"



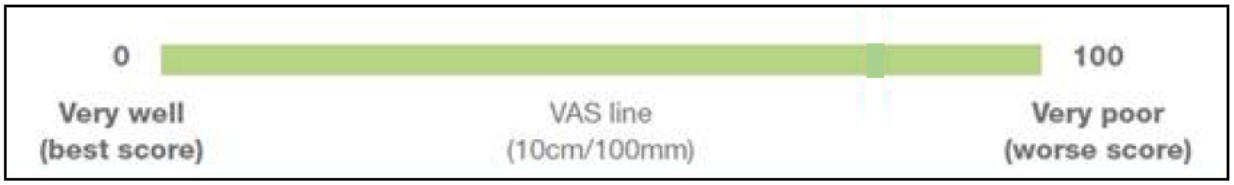
4. PATIENT'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY – VAS

The patient global activity VAS or patient global assessment of disease activity is a simple 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 (very well) to 100 (very poor) where the patient marks on the line.



5. PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY – VAS

'What is your assessment of the patient's current disease activity?' (0= very well, 100=very poor)



6. HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

The HAQ focuses on 2 dimensions of health status, physical disability (8 subscales) and pain.

Name: _____ **Date:** _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor**?**	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

Completely	Mostly	Moderately	A Little	Not At All
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?

On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

7. ACUTE-PHASE REACTANT VALUE

A westergren erythrocyte sedimentation rate (ESR) or a C-reactive protein (CRP) level will be assessed.

References

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APPENDIX H: TUBERCULIN SKIN TESTING

An intradermal tuberculin skin test (Mantoux) must be performed within 1 month prior to the first administration of study drug following the instructions provided below. Multiple puncture tests (Tine and Heaf) are not acceptable methods of testing.

Administering the Mantoux Tuberculin Skin Test

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

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied here, even though the patients entering this study may or may not be immunocompromised at baseline. The purpose of using this conservative definition of positivity is to maximize the likelihood of detecting latent TB. In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

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

Treatment of Latent Tuberculosis

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

References

- Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human
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- Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

APPENDIX I: QUANTIFERON-TB GOLD TESTING

A QuantiFERON-TB Gold test must be performed **within 1 month** prior to the first administration of study drug.

Background

The Mantoux tuberculin skin test (CDC, 2000) is the currently accepted, standard method of identifying persons infected with *Mycobacterium tuberculosis*. However, the tuberculin skin test has less specificity due to cross-reactivity with BCG and environmental mycobacteria, and reduced sensitivity, especially in immunocompromised persons (ATS, 2000, Huebner et al, 1993, Jasmer et al, 2002, Shafer and Edlin, 1996). Variability in application and interpretation of the tuberculin skin test is also associated with the inaccuracy of the test (Pouchot et al, 1997). False-positive tuberculin skin test reactions lead to inappropriate treatment with long-term antibiotics, and false-negative tuberculin skin test reactions can result in morbidity and mortality from active TB that could have been prevented. Because of these tuberculin skin test inadequacies, research has focused on new testing methods for detecting TB infection.

The QuantiFERON-TB Gold test is one of the new interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2004). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP—10 in the standard format, as well as TB7.7(p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis* specific antigens. In M. tuberculosis-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some crossreactivity with the 3 Mycobacterium species *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

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

The sensitivity of the tuberculin skin test can decrease significantly in immunocompromised individuals. In asymptomatic HIV-positive persons who developed active TB, the sensitivity of the tuberculin skin test has been reported to be only 40 to 60% (Shafer and Edlin, 1996). There are yet no published studies of the performance of the QuantiFERON-TB Gold assay in immunosuppressed populations, but studies are ongoing and preliminary data suggest that sensitivity is maintained and better than the tuberculin skin test (personal communication, Cellestis). There has been 1 published study using a similar IFN-γ based blood test for *M. tuberculosis* infection (T Spot-TB test), which demonstrated a sensitivity of 90% in HIV-positive persons with active TB (Chapman et al, 2002). The ability of the new IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the new tests correlated better with the degree of exposure that contacts had to the index TB case than the tuberculin skin test (Brock et al, 2004, Ewer et al, 2004).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well-validated in the immunosuppressed population, experts believe these new tests will be at least as sensitive, if not more, and definitely more specific than the tuberculin skin test (Barnes, 2004). For these reasons, this protocol includes the use of the QuantiFERON-TB Gold assay in addition to the tuberculin skin test, the current standard for TB screening, to improve detection of latent TB infection and thereby enhance patient safety.

Performing the QuantiFERON-TB Gold Test

The QuantiFERON-TB Gold test is available in 2 formats, a standard method and an In-Tube method. The 2 formats differ logistically in the manner in which they are performed. In addition, the In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7(p4), which is thought to increase the specificity of the test. Results of the QuantiFERON-TB Gold test using either format are acceptable for subjects to enter this trial; however, only the In-Tube format will be provided for this study.

Published studies have only used the QuantiFERON-TB Gold test with the standard method; however, the manufacturing company Cellestis has performed some unpublished studies that demonstrate the comparability of the 2

formats (personal communication, Cellestis). Both formats of the QuantiFERON-TB Gold test are currently approved for commercial use in Europe and certain other countries in which this trial will be conducted. The QuantiFERON-TB Gold test with the standard method was recently approved by the FDA for use in the US. The In-Tube format will be submitted to the FDA for review in the next few years.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the M. tuberculosis-specific antigens. Approximately 3 tubes will be needed per patient, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is done by shaking the tubes. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 5 to 10 minutes at 1500 to 2200 g. Following centrifugation, plasma may be harvested from each tube and placed in aliquot tubes, or the centrifuged tubes themselves may be shipped to the central laboratory at 2°C to 8°C. The central laboratory will perform an enzyme-linked immunosorbent assay (ELISA) to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis

Interpreting the QuantiFERON-TB Gold Test Results

The central laboratory will analyze and report results for each subject, and study sites will be informed of the results prior to enrolment. Subjects who have a positive QuantiFERON-TB Gold test must receive the same treatment and evaluations for latent TB infection as subjects who have a positive tuberculin skin test to be enrolled in this trial.

Treatment of Latent Tuberculosis

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

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INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Johnson & Johnson Private Limited

Signature: PPD _____ Date: PPD

(Day Month Year)

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