1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled Phase 2a Study to Evaluate the Efficacy and Safety of Tildrakizumab in Subjects with Active Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis

Protocol No.: CLR_16_22	EUDRACT No.: 2016-003936-19
Test Product:	Tildrakizumab
Indication:	Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis
Sponsor:	Sun Pharma Global FZE Office at #43, Block Y SAIF Zone Sharjah, 122304 United Arab Emirates
Development Phase:	Phase 2a
Sponsor Signatory:	Patrick Burnett, M.D., Ph.D. 2 Independence Way, Princeton, NJ 08540
Sponsor Medical Expert:	Patrick Burnett, M.D., Ph.D. 2 Independence Way, Princeton, NJ 08540
Date of the Protocol:	14 June 2017
Version of the Protocol:	v2.0 Final

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Phase 2a Study to Evaluate the Efficacy and Safety of Tildrakizumab in Subjects with Active Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis

PROTOCOL NUMBER: CLR_16_22

Sun Pharma Global FZE

Patrick Burnett MD

Patrick Burnett, M.D, Ph.D.

15 June 2017

Date (day/month/year)

3 GENERAL INFORMATION

A Randomized, Double-Blind, Placebo-Controlled Phase 2a Study to Evaluate the Efficacy and Safety of Tildrakizumab in Subjects with Active Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis

Protocol No.:	CLR_16_22
Date of the Protocol:	14 June 2017
Date and Number of Amendment(s):	14 June 2017, Amendment 1
Sponsor:	Sun Pharma Global FZE Office at #43, Block Y SAIF Zone Sharjah, 122304 United Arab Emirates
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4 STUDY SYNOPSIS

Name of Sponsor/Company: Sun Pharma Global FZE	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
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Title of Study:
A Randomized, Double-Blind, Placebo-Controlled Phase 2a Study to Evaluate the Efficacy and Safety of Tildrakizumab in Subjects with Active Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis

Study Centers:
The study will be multinational and performed in approximately [redacted] study centers.

Publication(s):
None.

Planned Study Period:	**Development Phase:**
[redacted]	Phase 2a

Objectives:

Primary Efficacy Objective:

Part 1

- To evaluate the efficacy of tildrakizumab in subjects with ankylosing spondylitis (AS) or non-radiographic axial spondyloarthritis (nr-axSpA), as measured by the proportion of subjects achieving Assessment of SpondyloArthritis international Society (ASAS)[redacted] response criteria at [redacted]

Primary Safety Objective:

Parts 1 and 2

- To assess the safety/tolerability and immunogenicity of tildrakizumab in subjects with AS or nr-axSpA.

Secondary Objectives:

Parts 1 and 2

- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects achieving ASAS20 response criteria at Week 52, ASAS40 response criteria at Weeks 24 and 52, and proportion of subjects who require adjustment of background therapy.
- To characterize the pharmacokinetics (PK) of tildrakizumab in subjects with AS or nr-axSpA.

Exploratory Objectives

Parts 1 and 2

The exploratory objectives for Parts 1 and 2 of the study are:

- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects who achieve ASAS20 or ASAS40 at other measured time points.
- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects who achieve ASAS70 or ASAS5/6.
- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the change from Baseline in ASAS components, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL), Visual Analog Scale (VAS) (total back pain and nocturnal pain score), Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP),

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ASDAS erythrocyte sedimentation rate (ESR), Maastrict Ankylosing Spondylitis Enthesitis Score (MASES), short form 36 (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue, high-sensitivity CRP (hs)CRP, SpondyloArthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) Index of Disease Activity of the sacroiliac (SI) Joints, SPARCC MRI Index of Disease Activity of the Spine, and Modified Berlin Ankylosing Spondylitis Spine Magnetic Resonance Imaging Activity Score (ASspiMRI), swollen joint count of 44 joints (SJC44), and tender joint count of 46 joints (TJC46) at measured time points.

- To evaluate the tildrakizumab exposure/response relationship.

Part 3

The exploratory objectives for Part 3 of the study are:

- To assess the effect of investigational medicinal product (IMP) discontinuation on ASAS20, ASAS50, ASAS70, ASAS5/6, ASAS components, BASDAI, BASMI, BASFI, SF-36, VAS (total back pain and nocturnal pain score), MASES, FACIT-fatigue, TJC46, and SJC44 at measured time points.
- To evaluate immunogenicity following IMP discontinuation.
- To characterize the PK of tildrakizumab in subjects with AS or nr-axSpA following IMP discontinuation.

Endpoints:

All endpoints will be analyzed separately for AS and nr-axSpA, unless otherwise stated.

Primary Endpoint:

- The proportion of subjects who achieve ASAS20 at [redacted]
  ASAS20 response is defined as an improvement of [redacted] and absolute improvement of [redacted] from Baseline in a VAS [redacted]; Patient's Global Assessment (PtGA) of disease activity; Total Back Pain VAS; BASFI VAS; and Inflammation VAS (the mean of the [redacted] morning stiffness-related BASDAI VAS scores [redacted] of the BASDAI]). No worsening of [redacted] VAS on a [redacted] in the remaining [redacted] domain.

Secondary Endpoints [redacted]):

- The proportion of subjects who achieve ASAS20 at [redacted]
- The proportion of subjects who achieve ASAS40 at [redacted]
  ASAS40 response is defined as an improvement of [redacted] and absolute improvement of [redacted] from Baseline in a VAS for [redacted] of the [redacted] domains: PtGA; Total Back Pain; BASFI; and Inflammation. No worsening of [redacted] and [redacted] VAS on a [redacted] in the remaining [redacted] domain.
- The proportion of subjects who require adjustment of background therapy
- PK parameters: area under the concentration-time curve (AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), time of maximal concentration (T_{max}) and half-life ($T_{1/2}$). PK parameters will be analyzed separately for each subject population and pooled.

Exploratory Endpoints [redacted]):

- The proportion of subjects who achieve ASAS[redacted] or ASAS[redacted] at other measured time points
- The proportion of subjects who achieve ASAS[redacted] at measured time points
  ASAS70 response is defined as an improvement of [redacted] and absolute improvement of [redacted] from Baseline in a VAS for [redacted] of the [redacted]; PtGA; Total Back Pain; BASFI; and Inflammation. No worsening of [redacted] and [redacted] VAS on a [redacted] in the remaining [redacted] domain.
- The proportion of subjects who achieve a ASAS5[redacted] response at measured time points

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ASAS5[redacted] response is defined as a [redacted] improvement in [redacted] (physical function [BASFI], Total Back Pain, PtGA of disease activity, Inflammation [mean of Questions 5 and 6 of the BASDAI], spinal mobility [BASMI], and acute phase reactants [CRP]).

- Change from Baseline in ASAS components at measured time points
- Change from Baseline in BASDAI, BASMI, BASFI, and ASQoL at measured time points
- Change from Baseline in VAS (total back pain and nocturnal pain score) at measured time points
- Change from Baseline in ASDAS-CRP and ASDAS-ESR at measured time points
- Change from Baseline in MASES at measured time points
- Change from Baseline in SF-36 at measured time points
- Change from Baseline in FACIT-fatigue at measured time points
- Change from Baseline in TJC46 and SJC44 at measured time points
- Change from Baseline in hsCRP serum levels at measured time points
- Change From Baseline in SPARCC MRI Index of Disease Activity Score of the SI Joints at measured time points
- Change From Baseline in SPARCC MRI Index of Disease Activity Score of the Spine at measured time points
- Change From Baseline in Modified Berlin ASspiMRI at measured time points
- Population PK of tildrakizumab
- Tildrakizumab exposure/response relationship.

Exploratory Endpoint [redacted]

- ASAS20, ASAS50, ASAS70, ASAS5/6, ASAS components, BASDAI, BASMI, BASFI, SF-36, VAS (total back pain and nocturnal pain score), MASES, FACIT-fatigue, TJC46, and SJC44 at measured time points
- Incidence of anti-drug antibodies (ADA) at measured time points
- Population PK parameters

Safety Endpoints:

- Adverse events (AEs)
- Laboratory assessments
- Suicidal ideation and behavior (Columbia-Suicide Severity Rating Scale [C-SSRS])
- Vital signs, electrocardiogram (ECG), physical examination
- ADA to tildrakizumab, including titer and neutralizing antibodies, at measured time points

Anti-Drug Antibodies Endpoints

- Incidence of ADA and correlations with PK, safety and efficacy endpoints will be investigated across Part 1 to Part 3.

Methodology:

This is a randomized, double-blind, placebo-controlled, Phase 2a study. At least [redacted] subjects with active AS (Stage 1 of the study) and [redacted] subjects with active nr-axSpA (Stage 2 of the study) will be randomly assigned in a blinded fashion in a [redacted] ratio to receive either [redacted] tildrakizumab or placebo by [redacted] every [redacted] weeks ([redacted] Starting at [redacted] all subjects will receive [redacted] tildrakizumab administered [redacted] Recruitment for Stage 1 [redacted]) will begin upon study approval; recruitment for Stage 2 ([redacted]) will begin only upon written notification by

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the Sponsor to the Competent Authorities and Investigators.

[redacted]

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Subjects randomized to receive tildrakizumab during Part 1 of both stages of the study who achieve ASAS20 at [redacted] will receive treatment with [redacted] tildrakizumab [redacted] until [redacted]. Subjects receiving tildrakizumab during Part 1 who do not achieve ASAS20 at [redacted] will [redacted] e IMP treatment and enter the [redacted]. Subjects randomized to receive placebo during Part 1 who complete the Week 24 visit will continue to Part 2 and receive tildrakizumab [redacted] even if they do not achieve ASAS20.

Subjects discontinued from IMP at any time (apart from withdrawal of informed consent) will be required to complete the End of Treatment (EoT) [redacted] assessment a minimum of [redacted] after the last dose of IMP and enter the [redacted]. Subjects who withdraw from the study during Part 3 will [redacted] the [redacted] (End of Study [EoS]) assessments at [redacted] their last visit.

The primary endpoint for efficacy will be ASAS20 at [redacted] Secondary endpoints will include ASAS20 at Week 52; ASAS40 [redacted] and proportion of subjects who require adjustment of background therapy. The PK and immunogenicity of tildrakizumab will also be evaluated.

All sites will have an independent assessor to conduct tender and swollen joint counts, BASMI, and MASES assessments. The independent assessor will not be involved in the care of subjects and will not discuss disease activity or the treatment with subjects or the Principal Investigator (PI)/designee responsible for performing other efficacy and safety evaluations.

An interim analysis (IA) will be performed for futility assessment after data from [redacted] randomized subjects become available at [redacted]

Following the last subject's [redacted], an IA will be conducted on all available data to evaluate the primary efficacy outcome.

An independent Data Safety Monitoring Board (DSMB) will be established for periodic review of safety data, and a Clinical Adjudication Committee (CAC) will be established to evaluate cardiovascular events for this study.

The EoS is defined as the last visit of the 20-week wash-out period (EoS visit) of the last global subject.

This study will be conducted in compliance with the protocol and with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP).

Number of Subjects:

The sample size is approximately [redacted] subjects [redacted]

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion criteria:

Subjects may be included in the study if they meet all of the following criteria:

1. Subject has provided informed consent.
2. Subject is ≥ 18 years of age at time of Screening.
3. Definite AS based on the modified New York criteria (1984) with symptom duration of at least 3 months at Screening as defined by modified New York criteria (1984), or for nr-axSpA, a documented diagnosis of adult onset axial spondyloarthritis as defined by the specific ASAS criteria with at least 3 months symptom duration before Screening.
4. Subjects with nr-axSpA must have active inflammation (MRI) on Screening and no radiographic sacroiliitis that fulfils the 1984 modified New York criteria.
5. Active disease at Screening, defined as:

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– [redacted] and
– [redacted]

6. [redacted]

Tapering of any of these concomitant medications during the study is allowed only if there is toxicity (accompanied by recording of an AE on the electronic case report form [eCRF]); otherwise the dosage must remain the same throughout Part 1 of the study. Adjustment of concomitant medication is permitted throughout Part 2 [redacted] as needed [redacted] per Investigator discretion and therapeutic needs of the subject, or if the subject does not show minimal response to treatment (defined as [redacted] improvement from Baseline in pain [assessed by Total Back Pain VAS [redacted]] and inflammation [assessed using the last [redacted] stiffness assessments in the BASDAI]) at [redacted]

8. For subjects receiving NSAIDs ([redacted]): the subject must be on a stable dose for ≥ 4 weeks prior to initiation of IMP and be expected to maintain a stable dose for the first 24 weeks of the study, unless change in dosage is required due to toxicity. Stable dose ([redacted]) is defined as subjects taking an NSAID on average 4 days per week over the 4-week period prior to Screening.

9. [redacted]

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Exclusion Criteria:

Other medical conditions

1. Radiographic evidence of total ankylosis of the spine (defined by syndesmophytes present on the lateral views of spinal radiographs including intervertebral levels from T6 through S1; films will be read centrally).
2. Subjects with more than 16 fused cervical, thoracic and lumbar ankylosed discovertebral units (DVUs), anteriorly, posteriorly or both, that are radiographically diagnostically compatible with AS.
3. Subjects with evidence of bilateral SI joint fusion and 12 fused DVUs (per exclusion criterion 2 above).
4. Subjects with known diagnosis of fibromyalgia or complex regional pain syndromes.
5. Active uveitis or symptomatic inflammatory bowel disease requiring therapy at Screening.
6. Subject has a planned surgical intervention between Baseline and the Week 24 evaluation for a pre-treatment condition.
7. Subject has an active infection or history of infections as follows:
   - any active infection for which systemic anti-infectives were used within 28 days prior to first IMP dose, with the last dose having been received within 7 days of Screening,
   - any serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first investigational product dose, with the last dose having been received within 7 days of Screening,
   - recurrent or chronic infections, e.g., chronic pyelonephritis, chronic osteomyelitis, bronchiectasis, or other active infection that, in the opinion of the Investigator, might cause this study to be detrimental to the subject.
8. Major chronic inflammatory or connective tissue disease other than AS (e.g., psoriatic arthritis [PsA], rheumatoid arthritis, systemic lupus erythematosus, Lyme disease, and gout).
9. Subject has any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, or anemia) that, in the opinion of the Investigator, could cause this study to be detrimental to the subject.
10. Subject has known history of infection with hepatitis B, hepatitis C, or human immunodeficiency virus.
11. [redacted].
12. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
13. Subject has history of malignancy within 5 years EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, in situ cervical carcinoma, OR in situ breast ductal carcinoma.
14. Subjects with a history of alcohol or drug abuse in the previous 2 years.
15. [redacted]

Laboratory abnormalities

16. Subject has laboratory abnormalities at Screening, including any of the following:
   - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) [redacted] the upper limit of normal (ULN),
   - creatinine [redacted] ULN,

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- serum direct bilirubin [redacted],
- white blood cell (WBC) count [redacted],
- [redacted] test for rheumatoid factor,
- any other laboratory abnormality that, in the opinion of the Investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

Washouts and non-permitted drugs

17. Disease modifying anti-rheumatic drugs (DMARDs) other than NSAIDs, MTX or [redacted] must be discontinued 4 weeks prior to randomization, except for [redacted], which has to be discontinued for [redacted] prior to randomization ([redacted]
18. Subject has used any of the following within [redacted]:
    - high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine),
    - topical and parenteral corticosteroids including intramuscular or intraarticular administration,
    - live vaccines,
    - has a need for use of a live vaccine within 10 weeks of final dose of IMP.
19. [redacted]

General

20. Subject has known sensitivity to any of the products or any excipients to be administered during dosing.
21. Female subjects of childbearing potential must agree to abstain from heterosexual activity (as part of an existing lifestyle choice) or practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (eg, condom) if not surgically sterile (ie, vasectomy). Contraceptive methods must be practiced upon entering the study and through 16 weeks after the last dose of study treatment. If a subject discontinues prematurely, the contraceptive method must be practiced for 16 weeks following final administration of study drug. A follicle-stimulating hormone test should be performed to confirm menopause for those women with no menses for less than 1 year.
22. Female is pregnant or breast-feeding, or planning to become pregnant or initiate breast-feeding while enrolled in the study or up to 16 weeks after the last dose of IMP.
23. Subject will not be available for protocol-required study visits, to the best of the subject's and Investigator's knowledge.
24. [redacted]

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[redacted]

26. Subject has any kind of disorder that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent and/or comply with all required study procedures.
27. Donation or loss of [redacted] of blood within 8 weeks before dosing.
28. Subjects who have been placed in an institution on official or judicial orders.
29. Subjects who are related to or dependent on the Investigator, Sponsor, or study site such that a conflict of interest may arise.

Test Product, Dose and Mode of Administration:

Each pre-filled syringe (PFS) of IMP contains [redacted] of tildrakizumab and [redacted] of solution.

Placebo will be presented in identical containers with the same excipients (with no active drug) and stored/packaged the same as tildrakizumab.

Subjects will receive either [redacted] of tildrakizumab as [redacted] of [redacted] tildrakizumab, or [redacted] of placebo [redacted] until [redacted] Starting at [redacted], all subjects will receive [redacted] tildrakizumab administered [redacted].

Concomitant Medications, Supportive Care, and Study Restrictions:

The following restrictions will apply to all subjects during the study.

Concomitant medications limited throughout the study [redacted]

- Analgesics: Acetaminophen may be used by the subject [redacted] except within [redacted] before a scheduled study efficacy evaluation.

Concomitant medications will be limited during Part 1 of the study [redacted]) as follows:

- NSAIDs: For subjects receiving NSAIDs [redacted]): the subject must be on a stable dose for [redacted] prior to [redacted] of IMP and be expected to maintain a stable dose for the [redacted] of the study, unless change in dosage is required due to toxicity. Stable dose [redacted] is defined as subjects taking an NSAID on average [redacted] for the [redacted] period prior to Screening.
- Corticosteroids: Subjects taking oral corticosteroids (not to exceed the equivalent of 10 mg of prednisone per day) must remain on a stable dose.
- DMARDs: Subjects taking either MTX (not to exceed 25 mg/week) or sulfasalazine (up to 3 g a day) must remain on a stable dose, unless a decrease in dose is required because of toxicity or intolerance. Other DMARDs are not allowed and oral MTX cannot be changed to parenteral dosing during the period of observation. Subjects may not take MTX and sulfasalazine in combination.

Tapering of any of these concomitant medications during the study is allowed only if there is toxicity (accompanied by recording of an AE on the eCRF); otherwise the dosage must remain the same throughout Part 1 of the study. Adjustment of these concomitant medications is permitted throughout Part 2 [redacted] as needed per Investigator discretion and therapeutic needs of the subject, or if the subject does not show minimal response to treatment (defined as [redacted]t from Baseline in pain [assessed by Total Back Pain [redacted]] and inflammation [assessed using the last [redacted] assessments in the BASDAI]) at [redacted]

For subjects receiving non-drug therapy (including but not limited to physical therapy, massage, diet, exercise, emollients, and joint taping), this must be stable for the 4-week period prior to IMP initiation through to the end of Part 1.

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Statistical Methods:

Sample Size Calculation

In each subject cohort (AS and nr-axSpA), approximately [redacted] subjects will be randomized per arm in a [redacted] ratio to tildrakizumab [redacted] or placebo, stratified by anti-TNF use (yes/no). This sample size achieves [redacted] power (accounting for futility assessment) to detect a treatment effect in ASAS20 at [redacted] of [redacted] (placebo ASAS20 = [redacted]; tildrakizumab ASAS20= [redacted]). The test statistic used is the [redacted] Cochran-Mantel-Haenszel (CMH) test at the [redacted] significance level. A [redacted] drop-out rate has been assumed.

An interim analysis will be performed for futility assessment after data at Week 16 from 30 randomized subjects become available. Futility assessment will be based on a futility threshold of 12% (difference between response rates on active arm and placebo) at Week 16.

Statistical Analysis:

The primary efficacy analysis population will be the Full Analysis Set (FAS) defined as all randomized subjects who have received at least [redacted] of IMP. The primary analysis will be based on the CMH test, incorporating anti-TNF use as a stratification factor, to compare the response rates for the primary endpoint ASAS20 [redacted] between placebo and the active dose group within AS and nr-axSpA separately. In addition, the Mantel-Haenszel common risk (the response rate) difference between placebo and the active dose arm and corresponding confidence interval (CI) will be estimated. Should CMH assumptions per the Mantel-Fleiss criterion not be satisfied, the treatment comparison will be based on a Chi-square tests following collapsing of the strata. Early withdrawals or any other subjects with incomplete data at [redacted] will be classified as non-responders for the primary endpoint ASAS20. Subjects who fail to show minimal response to treatment (defined as [redacted] from Baseline in pain [assessed by Total Back Pain [redacted]] and inflammation [assessed using the last [redacted] assessments in the BASDAI]) at Week 16 may have their background medications adjusted according to the maximum permitted daily dose [redacted] and continue in the study. Any subject requiring these adjustments will be counted as a non-responder for the primary analysis.

Binary secondary and exploratory efficacy endpoints (e.g. other proportions) will be evaluated similarly.

Continuous efficacy endpoints measured at several post-Baseline time points will be analyzed based on a mixed model repeated measure (MMRM) analysis that will include fixed effects for treatment, visit, treatment by visit interaction, prior anti-TNF use and subject specific Baseline values. Continuous endpoints measured once post-Baseline will be evaluated based on an Analysis of Covariance (ANCOVA) with terms for treatment, prior anti-TNF use, and subject specific Baseline values.

Efficacy analyses will be based on randomized treatment assignments.

Safety endpoints will be analyzed descriptively based on the Safety Analysis Set, defined as all subjects who received at least [redacted] dose of IMP. Subjects will be summarized based on the actual treatment they received.

A DSMB will be established for periodic review of safety data for this study.

Following the last subject's [redacted], an IA will be conducted on all available data to evaluate the primary efficacy outcome.

Date of the Protocol: 14 June 2017

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP	Anterior-posterior
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AS	Ankylosing Spondylitis
ASQoL	Ankylosing Spondylitis Quality of Life questionnaire
ASspiMRI	Ankylosing Spondylitis spine Magnetic Resonance Imaging
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BME	Bone marrow edema
β-hCG	Beta human chorionic gonadotrophin
CAC	Clinical Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
C_{min}	Minimum concentration
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DMARD	Disease modifying anti-rheumatic drug
DSMB	Data Safety Monitoring Board
DVU	Discovertebral unit
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End of study
EoT	End of treatment

ESR	Erythrocyte sedimentation rate
EU	European Union
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
FACIT	Functional assessment of chronic illness therapy
FDA	Food and Drug Administration
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HLA	Human leukocyte antigen
hsCRP	High-sensitivity C-reactive protein
IA	Interim analysis
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice recognition system
LATAM	Latin America
MACE	Major adverse cardiovascular events
MASES	Maastricht ankylosing spondylitis enthesitis score
MMRM	Mixed model repeated measure
MRI	Magnetic resonance imaging
MTX	Methotrexate
N	Number
NOAEL	No observed adverse effect level
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PA	Posterior-anterior
PASI	Psoriatic Area Severity Index
PD	Pharmacodynamic

PGA	Physician's Global Assessment
PFS	Pre-filled syringe
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-Protocol
PPAS	Per-Protocol Analysis Set
PRN	As needed
PQC	Product quality complaint
PsA	Psoriatic arthritis
PsO	Plaque psoriasis
PtGA	Patient's Global Assessment
q	Every
QoL	Quality of life
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous
SD	Standard deviation
SF-36	Short form 36
SI	Sacroiliac
SIB	Suicidal ideation and behavior
SJC44	Swollen joint count of 44 joints
SOP	Standard operating procedure
SpA	Spondyloarthritis
SPARCC	SpondyloArthritis Research Consortium of Canada
$T_{1/2}$	Half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC46	Tender joint count of 46 joints
T_{max}	Time of maximal concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
UK	United Kingdom

US	United States
VAS	Visual analog scale
WBC	White blood cell

7 INTRODUCTION

7.1 Background

Tildrakizumab (anti-interleukin [IL]-23 humanized monoclonal antibody), also known as SCH 900222 or MK-3222, is a high-affinity (297 pM) humanized immunoglobulin G1 (IgG1)/κ antibody. Tildrakizumab specifically binds to the p19 protein of the IL-23 heterodimer but does not bind human IL-12 (IL-12p40 and p35 heterodimer) or human p40.[1]

The IL-23/IL-17 axis has been studied in ankylosing spondylitis (AS), and both cytokines are implicated in AS disease activity. In view of the efficacy of the anti-IL-17 secukinumab in AS and the data emerging on the efficacy of anti-IL-12/23 monoclonal antibodies in AS, it is expected that tildrakizumab will also demonstrate efficacy in this population via its targeting the IL-23 component of this axis, which is upstream of IL-17. Furthermore, by not blocking IL-12, it is anticipated that tildrakizumab may potentially avoid adverse effects on cell-mediated immunity, where IL-12 has an important role.

Tildrakizumab is being developed for chronic plaque psoriasis (PsO), and Phase 3 studies have recently been unblinded, with subjects continuing in the long-term open-label extension. The Phase 3 doses in PsO were [redacted] thereafter. In the Phase 2b study (Protocol P05495) for PsO, all [redacted] dose levels [redacted] administered at [redacted] thereafter) were demonstrated to be safe and more efficacious than placebo (primary endpoint of Psoriasis Area and Severity Index [PASI]75 at [redacted]). A subset of subjects in the tildrakizumab PsO Phase 2b study also had psoriatic arthritis (PsA) and received additional assessments to evaluate efficacy related to PsA. These data suggest that for tildrakizumab, clinically effective doses for PsO are also potentially effective in PsA, a spondyloarthropathy that is related to AS.

Further information relating to efficacy and safety data from clinical trials of tildrakizumab is available in the Investigator's Brochure (IB).

The proposed Phase 2 study in subjects with AS and non-radiographic axial spondyloarthritis (nr-axSpA), a related indication that includes patients who do not meet the diagnostic criteria for AS, will be the first clinical study of tildrakizumab in these subject populations.

7.2 Rationale for Dose Selection

The proposed tildrakizumab dose is [redacted] then every [redacted] hereafter. Tildrakizumab [redacted] represents a dose that should provide robust suppression of the IL-23 pathway in order to safely test the hypothesis that IL-23 signaling is important for disease activity in AS and nr-axSpA.

The dose of [redacted] has not been used previously in clinical studies; however, the predicted (area under the curve [AUC]$_{0\text{-}4wks}$) exposure for subjects is lower than that tested in Phase 1 studies (using a different dosing frequency) and offers a [redacted] based

upon the relevant non-clinical toxicology studies. The estimated safety margin was derived from the systemic exposure at the no observed adverse effect-level (NOAEL) dose [redacted] in the 9-month repeat-dose primate toxicology study, and the human exposures obtained from the Phase 1 studies. At the NOAEL dose, the tildrakizumab exposure (AUC_{0-14d}) was [redacted]. The human exposure at steady-state for the Phase 2/3 dosing paradigm (once q12 weeks) was estimated by the observed exposure of $AUC_{0-\infty}$ [redacted] following a [redacted] single dose of [redacted] in Phase 1 clinical studies (P05776 and P06303), respectively. For the Phase 2/3 studies in PsO, the NOAEL AUC was multiplied by the number of doses [redacted] the monkeys received during the [redacted] dosing interval used in the PsO Phase 2/3 studies. Hence the most conservative exposure multiple for the Phase 2/3 PsO studies of [redacted] For the dosing paradigm of [redacted] s, the monkeys were dosed 2 times for each human dose, hence the exposure multiple is [redacted].

For reference, the AUC0-∞ values observed in Phase 1 studies P05661 and P06303 at exposures higher than those associated with [redacted] were [redacted] ([redacted]

Tildrakizumab [redacted] administered [redacted] is the highest dose tested in the PsO dose-range finding study [redacted] and the PsO Phase 3 studies. To date, tildrakizumab has been well tolerated at doses up to [redacted] and no dose-related toxicities have been observed. As discussed, tildrakizumab [redacted] is anticipated to exhibit a similar safety profile. Moreover, administration of tildrakizumab [redacted], as opposed to [redacted], is expected to result in higher serum trough levels, just before the next dose, yielding more consistent suppression of IL-23 throughout the entire dosing interval, which may prove to be important for the effective treatment of AS.

7.3 Rationale and Study Purpose

This will be the first study conducted with tildrakizumab in subjects with AS and nr-axSpA. As tildrakizumab is in development (Phase 3 completed, long-term safety studies ongoing) for the PsO indication, substantial pharmacokinetic (PK) and pharmacodynamics data exist that can inform dose selection in AS, as described. Under these circumstances, the next step for development is to evaluate efficacy and safety in the AS population. The purpose of this study is to determine if tildrakizumab, by suppressing the IL-23 pathway, can reduce disease activity in subjects with AS or nr-axSpA, as determined by the Assessment of SpondyloArthritis international Society (ASAS) criteria defined as [redacted] in 3 of 4 assessment domains (ASAS20) responder rate, compared to placebo. The study will also provide safety and tolerability information for tildrakizumab in these patient populations.

8 STUDY OBJECTIVES

8.1 Primary Efficacy Objective

Part 1

- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects achieving ASAS20 response criteria at Week 24.

Hypothesis: tildrakizumab is superior to placebo in the treatment of AS and nr-axSpA, as measured by the proportion of subjects achieving ASAS20 response at Week 24.

8.2 Primary Safety Objective

Parts 1 and 2

- To assess the safety/tolerability and immunogenicity of tildrakizumab in subjects with AS or nr-axSpA.

8.3 Secondary Objectives

Parts 1 and 2

Secondary objectives for Part 2 of the study are:

- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects achieving ASAS20 response criteria at Week 52, ASAS40 response criteria at Weeks 24 and 52, and proportion of subjects who require adjustment of background therapy.
- To characterize the PK of tildrakizumab in subjects with AS or nr-axSpA.

8.4 Exploratory Objectives

Parts 1 and 2

The exploratory objectives for Parts 1 and 2 of the study are:

- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects who achieve ASAS20 or ASAS40 at other measured time points.
- To evaluate the efficacy of tildrakizumab in subjects with AS or nr-axSpA, as measured by the proportion of subjects who achieve ASAS70 or ASAS5/6.
- To evaluate the efficacy of tildrakizumab in subjects with AS of nr-axSpA, as measured by the change from Baseline in ASAS components, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL), Visual Analog Scale (VAS) (total back pain and nocturnal pain score), Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-reactive protein (CRP),

ASDAS-erythrocyte sedimentation rate (ESR), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), short form 36 (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue, high-sensitivity CRP (hs)CRP, SpondyloArthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Index of Disease Activity of the Sacroiliac (SI) Joints, SPARCC MRI Index of Disease Activity of the Spine, and Modified Berlin Ankylosing Spondylitis Spine Magnetic Resonance Imaging Activity Score (ASspiMRI), swollen joint count of 44 joints (SJC44), and tender joint count of 46 joints (TJC46) at measured time points.

- To evaluate the tildrakizumab exposure/response relationship.

Part 3

The exploratory objectives for Part 3 of the study are:

- To assess the effect of investigational medicinal product (IMP) discontinuation on ASAS20, ASAS50, ASAS70, ASAS5/6, ASAS components, BASDAI, BASMI, BASFI, VAS (total back pain and nocturnal pain score), MASES, SF-36, FACIT-fatigue, TJC46, and SJC44 at measured time points.
- To evaluate immunogenicity following IMP discontinuation.
- To characterize the PK of tildrakizumab in subjects with AS or nr-axSpA following IMP discontinuation.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a randomized, double-blind, placebo-controlled, Phase 2a study. The study will be multinational and performed in approximately [redacted] study centers. At least [redacted] subjects with active AS (Stage 1 of study) and [redacted] subjects with active nr-axSpA (Stage 2 of study) will be randomly assigned in a blinded fashion in a [redacted] ratio to receive either [redacted] tildrakizumab or placebo by [redacted] Starting at [redacted] all subjects will receive [redacted] tildrakizumab administered [redacted] until [redacted] A flow diagram of the study design is presented in [redacted]. Recruitment for Stage 1 (subjects with AS) will begin upon study approval; recruitment for Stage 2 (subjects with nr-axSpA) will begin only upon written notification by the Sponsor to the Competent Authorities and Investigators.

Each stage of the study will consist of a Screening period [redacted], a double-blind, placebo-controlled period [redacted] Part 2, a [redacted] period [redacted] and Part 3, a [redacted]). The Sponsor and some [redacted] members not directly related to the clinical conduct of the study will be unblinded during Part 2. Investigational sites and subjects will remain blinded to individual study treatment assignments until the last subject completes the study ([redacted] During the washout period subjects will no longer receive tildrakizumab and will be treated according to the physicians' discretion.

Randomization will be stratified by prior anti-tumor necrosis factor (TNF) use (yes, no). Subjects with prior anti-TNF use will be capped at [redacted] the total number of subjects.

Subjects who fail to show minimal response to treatment [redacted] and inflammation [assessed using the [redacted]]) at [redacted] in both stages of the study may have their background medications adjusted according to the maximum permitted daily dose (see inclusion criterion 7) and continue in the study.

Subjects randomized to receive tildrakizumab during Part 1 of both stages of the study who achieve ASAS20 at [redacted] receive treatment with [redacted] tildrakizumab [redacted] until [redacted] Subjects receiving tildrakizumab during Part 1 [redacted] will discontinue IMP treatment and enter the [redacted]. Subjects randomized to receive placebo during Part 1 of both stages of the study who complete the Week 24 visit will continue to Part 2 and receive tildrakizumab [redacted] until [redacted] even if they do not achieve ASAS20. Subjects discontinued from IMP at any time (apart from withdrawal of informed consent) will be required to complete the End of Treatment (EoT) [redacted] a minimum of [redacted] after the last dose of IMP and enter the [redacted]

washout period. Subjects who withdraw from the study during Part 3 will undergo the [redacted] (End of Study [EoS]) assessments at [redacted] after their last visit.

The primary endpoint for efficacy will be ASAS20 at [redacted] Secondary endpoints will include ASAS20 at [redacted] ASAS40 at [redacted]; and the proportion of subjects who require adjustment of background therapy. The PK and immunogenicity of tildrakizumab will also be evaluated.

All sites will have an independent assessor to conduct the assessments detailed in [redacted]. The independent assessor will not be involved in the care of subjects and will not discuss disease activity or the treatment with subjects or the Principal Investigator (PI)/designee responsible for performing other efficacy and safety evaluations.

An interim analysis (IA) will be performed for futility assessment after data from [redacted] randomized subjects become available at [redacted]

Following the last subject's [redacted], an IA will be conducted on all available data to evaluate the primary efficacy outcome.

A Data Safety Monitoring Board (DSMB) will be established for periodic review of safety data for this study, and a Clinical Adjudication Committee (CAC) will be established to evaluate cardiovascular events [redacted]

Central review of radiographs used for inclusion/exclusion (except chest X-rays for tuberculosis [TB] evaluation, where applicable) will be performed to ensure consistent assessment across sites. Scoring of MRI data collected throughout the study will be conducted by a central reader who will be blinded to the time sequence and subject treatment.

The EoS is defined as the last visit of the [redacted] of the last global subject.

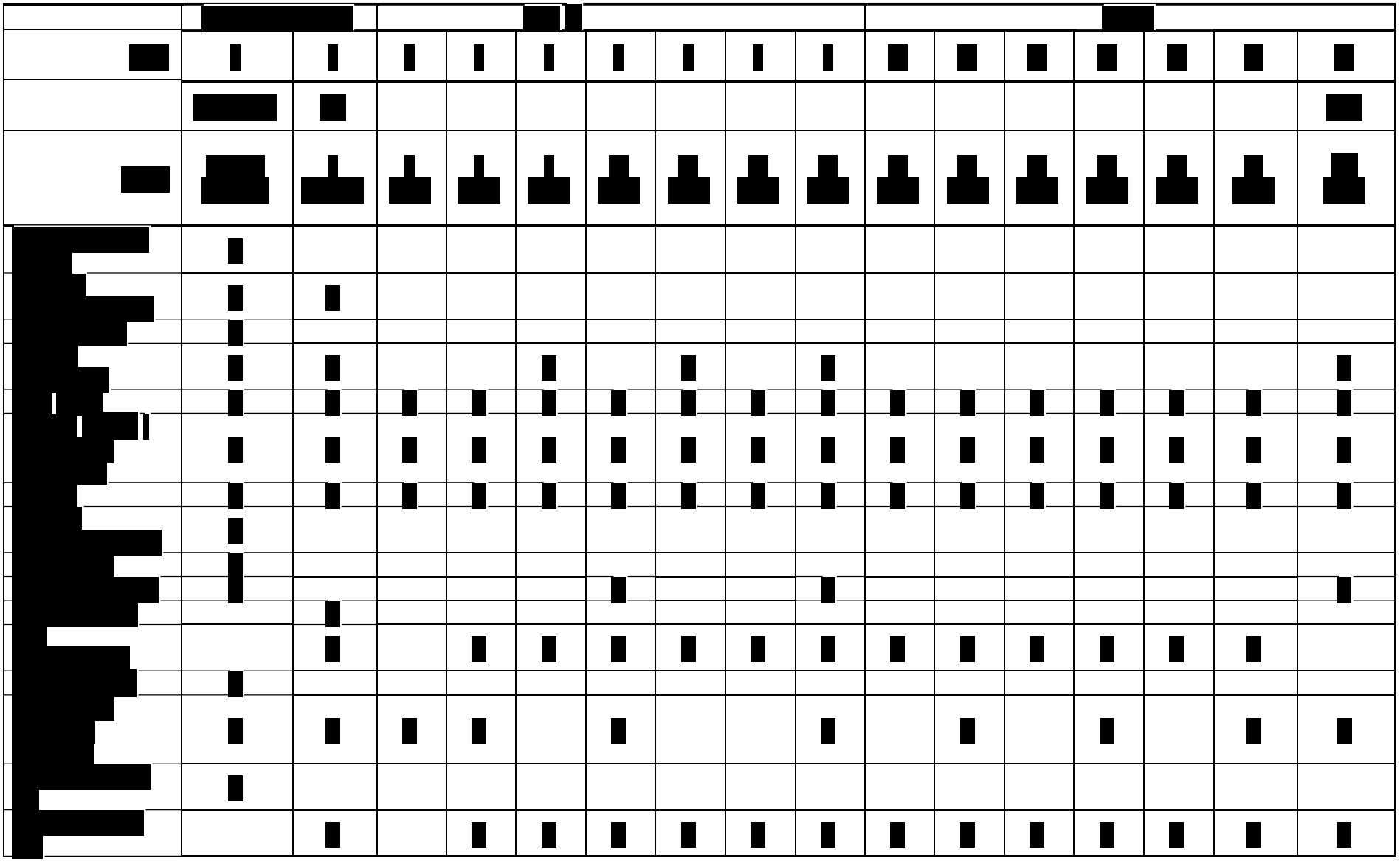
This study will be conducted in compliance with the protocol and with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP).

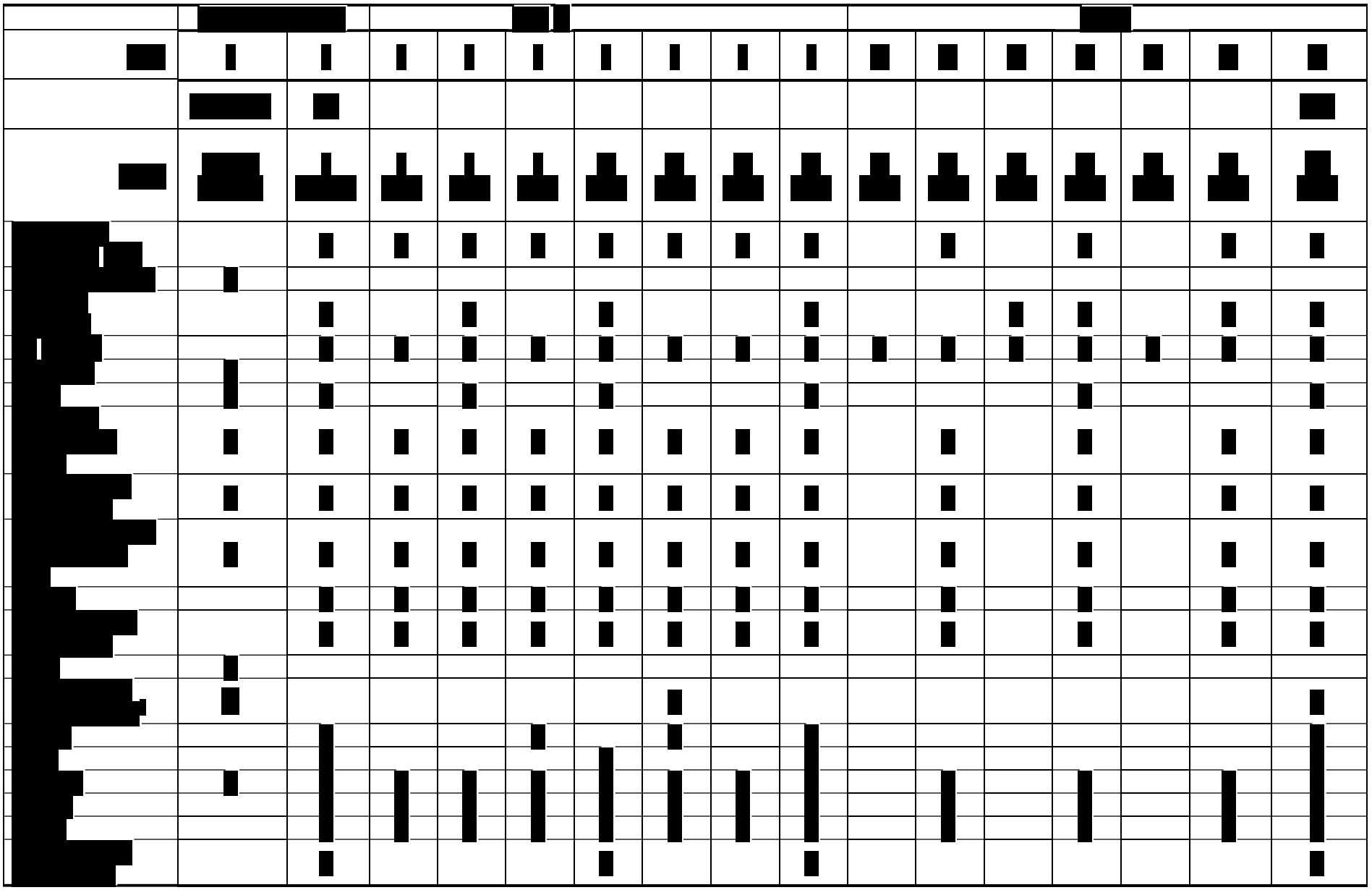
[redacted]

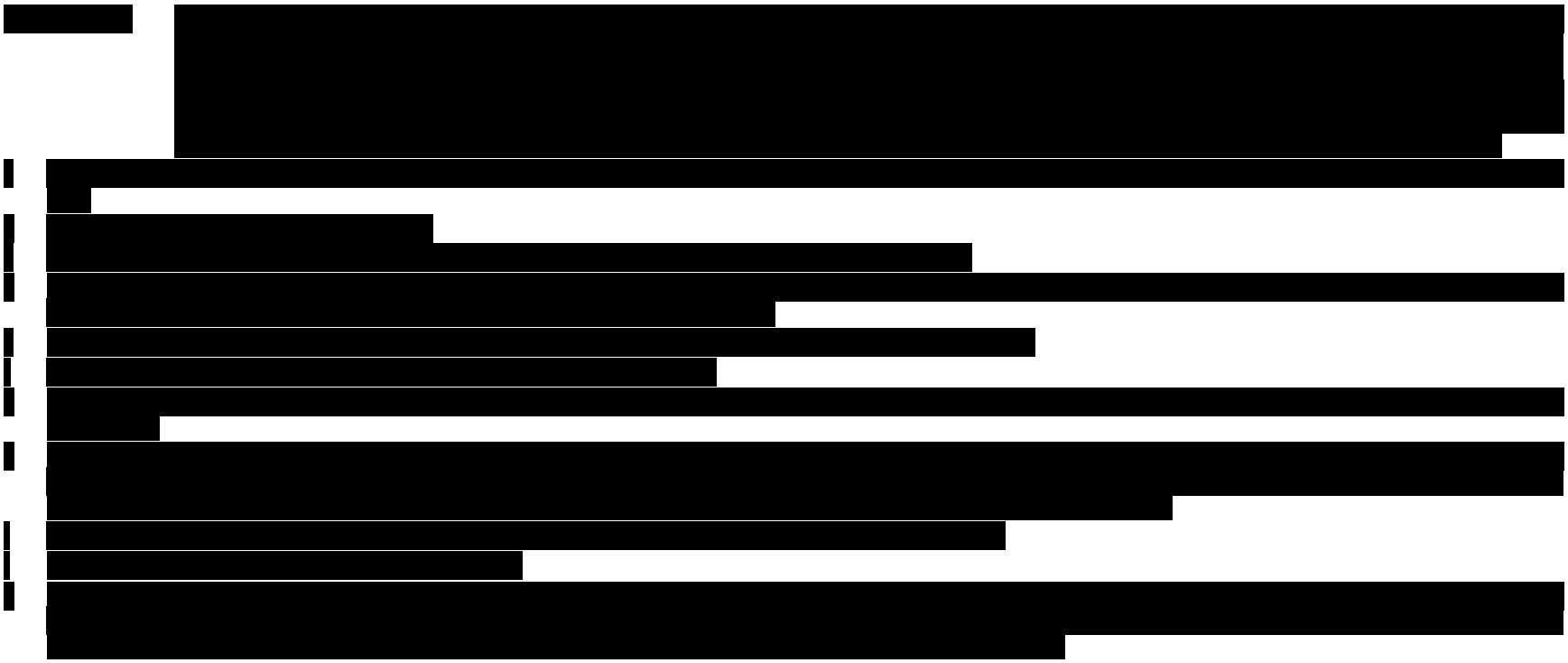
9.1.2 Schedule of Assessments

The Schedule of Assessments is presented in [redacted] and is applicable to both Stage 1 and Stage 2 of the study.

Table 9–1 [redacted]







[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]

[redacted]

9.1.2.1 Blood Samples for Determination of Anti-Drug Antibodies (ADA)

A sample of blood to obtain sufficient serum for ADA determination will be collected prior to IMP administration at the specified time points in [redacted] The sample will be collected into appropriate tubes (see laboratory manual for sample volumes, acquisition, shipping and labeling instructions). Sample collection times are to be recorded in the electronic case report form (eCRF).

Sample collection time deviations will be determined by the Sponsor using the actual collection times provided and do not need to be recorded in the eCRF. However, any other deviation (e.g. missed sample, broken sample, inappropriate sample handling, etc.) must be recorded on the comments page of the eCRF.

9.1.2.2 Blood Samples for Determination of Serum Concentrations of Tildrakizumab (PK)

A blood sample to obtain sufficient serum for PK assessment will be collected prior to IMP administration at specified time points indicated in [redacted] The sample will be collected into the appropriate tubes (see laboratory manual for sample volumes, acquisition, shipping and labeling instructions). Actual sample collection times are to be recorded on the eCRF.

Samples for both PK and ADA should be collected pre-dose.

9.1.3 Study Assessments

[redacted]

[redacted]

[redacted] all test results are available, the Sponsor should be consulted to confirm if this is acceptable.

[redacted]

[redacted]

- [redacted]

[redacted] window can be extended, with approval by the Sponsor, to allow completion of the MRI.

Further details of radiographs and MRI are provided in the Imaging Manual.

Laboratory assessments may be repeated once for any laboratory parameter that falls within the relevant exclusion criteria provided they are completed within the 4-week period. The repeat laboratory test finding will be used for any decision regarding subject eligibility.

Clinic personnel must contact the [redacted] Medical Advisor if they wish to re-screen a subject. Such requests will be handled on a case-by-case basis, in discussion with the Sponsor's Regional Clinical Lead or a delegate where necessary, and will only be allowed once per subject. The decision on allowing the re-screening or not will be documented in an email sent to the clinic personnel and the relevant members of the Sponsor and [redacted] team. A re-screened subject will receive a new subject number and will undergo full re-screening; all laboratory tests should be performed again. However, repeat QuantiFERON testing is not required if the result was negative at first Screening; additional chest X-rays and MRIs are not required if the previous tests were performed in the last [redacted] months; and additional spine and SI joint X-rays are not required if performed within the last [redacted] months. There is not a study-specific re-screening form for this study. Any subject who is started on prophylactic treatment for latent TB during the Screening period may be randomized [redacted] weeks after initiation of treatment without the need for re-screening. This process is also included in the [redacted] plan and communicated to the clinic personnel at study initiation visits and at the Investigator meeting.

Baseline assessments (prior to IMP administration)

- Record physical examination findings and concomitant medications.
- Check inclusion/exclusion criteria (e.g., results of tests performed at Screening and Baseline).
- Perform a urine pregnancy test (at the site using materials supplied by the central laboratory).
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
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  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]

9.1.3.2 Double-Blind Treatment Period

Following randomization, subjects will receive their dose of IMP

During the k double-blind, placebo-controlled period, all subjects will receive tildrakizumab or placebo as described in

- Perform safety assessments including:
  - will be performed at the site using materials supplied by the central laboratory),

[redacted]

9.1.3.5 Unscheduled Visits

An unscheduled visit is defined as any visit to the Investigator site outside of the Protocol-specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, confirmation of out-of-range results), where the subject is seen by study personnel.

All unscheduled visits and assessments performed during the visits will be recorded in the subject's eCRF. During any unscheduled visits the Investigator will record any AEs and concomitant medications as well as performing any assessments or collecting samples deemed necessary at the discretion of the Investigator.

9.2 Discussion of Study Design

This is a randomized, double-blind, placebo-controlled, Phase 2a study designed to evaluate the efficacy and safety of tildrakizumab in subjects with AS (Stage 1 of the study) or nr-axSpA (Stage 2 of the study), a related indication. The primary efficacy endpoint is based on the proportion of subjects achieving ASAS20 at [redacted] which is well established for the evaluation of clinical outcome. Secondary endpoints are based on the proportion of subjects achieving ASAS20 at Week 52, ASAS40 at Weeks 24 and 52, proportion of subjects who require adjustment of background medication, and on evaluation of PK parameters.

The study has been designed with [redacted] phases [redacted] for both [redacted] of the study. This enables scientific evaluation of efficacy at [redacted], a longer evaluation of safety and efficacy through [redacted], and ensures subject safety via a monitored [redacted] period. All safety measures are consistent with evaluations used in clinical studies and previous studies with tildrakizumab.

9.2.1 Risk/Benefit and Ethical Assessment

As this is the first study in patients with AS and nr-axSpA the benefits of tildrakizumab in these patient populations remains uncertain. Given that efficacy benefits were reported for subjects with concurrent PsA in the completed Phase 2b study in PsO (Protocol PO5495), there is an expectation that subjects treated with tildrakizumab may experience improvement in AS and

nr-axSpA disease activity as these conditions are related to PsA. However, the study design allows early identification of subjects who have not received a minimum level of improvement at [redacted] to enable the Investigator to adjust background therapy or remove IMP and initiate other treatment at their discretion.

The study has also been designed to minimize potential risks to subjects; all subjects will undergo Screening procedures aimed at reducing the likelihood and impact of any such risks. Radiographs used for inclusion/exclusion at Screening will be read centrally to ensure consistent assessment across sites. In addition, regular safety monitoring during the treatment period for all subjects will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately. In view of the long half-life ($T_{1/2}$) of tildrakizumab at doses previously studied, subjects will continue to be monitored throughout a [redacted] period following the [redacted] visit, during which no active IMP will be administered and subjects can receive other treatments at the Investigator's discretion.

In addition, an independent DSMB will review selected data across the study. The DSMB in conjunction with the Sponsor is empowered to make recommendations regarding continuation, termination or modification of the study, as appropriate.

Overall, based on data from non-clinical and clinical studies of tildrakizumab to date and the risk minimization strategies discussed above, the risk:benefit profile of the current study is considered acceptable.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Subject has provided informed written consent
2. Subject is ≥ 18 years of age at time of Screening.
3. Definite AS based on the modified New York criteria (1984) with symptom duration of at least 3 months at Screening as defined by modified New York criteria (1984), or for nr-axSpA, a documented diagnosis of adult onset axial spondyloarthritis as defined by the specific ASAS criteria with at least 3 months symptom duration before Screening (see Appendix 1 for defined AS and nr-axSpA diagnostic criteria).
4. Subjects with nr-axSpA must have active inflammation (MRI) on Screening and no radiographic sacroiliitis that fulfils the 1984 modified New York criteria.
5. Active disease at Screening, defined as:
   - BASDAI score of at[redacted] and

[redacted]

6. [redacted]

[redacted]

Tapering of any of these concomitant medications during the study is allowed only if there is toxicity (accompanied by recording of an AE on the eCRF); otherwise the dosage must remain the same throughout Part 1 of the study. Adjustment of concomitant medication is permitted throughout Part 2 ([redacted] as needed per Investigator discretion and therapeutic needs of the subject, or if the subject does not show minimal response to treatment (defined as [redacted] improvement from Baseline in pain [assessed by Total Back Pain VAS [redacted]] and inflammation [assessed using the last [redacted] stiffness assessments in the BASDAI]) at [redacted]

8. For subjects receiving NSAIDs [redacted] the subject must be on a stable dose for ≥ 4 weeks prior to initiation of investigational product and be expected to maintain a stable dose for the first 24 weeks of the study, unless change in dosage is required due to toxicity. Stable dose [redacted]) is defined as subjects taking an NSAID on average 4 days per week for the 4-week period prior to Screening.

9. [redacted]

[redacted]

9.3.2 Exclusion Criteria

Subjects should be excluded from the study if they meet any of the following criteria:

Other medical conditions

1. Radiographic evidence of total ankylosis of the spine (defined by syndesmophytes present on the lateral views of spinal radiographs including intervertebral levels from T6 through S1; films will be read centrally).
2. Subjects with more than 16 fused cervical, thoracic and lumbar ankylosed discovertebral units (DVUs), anteriorly, posteriorly or both, that are radiographically diagnostically compatible with AS.
3. Subjects with evidence of bilateral SI joint fusion and 12 fused DVUs (per exclusion criterion 2 above).
4. Subjects with known diagnosis of fibromyalgia or complex regional pain syndromes.
5. Active uveitis or symptomatic inflammatory bowel disease requiring therapy at Screening.
6. Subject has a planned surgical intervention between Baseline and the Week 24 evaluation for a pre-treatment condition.
7. Subject has an active infection or history of infections as follows:
   - any active infection for which systemic anti-infectives were used within 28 days prior to first IMP dose, with the last dose having been received within 7 days of Screening,
   - any serious infection, defined as requiring hospitalization or IV anti-infectives within 8 weeks prior to the first investigational product dose, with the last dose having been received within 7 days of Screening,
   - recurrent or chronic infections, e.g., chronic pyelonephritis, chronic osteomyelitis, bronchiectasis, or other active infection that, in the opinion of the Investigator, might cause this study to be detrimental to the subject.

8. Major chronic inflammatory or connective tissue disease other than AS (e.g., PsA, rheumatoid arthritis, systemic lupus erythematosus, Lyme disease, and gout).
9. Subject has any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, or anemia) that, in the opinion of the Investigator, could cause this study to be detrimental to the subject.
10. Subject has known history of infection with hepatitis B, hepatitis C, or human immunodeficiency virus.
11. [redacted]
12. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
13. Subject has history of malignancy within 5 years EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, in situ cervical carcinoma, OR in situ breast ductal carcinoma.
14. Subjects with a history of alcohol or drug abuse in the previous 2 years.
15. [redacted]

Laboratory abnormalities

16. Subject has laboratory abnormalities at Screening, including any of the following:
    - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) [redacted] the upper limit of normal (ULN),
    - creatinine [redacted] ULN,
    - serum direct bilirubin [redacted]
    - white blood cell (WBC) count [redacted]
    - positive test result for rheumatoid factor,
    - any other laboratory abnormality that, in the opinion of the Investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

Washouts and non-permitted drugs

17. Disease modifying anti-rheumatic drugs (DMARDs) other than NSAIDs, MTX or [redacted] must be discontinued 4 weeks prior to randomization, except for [redacted],

which has to be discontinued for [redacted] prior to randomization [redacted]

18. Subject has used any of the following within [redacted]
    - high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine),
    - topical and parenteral corticosteroids including intramuscular or intraarticular administration, live vaccines,
    - has a need for use of a live vaccine within 10 weeks of final dose of IMP.

[redacted]

General

20. Subject has known sensitivity to any of the products or any excipients to be administered during dosing.
21. Female subjects of childbearing potential must agree to abstain from heterosexual activity (as part of an existing lifestyle choice) or practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (eg, condom) if not surgically sterile (ie, vasectomy). Contraceptive methods must be practiced upon entering the study and through 16 weeks after the last dose of study treatment. If a subject discontinues prematurely, the contraceptive method must be practiced for 16 weeks following final administration of study drug. A FSH test should be performed to confirm menopause for those women with no menses for less than 1 year.

22. Female is pregnant or breast-feeding, or planning to become pregnant or initiate breast-feeding while enrolled in the study or up to 16 weeks after the last dose of IMP.
23. Subject will not be available for protocol-required study visits, to the best of the subject's and Investigator's knowledge.
24. [redacted]
25. [redacted]
26. Subject has any kind of disorder that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent and/or comply with all required study procedures.
27. Donation or loss of [redacted] of blood within 8 weeks before dosing.
28. Subjects who have been placed in an institution on official or judicial orders.
29. Subjects who are related to or dependent on the Investigator, Sponsor, or study site such that a conflict of interest may arise.

9.3.3 Strategies for Subject Recruitment and Retention

All recruitment material will be approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to implementation.

Regular study monitoring will enable identification of any potential issues related to subject retention.

9.3.4 Withdrawal of Subjects

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a subject does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study-related contact, or allow analysis of already obtained biologic material.

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information on the treatment disposition eCRF page. If the subject decides to completely withdraw from the study (refuses any further study participation or contact), all study participation for that subject will cease and data to be collected at subsequent visits will be considered missing. Investigational treatments must be discontinued and no further assessments conducted. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

However, for safety reasons, [redacted] assessments should be conducted for subjects withdrawing during [redacted] if the withdrawn subject is willing to undergo the assessments. For subjects withdrawing during [redacted] and willing to undergo final assessments, the [redacted] assessments should be conducted at least [redacted] after their [redacted]

The appropriate personnel from the site and [redacted] will assess whether investigational treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

The Investigator must also contact the interactive response technology (IRT) to register the subject's discontinuation from investigational treatment.

9.3.5 Investigational Medicinal Product Discontinuation

Subjects may voluntarily discontinue IMP for any reason at any time and enter the [redacted], or completely withdraw from the study [redacted] Subjects who consent to enter the washout period will undergo the [redacted] assessments a minimum of [redacted] after administration of the [redacted] of IMP.

The Investigator should discontinue investigational treatment of a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Investigational treatment must be discontinued under the following circumstances and the further steps need to be discussed with the medical monitor:

[redacted]

Reasons for Temporary Discontinuation of Study Drug

Study drug dosing may be temporarily suspended in the event of:

[redacted]

After a laboratory abnormality leading to suspension of dosing normalizes sufficiently, study treatment may resume at the discretion of the PI in consultation with the medical monitor. Similarly, study treatment may resume after the medication leading to suspension of dosing is discontinued. A decision to discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. The Investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

9.3.6 Continued Study Participation

The Investigator must determine the primary reason for the subject's premature discontinuation of investigational treatment and record this information on the treatment disposition eCRF page. The Investigator and study staff must discuss with the subject, the subject's continued participation in the study and request subjects to continue attending follow-up study visits according to the study visit schedule.

9.3.7 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes or emails (not performed on the same day), as well as a lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death and as much other information as can be obtained, including post-mortem reports.

Data to be collected at subsequent visits will be considered missing.

9.3.8 Discontinuation of Study Sites

Study site participation may be discontinued if Sun Pharma Global FZE or designee, the Investigator or IRB/IEC of the study site judges it necessary for medical or safety reasons consistent with applicable laws, regulations and GCP.

9.3.9 Discontinuation of Study

The study will be discontinued if Sun Pharma Global FZE or designee, including through DSMB recommendation, judges it necessary for medical, safety, or business reasons consistent with applicable laws, regulation and GCP.

10 TREATMENT OF SUBJECTS

10.1 Identity of Study Treatment(s)

10.1.1 Administration of Study Treatment(s)

Subjects will receive either [redacted] of tildrakizumab as [redacted] of [redacted] tildrakizumab, or [redacted] of placebo [redacted]. Starting at [redacted] all subjects will receive [redacted] tildrakizumab administered [redacted] until [redacted].

If a subject misses a visit and/or a scheduled dose of IMP, the site must reschedule a visit to ensure the dose of IMP is taken as soon as possible within the visit window. If after 2 attempts to reschedule, the subject is still unable to take the dose, the Sponsor should be contacted to determine if the subject should be discontinued from the study.

10.2 Study Treatment Packaging and Labeling

10.2.1 Packaging

Each pre-filled syringe (PFS) of IMP contains [redacted] of solution. A PFS of tildrakizumab contains [redacted]/mL) of active drug.

Placebo will be presented in identical containers with the same excipients (with no active drug) and stored/packaged the same as tildrakizumab.

10.2.2 Labeling

Medication labels will comply with the legal requirements of each country and be printed in the local language. They will supply no information about the subjects.

10.2.3 Storage

All drug supplies for this study must be stored under refrigerated conditions [redacted] and according to labeled storage conditions. Until dispensed for administration to subjects, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

10.2.4 Blinding and Randomization of Study Treatment(s)

Both Stage 1 and Stage 2 of this study will be performed as a randomized, double-blind study stratified by prior anti-TNF use [redacted] Subjects will be randomized according to a list produced by [redacted]. Prior to production, the randomization specification will be reviewed and agreed by the study team (Sponsor [redacted] As block size is considered potentially unblinding information, it will be known to the Study Biostatistician only.

An [redacted] will be responsible for the allocation of randomization numbers to individual subjects. Randomization will take place at [redacted] after confirmation that the subject continues to meet the inclusion/exclusion criteria

[redacted] Subjects will be randomized [redacted] either tildrakizumab [redacted] or placebo, administered by [redacted].

A copy of the [redacted] with true treatment allocations will be held by [redacted] during the study. Another [redacted] list (containing [redacted] and [redacted]) will be provided to clinical supplies. The randomization codes associated with each subject will be disclosed to PK analysts who will keep PK results confidential until database lock.

Should a situation arise where unblinding is required, the Investigator at that site may perform immediate unblinding via the [redacted] without the need for communication with the Sponsor. This can only occur in emergency situations [redacted]

At the time of the IA, a specified team of personnel will be unblinded to allow reporting of the primary objective at [redacted]

The following assessments will be performed by an independent joint assessor:

- [redacted]
- [redacted]
- [redacted]

The PGA of disease activity will be performed by the treating physician. All other assessments will be administered by the study co-ordinator or PI/designee [redacted]

10.3 Procedure for Breaking the Randomization Code

Following the last subject's [redacted] visit [redacted] an IA will be conducted on all available data to evaluate the primary efficacy outcome.

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency code breaks are performed using the [redacted]. When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The Investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the [redacted], the medical monitor, and the [redacted] Project Manager that the [redacted] has been broken, but no treatment assignment will be communicated.

It is the Investigator's responsibility to ensure that there is a procedure in place to allow access to the [redacted] in case of emergency. The Investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The Investigator will provide the

protocol number, investigational treatment name if available, subject number, and instructions for contacting the local entity which has responsibility for emergency code breaks to the subject in case an emergency treatment code break is required at a time when the Investigator and backup are unavailable.

10.4 Subject Compliance

The dosage, timing and mode of administration of study medication may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

Study medication accountability and subject compliance will be documented throughout the treatment periods (Parts 1 and 2) using study-specific medication administration record forms. If a subject does not receive the scheduled dose, every effort should be made to administer the dose as soon as possible [redacted]

Deviations from the intended regimen could occur due to: (1) receiving unscheduled IMP injections, (2) missing an injection, and (3) receiving the incorrect IMP dose.

10.5 Study Treatment Accountability

Records shall be maintained of the delivery of study treatment to the study centers, the inventory at the study centers, the use of each subject and the return to the Sponsor.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study medication and to the study subjects.

The Investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study medication received from the Sponsor is reconciled. All study medication must be returned to the Sponsor at the end of the study.

10.6 Concomitant Therapy

The following restrictions will apply to all subjects during the study.

Concomitant medications limited throughout the study [redacted]

- Analgesics: Acetaminophen may be used by the subject [redacted] except within [redacted] before a scheduled study efficacy evaluation.

Concomitant medications will be limited during Part 1 of the study [redacted] as follows:

- NSAIDs: For subjects receiving NSAIDs [redacted] the subject must be on a stable dose for [redacted] prior to [redacted] of IMP and be expected to maintain a stable dose for the [redacted] of the study, unless change in dosage is required due to toxicity. Stable dose [redacted] is defined as subjects taking an NSAID on average [redacted] per week for the [redacted] prior to [redacted] g.

- Corticosteroids: Subjects taking oral corticosteroids [redacted]
- DMARDs: Subjects taking either MTX [redacted] or [redacted] must remain on a stable dose, unless a decrease in dose is required because of toxicity or intolerance. Other [redacted] and oral MTX [redacted] be changed to [redacted] dosing during the period of observation. Subjects [redacted] MTX and [redacted].

Tapering of any of these concomitant medications during the study is allowed only if there is toxicity (accompanied by recording of an AE on the eCRF); otherwise the dosage must remain the same throughout Part 1 of the study. Adjustment of these concomitant medications is permitted throughout Part 2 (Week 25 to 52) as needed per Investigator discretion and therapeutic needs of the subject, or if the subject does not show minimal response to treatment (defined as < 10% improvement from Baseline in pain [assessed by Total Back Pain VAS 0 to 100] and inflammation [assessed using the last 2 stiffness assessments in the BASDAI]) at Week 16.

For subjects receiving non-drug therapy (including but not limited to physical therapy, massage, diet, exercise, emollients, and joint taping), this must be stable for the 4-week period prior to IMP initiation through to the end of Part 1.

11 ASSESSMENT OF EFFICACY

The following efficacy assessments will be undertaken, as outlined in the Schedule of Assessments [redacted]

11.1 Efficacy Assessments

11.1.1 ASAS Improvement Criteria

The ASAS has developed improvement criteria for clinical studies in AS which include the ASAS20, ASAS40 and ASAS5/6 assessments[redacted]. These composite scores are derived from several of the Patient Reported Outcome measures or Disease Activity Assessments. ASAS20 and ASAS40 assess [redacted] domains: the PtGA of disease activity, Total Back Pain, Function (BASFI) and Inflammation (mean of BASDAI [redacted]).

ASAS20 response is defined as an improvement of [redacted] domains: PtGA; Total Back Pain; BASFI; and Inflammation. No worsening of [redacted] on a [redacted] in the remaining [redacted] domain.

ASAS40 response is defined as an improvement of [redacted] domains; PtGA of disease activity; Total Back Pain VAS; BASFI VAS; and Inflammation VAS [redacted]. No worsening of [redacted] on a [redacted] in the remaining [redacted] domain.

ASAS70 response is defined as an improvement of [redacted] domains; PtGA; Total Back Pain; BASFI; and Inflammation. No worsening of [redacted] in the remaining [redacted] domain.

ASAS5/6 improvement is defined as and improvement of [redacted] domains (PtGA, Total Back Pain, Function and Inflammation, CRP, Spinal mobility [lateral spinal flexion]).

11.1.2 Joint Counts

11.1.2.1 Tender Joint Counts (TJC46)

The number of tender or painful joints from [redacted] anatomical joints will be assessed for both the right and left side of the body by an independent joint assessor. The presence of a tender or painful joint will be scored as [redacted] and absence as [redacted]. The total TJC will be the sum of the scores for a range of TJC from [redacted] Joints to be assessed for tenderness include sternoclaviculars,

acromioclaviculars, shoulders, elbows, wrists, metacarpophalangeals, interphalangeal of thumb, proximal interphalangeal, hips, knees, ankles, and metatarsophalangeals.

11.1.2.2 Swollen Joint Counts (SJC44)

The number of swollen joints from [redacted] anatomical joints will be assessed for both the right and left side of the body by an independent joint assessor. The presence of a swollen joint was scored as [redacted] and absence as [redacted]. The total SJC will be the [redacted] of the scores for a range of SJC from [redacted] The joints to be assessed for swelling are the same as those assessed for tenderness, except the hip joints are not included. [3]

11.1.3 Physician Global Assessment (PGA) of Disease Activity

The treating physician will evaluate the status of the subject's AS by means of a VAS. The subject will be assessed according to how their AS is at the time. The VAS will be anchored with verbal descriptors of "very good" to "very poor".

11.1.4 Patient Global Assessment (PtGA) of Disease Activity

The subject will make an overall assessment of their condition [redacted] by means of a VAS. The VAS will be anchored with verbal descriptors of "no pain" to "very severe pain".

11.1.5 Total Back Pain (Spine Pain) and Nocturnal Pain

The subject will assess total back pain [redacted] and nocturnal back pain [redacted] using a VAS ("no pain" to "most severe pain").

11.1.6 Bath Ankylosing Spondylitis Functional Index (BASFI)

BASFI is a validated index for the assessment of functional limitation in patients with AS. It comprises [redacted] questions; the first [redacted] questions evaluate activities related to functional anatomical limitations and the final [redacted] questions evaluate ability to cope with everyday life. A VAS ("easy" to "impossible") is used to score each question.

11.1.7 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

BASDAI is a simple index demonstrating statistically significant [redacted] reliability. The index is sensitive to change within a short period of time [redacted] physiotherapy course, [redacted] improvement. The VAS ranges from "[redacted] and comprises [redacted] questions pertaining to the [redacted] major symptoms of AS – [redacted] To give each symptom equal weighting, the mean of the [redacted] scores relating to morning stiffness is taken.

11.2 Exploratory Assessments

11.2.1 Bath Ankylosing Spondylitis Metrology Index (BASMI)

BASMI is a combined index to assess spinal mobility. Tragus-to-wall distance, lumbar flexion, lumbar side flexion and intermalleolar distance are measured in centimeters. Cervical rotation is measured in degrees using a gravity goniometer. A scale in [redacted] and in [redacted] is associated with a numerical scale from [redacted]

11.2.2 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL is a validated [redacted] self-administered questionnaire which has been used worldwide in clinical studies. The scale can measure the quality of life (QoL) associated with a wide range of perceived disease severity and activity. The amount of restriction on daily activities, level of pain and fatigue, and impact on the subject's emotional state is assessed. Each item is scored as "yes" or "no".

11.2.3 36-item Short Form (SF-36)

The SF-36 v2 is a multipurpose survey that measures [redacted] domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 domains and 2 summary measures of physical and mental health: the Physical Component Summary and the Mental Component Summary. The SF-36 v2 acute format will be used in this study, which asks the respondent to answer the questions as they pertain to the way he or she felt or acted during the past week.

11.2.4 Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and ASDAS-ESR

The ASDAS-CRP and ASDAS-ESR endpoint is derived from the BASDAI, CRP and ESR. It comprises Total Back Pain (BASDAI Question 2), PtGA, Peripheral pain/swelling (BASDAI Question 3), Duration of morning stiffness (BASDAI Question 6), CRP (in mg/L) or ESR. [redacted]

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

FACIT scales are a collection of QoL questionnaires targeted to the management of chronic illness. They are designed for self-administration but can also be administered by an appropriately trained interviewer. The questionnaires are used by major co-operative clinical study groups, for international industry-sponsored research, government and military research,

and in health practice self-studies. They have demonstrated equivalence in mode of administration, as well as reliability, validity and sensitivity to change. The FACIT-fatigue questionnaire is a [redacted] standalone subscale ([redacted]

11.2.6 Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

MASES was originally a clinical scoring system for enthesitis in AS and is now also used in PsA and spondyloarthritis (SpA) in general. It is recommended by the ASAS for use in randomized controlled studies of AS and SpA. Tenderness on examination is recorded as either present (1) or absent (0) for the fifth lumbar spinous process and each of 12 bilateral sites, including the first costachondral joints, seventh costochondral joints, anterior superior iliac spines, iliac crests, posterior iliac spines, and the proximal insertion of Achilles tendons.

11.2.7 Magnetic Image Resonance (MRI)

MRI allows objective measurement of disease activity in AS by monitoring changes in inflammation. Through the incorporation of [redacted]n techniques, MRI enables direct visualization of inflammatory lesions within the bone marrow that are often obscured by marrow fat. These lesions are thought to be predictive of future locations of erosion and subsequent osteoproliferation, and thus may offer detection and objective monitoring of active disease which is not possible with radiography.

11.2.7.1 SpondyloArthritis Research Consortium of Canada (SPARCC) MRI Indices

SPARCC MRI indices are validated scoring methodologies for spine and SI joint inflammation in patients with AS. These indices assess the presence, 3-dimensional extent and signal intensity of active inflammatory lesions represented by bone marrow edema (BME) in the spine and SI joints of affected patients. In the spine, the scoring system measures BME in the bone marrow of DVUs, each unit representing the region between [redacted] imaginary lines drawn through the middle of adjacent vertebrae. The[redacted] DVU are selected for assessment, a method that has been shown to be equally discriminatory as an assessment of all [redacted] DVUs. The scoring system also measures BME in the iliac and sacral bone marrow of the SI joints by assessing lesions in consecutive coronal slices through the synovial portion of the joint.

11.2.7.2 Modified Berlin Ankylosing Spondylitis Spine MRI (ASspiMRI)

The volume of BME in each DVU is scored on a scale of [redacted] The score is designed to evaluate MRIs of the total spine including [redacted] DVUs; score range[redacted]

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in [redacted].

12.1 Adverse Events

12.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The [redacted] is responsible for ensuring this.

12.1.1.1 Adverse Event/Reaction

An AE is defined as "any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product".

Any relevant observations made at the [redacted] are to be recorded on the AE eCRF, but will not be considered treatment-emergent AEs (TEAEs) and will be reported separately from TEAEs. Any relevant observations following the first dose of IMP will be recorded as an AE in the subject's AE eCRF; this includes physical examination findings, clinically relevant abnormal vital signs, clinically relevant laboratory abnormalities, and clinically relevant ECG findings. An AE relating to a pre-existing condition will only be recorded if there is a worsening of the pre-existing condition during study conduct with regard to nature, severity or frequency.

An adverse drug reaction is an "untoward and unintended response to an IMP related to any dose administered".

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments which suggest a causal relationship.

12.1.1.2 Serious Adverse Event

An SAE is defined as, but is not limited to, an event one that:

[redacted]

[redacted]

12.1.1.3 Adverse Events of Special Interest (AESIs)

The events of severe infections, malignancies (including non-melanoma and melanoma skin cancer), confirmed Major Adverse Cardiovascular Events (MACE), and drug-related hypersensitivity reactions [redacted] will be identified a priori as AESIs for summarizing in this study [redacted] Major Adverse Cardiovascular Events include non-fatal stroke, non-fatal myocardial infarction and cardiovascular death. All MACE events will be evaluated and adjudicated by a CAC [redacted]

An AESI must be reported as if it were an SAE (Section 12.1.7).

12.1.1.4 Events of Clinical Interest (ECI)

An ECI is a non-serious AE or occurrence that is designated to be of special interest and must be reported to the Sponsor as though it were an SAE [redacted]

The following events are considered ECIs for this study:

[redacted]

12.1.1.5 Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the [redacted] IMP.

12.1.1.6 Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than is normally used. Every overdose must be reported to [redacted] Pharmacovigilance and Safety Services within 24 hours of awareness, using the details provided in [redacted] irrespective of whether the overdose was associated with an AE/SAE.

Overdose in this study is specifically defined as any dose greater than the intended protocol dose [redacted] In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

12.1.1.7 Product Quality Complaint

A product quality complaint (PQC) is related to a potential quality issue during manufacturing, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system. In addition, it includes any reports in which a suspicion of counterfeit/tampering exists. It is important to note that not all PQCs involve a subject. A PQC should be reported within 24 hours using the details provided in [redacted]

12.1.1.8 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the study, it must be reported as an AE.

12.1.1.9 Incident

A device-related incident is any product complaint that led to or might have led to death or serious deterioration of health/serious injury/serious illness for the user of the product or any other person. Note that "device" refers to the PFS for this study. The incident should be reported within 24 hours using the details provided in [redacted]

12.1.2 Recording of Adverse Events

Any relevant observations made before the end of the [redacted] are to be recorded on the AE eCRF, but [redacted] considered TEAEs and will be reported separately from TEAEs. Any relevant observations made after the first dose of IMP will be recorded as an AE in the subject's AE eCRF [redacted]

In view of the long $T_{1/2}$ of tildrakizumab at doses previously studied, subjects will continue to be monitored throughout the [redacted] period following the [redacted] visit. For the purposes of this study, any detrimental change in the subject's condition, after first dose of IMP and up to completion of the EoS visit, should be considered an AE. For those subjects who may withdraw during the [redacted], at least [redacted] should be made to collect AEs from sites.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome. A new AE must be recorded if the severity of the AE changes.

All AEs/SAEs have to be reported to the Sponsor, whether or not considered causally related to the IMP or to the study procedure(s).

All ongoing AEs/SAEs should be followed up until resolution or stabilization or the last visit if in the Investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease.

At any time after the subject has taken the first dose of IMP, if an Investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the Sponsor.

The Investigator will assess the intensity of AEs based on the following definitions:

- [redacted]
- [redacted]
- [redacted]

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in [redacted]

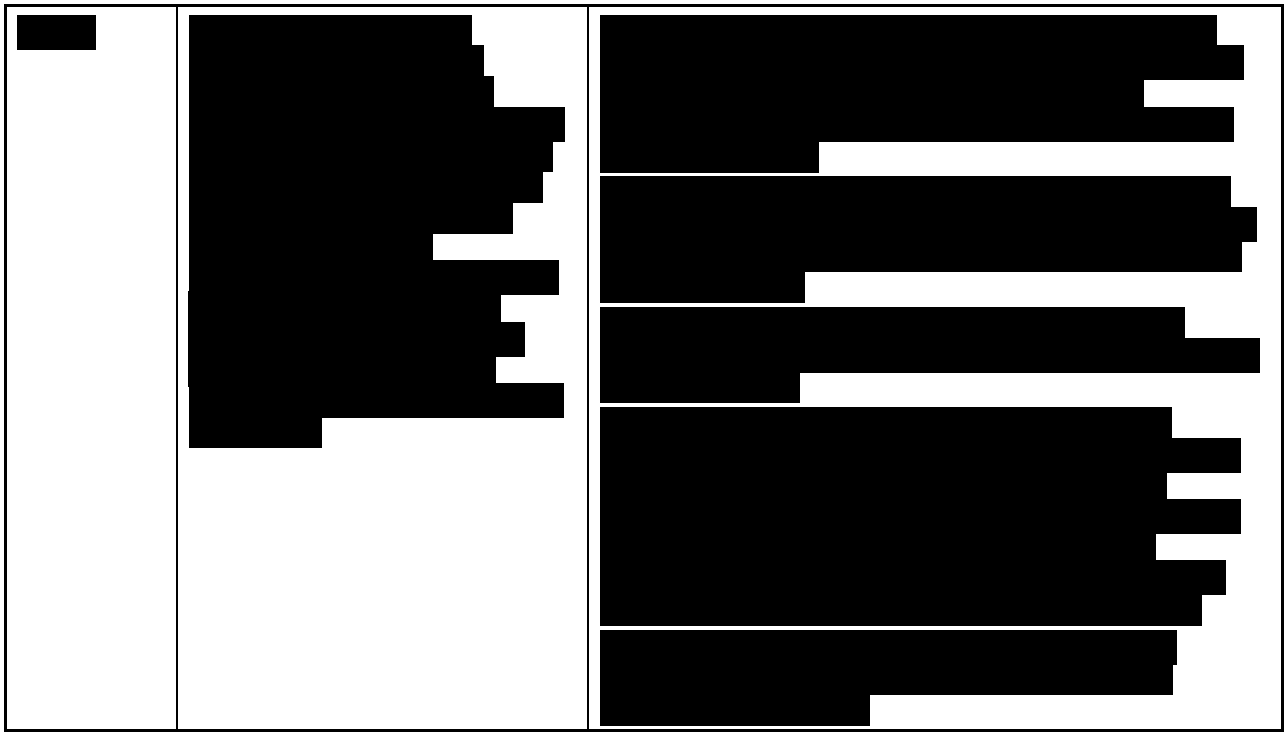
An AE of severe intensity need not necessarily be considered [redacted]. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

For an AE to be a suspected drug-related event, there should be at least [redacted] relationship between the IMP and the AE.

12.1.3 Causal Assessment

The relationship of AEs to study drug will be assessed by the Investigator (Global Introspection assessment), and will be a clinical decision based on all available information.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



The Investigator should consider the following, before reaching a decision on causality assessment:

[redacted]

[redacted]

[redacted]

12.1.4 Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as AEs/SAEs if it is clinically significant and any of the following criteria is met:

- Result is associated with signs/symptoms
- Requires additional diagnostic testing and/or intervention
- Leads to discontinuation or interruption of the IMP

Any test result determined to be an error or simple repetition of a laboratory test is not required to be reported as an AE.

12.1.5 Anaphylaxis

The clinical criteria for diagnosing anaphylaxis are as follows:

[redacted]

12.1.6 Pregnancy

Pregnancy itself is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further IMP will be administered to this subject and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow-up should be performed up to delivery and examination of the new-born, after which a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth.

All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs, but should be reported as a follow-up report for

the pregnancy. All outcomes of pregnancy must be reported to the Sponsor on a Pregnancy Outcomes Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to [redacted] Pharmacovigilance and Safety Services using the reporting details provided in [redacted] within 24 hours of awareness.

12.1.7 Reporting of Serious Adverse Events, Adverse Events of Special Interest, and Events of Clinical Interest

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements.

Investigators and other site personnel must inform appropriate [redacted] Pharmacovigilance and Safety Services of any SAE that occurs during the course of the study (from the time of informed consent until 30 days after the last EoS visit), whether or not it is considered causally related to the IMP or to the study procedure(s), and within 24 hours of when he or she becomes aware of it. An SAE with an onset day greater than 30 days from the EoS visit will be recorded only for fatal SAEs and those deemed by the Investigator to be drug-related or AESIs/ECIs [redacted] The Investigator should make every effort to obtain follow-up information on the outcome until the event is considered resolved, chronic and/or stable.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to [redacted] within 24 hours as described above. The start date of the SAE is not the start date, but the date when the AE becomes serious; analogously, the stop date is the date when any seriousness criterion is no longer applicable, not the date when the AE is resolved.

All SAEs will also be recorded in the eCRF. The Investigator is responsible for informing the Ethics Committee of the SAE as per local requirements.

Paper SAE forms should be completed at the site and faxed/emailed to the relevant [redacted] Pharmacovigilance and Safety Services or emailed to the global email distribution list within 24 hours of awareness of the event.

SAE, AESI, and ECI reports should be sent to:

Central Receipt mail box: [redacted]

If the report is sent via email then the completed and signed SAE or Pregnancy Report Form must be attached to the email. A notification email of the event describing it in the email text is not sufficient.

Alternatively, the following fax number can be used for completed SAE reporting forms.

Telefax: [redacted]

Telefax: (US/LATAM): +1 215 616 3096

If the SAE/AESI/ECI cannot be reported via the email (primary option) or by fax (secondary option), the following telephone numbers may be used to record the event:

[redacted]

There may be situations when an SAE (or AESI/ECI) has occurred and the Investigator has minimal information to include in the initial SAE report. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE report form. Minimum criteria are identifiable subject (number), a suspect product (i.e. IMP or concomitant medication), an identifiable reporting source (Investigator/study site identification), and an event or outcome that can be identified as serious. The Investigator may change his/her opinion of causality in the light of follow-up information, amending the SAE report form accordingly. The causality assessment is the criteria used when determining regulatory reporting requirements for SAEs.

12.1.7.1 Safety Reporting to Sponsor

[redacted] Pharmacovigilance and Safety Services will forward the SAE and Pregnancy report to the following Sponsor's safety representatives within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

Dr. Harshit Mehta, Safety Physician 17/B Mahal Industrial Estate Mahakali Caves Road, Andheri (E), Mumbai-93 [redacted]	Dr. Victoria Bodea, EUQPPV 124 Fabricii Str., Cluj-Napoca Romania 400632 [redacted]

12.1.7.2 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators

[redacted] will notify the Sponsor of any SAE and will perform follow-up activities with the concerned site. The Sponsor will bear responsibility of expedited and periodic reporting to the Health Authorities according to national requirements. Procedure and timelines for safety reporting are provided in the Safety Management Plan as agreed by [redacted] the Sponsor.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) to the IEC/IRB that approved the study. Investigators should provide written documentation of IEC/IRB notification for each report to the [redacted] Pharmacovigilance and Safety Services.

In accordance with ICH GCP, [redacted] Pharmacovigilance and Safety Services will inform the Investigators of findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IEC's/IRB's approval/favorable opinion to continue the study, as assessed by the Sponsor. In particular and in line with respective regulations, [redacted] Pharmacovigilance and Safety Services will inform the Investigators of SAEs. The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the [redacted] Pharmacovigilance and Safety Services will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the [redacted] Pharmacovigilance and Safety Services and of filing copies of all related correspondence in the Investigator Site File.

12.2 Safety Endpoints

All safety endpoints are listed in [redacted]

12.3 Laboratory Assessments

Laboratory measurements for blood chemistry, hematology and urinalysis will be performed according to the Schedule of Assessments [redacted] Specific details not mentioned in this section (including shipping requirements) are included in the laboratory manual.

For visits where lipid panel laboratory parameters will be assessed [redacted] blood samples are to be collected (pre-dose where applicable) after [redacted], following ECG and vital sign measurements.

12.3.1 Clinical Laboratory Tests

Unless otherwise indicated, all chemistry and hematology parameters will be analyzed using a central laboratory. The following parameters will be collected:

[redacted]

12.3.2 Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening visit. Urine pregnancy test with sensitivity of at least [redacted], will be performed according to the Schedule of Assessments [redacted] If at any point during the study there is a case of a positive urine β-hCG test, the subject will have IMP stopped and will be

withdrawn from the study. To confirm menopause in female subjects with no menses for less than [redacted], a FSH test should be performed at the Screening visit to confirm they are not of childbearing potential.

Pregnancy tests will also be performed whenever [redacted] menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected), to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

12.4 Assessment of Suicidal Ideation and Behavior

Subjects will be assessed for suicidal ideation and behavior at Screening using the Baseline (Lifetime) C-SSRS, and each subsequent visit using the C-SSRS [redacted]. There are [redacted] questions relating to levels of suicidal ideation which prompt questioning about suicidal behavior or intensity of ideation, depending on response. Subjects acknowledging active thoughts of self-harm but lacking an articulated plan for doing so are classified at the intermediate risk level; those presenting a defined self-harm plan or lacking needed impulse control are judged to be at the high risk level. Subjects who have high risk of suicidality at the Screening assessment based on Investigator's judgment or, if appropriate, as indicated by a response of [redacted] within the last [redacted] to Questions [redacted] in the suicidal ideation section, or any [redacted] response in the behavioral section of the C-SSRS should not be enrolled in the study. Those who develop suicidal ideation during the study rated as high risk according to the above classification must be [redacted] from receiving IMP and referred promptly for psychiatric evaluation. Subjects rated as displaying the intermediate level of suicidal ideation should receive psychological support and be assessed on an individual basis. All individuals assessed as exhibiting suicidal behavior, except preparatory acts, must discontinue IMP permanently. The presence of non-suicidal self-injurious behavior should be assessed on an individual basis.

12.5 Electrocardiogram Assessments

Computerized [redacted] d ECG recordings will be obtained at scheduled study visits after the subject has rested for at least [redacted] in the supine position. ECG data will be submitted to a central laboratory for measurement. The Investigator will document the occurrence of any clinically significant [redacted] ECG abnormalities within the eCRF (AE module) based on correlation between the central reading report and clinical findings. Repeat measurements will be performed if needed.

The following ECG parameters will be obtained directly from the computerized [redacted] ECG recordings: rhythm, ventricular rate, P-R interval (the portion of the ECG between the onset of the P wave and the QRS complex), QRS duration and QT/QTcF where, according to the Fridericia formula, (QTcF) is the observed QT interval (the time from the beginning of the Q

wave to the end of the T wave) divided by the cubed root of the R-R interval (interval from the peak of one QRS complex to the peak of the next) in seconds:

[redacted]

QTcB (QTc corrected according to Bazett's formula) will also be recorded, where:

[redacted]

12.6 Physical Examination

A standard complete physical examination will be performed at the weeks specified in [redacted] and [redacted] The following parameters and body systems will be examined and any abnormalities described: height, weight, general appearance, skin (presence of rash), HEENT (head, ears, eyes, nose, throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremity exam, abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant changes from Baseline [redacted] should be recorded as AEs.

12.7 Vital Signs

Body temperature (oral), systolic and diastolic cuff blood pressure (measured after at least [redacted] in the supine position) and pulse rate (measured after at least [redacted] in the supine position) will be recorded according to the Schedule of Assessments [redacted] Automatic or manual devices may be used, but the same device will be used for any given subject throughout the study. The same method of measuring body temperature will be used throughout the study. The same arm will be used for all measurements. All devices must hold valid calibration at the time of use.

12.8 Tuberculosis Testing

During the Screening period, it must be determined and documented that a subject does not show evidence of [redacted] TB. The subject must have a negative evaluation for TB within [redacted] before initiating IMP, defined as a negative QuantiFERON test.

Subjects with a positive or 2 successive indeterminate QuantiFERON tests are allowed if they have no history of active TB or symptoms of TB, and a PA chest radiogram performed (and with a report available at the site) within 3 months of Screening with no evidence of TB (or of any other pulmonary infectious diseases). If there is evidence of prior latent TB infection, subjects must have history of adequate prophylaxis per local standard of care. If presence of latent TB is established, treatment according to local country guidelines must have been followed for at least 4 weeks prior to inclusion in the study.

12.8.1 QuantiFERON Test

QuantiFERON-TB Gold In-Tube[7] is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-γ by Enzyme-Linked Immunoabsorbent Assay is used to identify in vitro responses to these peptide antigens that are associated with TB infection. QuantiFERON-TB Gold In-Tube is an indirect test for Mycobacterium tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate (indeterminate results are generated when either of the control tubes does not produce their intended values). A maximum of [redacted] QuantiFERON tests are allowed. A re-test is only permitted if the [redacted] is indeterminate; the result of the [redacted] will then be used.

12.9 Chest Radiograph

A chest radiograph will be obtained at the Screening visit in subjects with positive or [redacted] successive indeterminate QuantiFERON tests unless it has been previously taken and documented within the [redacted] prior to Screening and is available with the associated report at the site. There must be no evidence of active TB or any other pulmonary infectious diseases for the subject to be considered eligible for the study.

12.10 Radiograph of Spine and Sacroiliac Joints

A radiograph of the spine and SI joints is [redacted] Subjects with AS must meet [redacted] for diagnosis, and nr-axSpA subjects must have no [redacted] that fulfils these criteria in order to be eligible for the study. Subjects must not have evidence of [redacted] as defined in the [redacted]. At Screening, the following radiographs must be acquired: AP, LPO and RPO SI joints; AP and lateral lower thoracic spine (T5 to L1); AP and lateral lumbar spine (T12 to S1). Radiographs must be submitted to the central reader for evaluation of quality and confirmation that the subject meets inclusion and exclusion criteria. Subjects should not be scheduled for MRI or Baseline visit until confirmation is received from the central reader.

12.10.1 Historical Radiograph

Previous radiographs of the spine and SI joints documenting diagnosis of AS or nr-axSpA will be acceptable providing they were performed within [redacted] months of the date of Screening. They should be used in lieu of performing Screening radiographs if they can be obtained and sent to the central reader for confirmation. The original films, or a copy must remain at the site and a copy should be sent to the central reader. If results are considered unevaluable by the central reader, the X-ray must be repeated.

12.10.2 New Radiograph

If historical radiographs cannot be obtained, [redacted] must be obtained at the Screening visit to visualize the spine and SI joints. This should be done after all Screening activities have been completed and if the subject does not fail to meet other study criteria.

12.11 Magnetic Resonance Imaging (MRI)

MRI of the entire spine and SI joints will be performed at the Screening visit (except for subjects who have an MRI scan and associated report available within the past [redacted] months), at [redacted] and at [redacted] using standard clinical scanners. If a subject is unable to complete the MRI procedure within the protocol-defined time window due to technical issues at the site (e.g. the MRI is not working) or subject difficulties (e.g. the subject is unable to lie flat and cannot achieve a quality scan), the Screening window can be [redacted], with approval by the Sponsor, to allow completion of the MRI. Imaging will use standardized commercially available sequences for evaluation of a validated endpoint such as the SPARCC MRI indices and/or ASspiMRI. Scoring of the data will be conducted by a central reader who will be blinded to the time sequence and subject treatment. Detailed procedures for obtaining and processing the MRI, conducting image Quality Assurance/Quality Control and endpoint analyses will be developed in study-specific documents and provided as appropriate to Investigators, MRI technicians and the central reader.

12.12 Anti-Drug Antibodies

The presence of ADA will be assessed at the visits indicated in the Schedule of Assessments Table 9–1 and Table 9–2. Samples will be collected as detailed in [redacted].

12.13 24/7 Medical Emergency Coverage

In a study-related emergency situation occurring outside of usual business hours, when assigned Medical Monitors for a study cannot be reached by a caller, an on-call physician can be reached 24 hours per day, 7 days per week [redacted]

13 STATISTICAL EVALUATION

13.1 Sample Size and Power

In each subject cohort [redacted], approximately [redacted] subjects will be randomized per arm in a [redacted] ratio to tildrakizumab [redacted] or placebo, stratified by anti-TNF use [redacted]). This sample size achieves [redacted] power (accounting for futility assessment) to detect a treatment effect in ASAS20 at [redacted]). The test statistic used is the [redacted] significance level. A [redacted] drop-out rate has been assumed.

An IA will be performed for futility assessment after data at [redacted] from [redacted] randomized subjects become available. Futility assessment will be based on a futility threshold of [redacted]

13.2 Randomization

A randomization schedule will be computer-generated before the [redacted]. After all Screening procedures are performed and results of Screening tests are available [redacted], eligible subjects will be activated in [redacted] and assigned randomly on a [redacted] basis to the following treatment groups:

- A: [redacted] tildrakizumab
- B: Placebo

by [redacted] Starting at [redacted], all subjects, except [redacted] will receive 200 mg tildrakizumab administered q4 weeks until Week 48. Subjects receiving tildrakizumab during [redacted] will discontinue IMP treatment and enter the [redacted] period. Subjects randomized to receive [redacted] will receive [redacted] tildrakizumab administered [redacted] weeks until [redacted] even if they do not achieve ASAS20.

Randomization will be performed by the [redacted]. Subjects will be stratified by prior anti-TNF use (yes/no). Subjects with prior anti-TNF use will be capped at [redacted].

13.3 Analysis Sets

The primary evaluation of the efficacy endpoint will be performed using the [redacted] Results for the Per-Protocol Analysis Set (PPAS) will be considered [redacted] Secondary endpoints will be analyzed for both the [redacted]. Safety endpoints will be analyzed using the [redacted].

PK data will be analyzed using the [redacted].

13.3.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects who have received [redacted] dose of IMP [redacted]). Analyses will be based on [redacted]. The evaluation of the efficacy endpoints will be performed based on the [redacted]

13.3.2 Per-Protocol Analysis Set (PPAS)

The PPAS will include all subjects in the FAS without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variables. The deviations can include but not limited to:

- Key inclusion/exclusion criteria not satisfied.
- Presence of relevant protocol violations with respect to factors likely to affect the efficacy of treatment where the nature of protocol violation will be defined before breaking the blind.
- Rescue medication use.
- Inadequate study medication compliance which will be determined before breaking the blind.

Major protocol violations to be excluded from the [redacted] will be defined and documented in a memo prior to the lock and unblinding of the database.

13.3.3 Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who received [redacted] dose of IMP. Analyses will be based on the actual treatment received. Safety endpoints will be analyzed based on the [redacted].

The Safety Analysis Set is the same definition as the [redacted].

13.3.4 Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects in the Safety Analysis Set who have sufficient [redacted] to obtain reliable estimates of the key PK parameters.

13.4 Endpoints

13.4.1 Study Subject Data

Demographic data and Baseline subject characteristics will be summarized descriptively.

IMP exposure and compliance will be summarized descriptively.

Incidence of prior and concomitant medication use will be summarized by World Health Organization Drug dictionary coded terms – Anatomic Therapeutic Chemical (ATC) classification and preferred term.

13.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who achieve ASAS20 at Week 24.

13.4.3 Secondary Efficacy Endpoints

Secondary endpoints include:

- The proportion of subjects who achieve ASAS20 at Week 52.
- The proportion of subjects who achieve ASAS40 at Weeks 24 and 52.
- The proportion of subjects who require adjustment of background therapy.

13.4.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints through Week 52 include:

- The proportion of subjects who achieve ASAS20 or ASAS40 at other measured time points.
- The proportion of subjects who achieve ASAS70 at measured time points.
- The proportion of subjects who achieve a ASAS5/6 response at measured time points.
- ASAS5/6 response is defined as a 20% improvement in 5 out of 6 domains (physical function [BASFI], Total Back Pain, Patient's Global Assessment of Disease Activity, Inflammation [mean of Questions 5 and 6 of the BASDAI], spinal mobility [BASMI], and acute phase reactants [CRP]).
- Change from Baseline in ASAS components at measured time points.
- Change from Baseline in BASDAI, BASMI, BASFI, and ASQoL at measured time points.
- Change from Baseline in VAS (total back pain and nocturnal pain score) at measured time points.
- Change from Baseline in ASDAS-CRP and ASDAS-ESR at measured time points.
- Change from Baseline in MASES at measured time points.
- Change from Baseline in SF-36 at measured time points.
- Change from Baseline in FACIT-fatigue at measured time points.
- Change from Baseline in TJC46 and SJC44 at measured time points.
- Change from Baseline in hsCRP serum levels at measured time points.
- Change from Baseline in SPARCC MRI Index of Disease Activity Score of the SI Joints at measured time points.
- Change from Baseline in SPARCC MRI Index of Disease Activity Score of the Spine at measured time points.
- Change from Baseline in Modified Berlin ASspiMRI of the Spine at measure time points.

Exploratory efficacy endpoints Weeks 53 to 72 include:

- Endpoints noted as primary and secondary above, relating to the following after IMP discontinuation: ASAS20, ASAS40, ASAS70, ASAS5/6, ASAS components, BASDAI, BASMI, BASFI, VAS (total back pain and nocturnal pain score), MASES, SF-36, FACIT-fatigue, TJC46, and SJC44.
- Incidence of ADA to tildrakizumab and their correlation with safety and efficacy.

13.4.5 Pharmacokinetics

Secondary PK endpoints through [redacted] include:

- AUC.
- Maximum concentration (C_{max}).
- Minimum concentration (C_{min}).
- Time of maximal concentration (T_{max}).
- $T_{1/2}$.

PK parameters will be analyzed separately for each subject population and pooled. Exploratory PK endpoints through [redacted] include an exposure-response relationship of tildrakizumab with ASAS. Other exploratory PK endpoints include population PK parameters through [redacted] and following IMP discontinuation ([redacted]).

13.4.6 Safety Endpoints

The following data will be collected for assessment of safety:

- AEs.
- Laboratory assessments.
- Suicidal ideation and behavior (C-SSRS).
- Vital signs.
- ECG.
- Physical examination.
- ADA to tildrakizumab, including titer and neutralizing antibodies.

13.4.7 Anti-Drug Antibodies Endpoints

- Incidence of ADA and correlations with PK, safety and efficacy endpoints will be investigated across [redacted].

13.5 Description of Statistical Analyses

13.5.1 General Considerations

The statistical evaluation will be performed by [redacted] using SAS®, Version 9.4 or later.

13.5.2 General Statistical Methods

Summaries for AS or nr-axSpA will be presented separately. Summary statistics will also be presented by treatment group. For [redacted] variables, unless otherwise stated, the number of available observations (n), mean, standard deviation (SD), median, and range will be provided. For [redacted] variables, the number and percentage in each category will be displayed.

Assessments of change from Baseline to post-Baseline will include only those subjects with both Baseline and post-Baseline measurements. The [redacted] of a variable taken before the [redacted] will be used as the Baseline value. Unless otherwise specified, [redacted] will not be imputed for the purpose of data analysis.

A more detailed description of study analyses will be presented in the statistical analysis plan (SAP).

13.5.3 Analysis of Primary Endpoint

The primary analysis will be based on the [redacted] test, incorporating prior anti-TNF use as a stratification factor, to compare response rates for the primary endpoint [redacted] between placebo and active dose arm within AS and nr-axSpA [redacted]. In addition, the [redacted] difference between placebo and the active dose arm and corresponding confidence interval (CI) will be estimated. Should assumptions per the [redacted] criterion not be satisfied, pairwise comparisons will be based on [redacted] tests following collapsing of the strata. In this case, the [redacted] difference and CI will be based on normal approximation without considering stratification. Early withdrawals or any other subjects with incomplete data at [redacted] will be classified as [redacted] for the primary endpoint [redacted] Subjects who fail to show minimal response to treatment [redacted] and inflammation [redacted] may have their background medications adjusted according to the maximum permitted daily dose [redacted] and continue in the study. Any subject requiring [redacted] will be counted as a non-responder for the primary analysis.

In the analysis of primary endpoint ASAS20 at [redacted], the overall p-value will be calculated using [redacted] against the critical value corresponding to the stage at which the study was stopped.

Analysis of the primary endpoint will be based on the [redacted].

A sensitivity analysis will be performed based on the [redacted]

Subgroup analyses may be performed for the following:

- Prior anti-TNF use [redacted]
- Body weight [redacted]

- Age [redacted]
- Gender.
- MTX [redacted]

Reasons for prior anti-TNF failure will be summarized.

13.5.4 Analysis of Secondary Endpoints

[redacted] endpoints up to [redacted] will be analyzed based on the methods described for [redacted].

Secondary endpoints will be analyzed for both the FAS and PPAS.

13.5.5 Analysis of Exploratory Efficacy Endpoints

[redacted] endpoints up to [redacted] will be analyzed based on the methods described for secondary endpoints above for the [redacted]. Continuous endpoints up to [redacted] will be analyzed based on a [redacted] analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, prior anti-TNF use (Yes/No), and Baseline value.

[redacted] endpoints measured once post-Baseline will be evaluated based on an Analysis of Covariance (ANCOVA) with terms for treatment, prior anti-TNF use, and subject specific Baseline values.

For [redacted], the following will be summarized descriptively based on the [redacted] Changes in Baseline for the components of [redacted] will also be summarized descriptively.

Incidence of ADA, defined as the % of subjects with positive ADA based on the [redacted], will be summarized and explored for correlation with various PK, safety and efficacy outcomes.

13.5.6 Safety Analyses

In general, missing safety data will not be replaced.

Adverse Events

AEs will be coded using the most recent version available of the Medical Dictionary for Regulatory Activities. TEAEs are defined as any AE occurring or worsening on or after the first dose of IMP.

The incidence of TEAEs will be summarized by system organ class and preferred term, as well as by study part. If a subject experiences the same preferred term multiple times then the event will be counted only once for the greatest severity during the treatment emergence period for the

part reported. Separate tables will be presented by severity; TEAEs considered to be related to IMP by Investigators will be summarized similarly.

AESIs and ECIs will be summarized descriptively. AESI-related safety endpoints include:

- Percent of subjects with severe infections, defined as any infection meeting the regulatory definition of a SAE, or any infection requiring IV antibiotics whether or not reported as a serious event, as per the regulatory definition.
- Percent of subjects with malignancies (excluding carcinoma in situ of the cervix).
- Percent of subjects with non-melanoma skin cancer.
- Percent of subjects with melanoma skin cancer.
- Percent of subjects with confirmed MACE.
- Percent of subjects with drug-related hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, etc.).

All AEs will be presented in full in a comprehensive listing including [redacted]. Details of SAEs and AEs leading to withdrawal will be listed separately. A more detailed description regarding presentation of AE data will be provided in the SAP.

AESIs and ECIs will be summarized descriptively.

Clinical Laboratory

Clinical laboratory parameter (e.g., albumin, etc.) observed values and changes from Baseline will be summarized at each scheduled visit.

Values outside the normal range will be categorized as [redacted] based on the laboratory's reference range and these will be flagged in the listings of individual subject data.

Suicidal ideation and behavior

Suicidal ideation and behavior assessment results will be summarized at each scheduled visit.

Vital Signs

Vital sign observed values and changes from Baseline will be summarized at each scheduled visit.

ECG

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with "Normal" "Abnormal, not clinically significant" and "Abnormal, clinically significant".

ECG parameter (e.g., QTcF) observed values and changes from Baseline will be summarized at each scheduled visit.

Physical Examination

Physical examination results will be summarized with incidence of [redacted] by body system at each scheduled visit.

ADA to Tildrakizumab

ADA titer and neutralizing antibodies will be summarized at each scheduled visit.

13.5.7 Analysis of PK Endpoints

Plasma tildrakizumab concentration data will be listed by individual subject and summarized by time.

PK parameters of AUC, C_{max}, C_{min}, T_{max} and $T_{1/2}$ will be summarized with descriptive statistics (n, mean, SD, geometric mean, % coefficient of variation, minimum, 1st, 2nd [i.e., median] and 3rd quartiles and maximum).

Exploratory analyses will be performed as below:

- Develop a mechanistic-based exposure-response (i.e. indirect) PK/PD model to explore the relationship of tildrakizumab exposure and ASAS response.
- Determine population PK parameters during and following IMP discontinuation.

Exploratory PK analyses may be described in separate SAPs.

[redacted]

13.5.8 Analysis of Anti-Drug Antibodies

Incidence of ADA will be summarized and explored for correlation with various PK, safety and efficacy outcomes.

13.5.9 Interim Analysis

After [redacted] randomized subjects complete [redacted], futility assessment will be based on a futility threshold of [redacted]
The purpose of the analysis is potentially to stop for futility. [redacted] If the difference between response rates of ASAS20 for the active arm and placebo is [redacted] the study will be stopped for futility.

Following the last subject's [redacted], an [redacted] will be conducted on all available data to evaluate the primary efficacy outcome. The Sponsor and some [redacted] members not directly related to the clinical conduct of the study will be unblinded during Part 2. Subjects, Investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of

the treatment from the time of randomization until the last subject completes the study [redacted]. A separate document will provide further details related to unblinding of personnel involved in reporting activities for the IA. Sharing of subject-level unblinded information for the IA will be confined to a designated unblinded study team.

13.5.10 Data Safety Monitoring Board

A DSMB will be established for periodic review of safety data for this study. The composition and responsibilities of the DSMB will be described in detail within the DSMB Charter for this study [redacted]

13.5.11 Clinical Adjudication Committee

A CAC will evaluate an extensive set of cardiovascular events and all deaths to determine which of these meet pre-specified endpoint criteria. Cardiovascular events for adjudication will be identified based on Investigator reports with specific adverse event terms. Instructions for obtaining source documentation for all events to be adjudicated will be provided to the Investigator sites in a separate document. All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding the cardiovascular endpoints to be analyzed, including the endpoint definitions and criteria can be found in the Adjudication Committee Charter.

14 DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator/institution shall provide [redacted] to source data/documents for study-related monitoring, audits, IEC/IRB review and regulatory inspection.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Conduct of the Study

[redacted] Sun Pharma Global FZE shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013)[8], FDA (CFR, Sections 312.50 and 312.56), EU (Annex 1, Directive 2001/83/EC) and UK regulations (The Medicines for Human Use [Clinical Trials] Regulations 2004 [no.1031]), and with ICH GCP (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

15.2 Study Monitoring

The Investigator shall permit the [redacted] to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator will provide access [redacted] for the monitor in order that entries in the eCRF may be verified. The Investigator, as part of his/her responsibilities, is expected to co-operate with [redacted] in ensuring that the study adheres to GCP requirements.

The Investigator may not recruit subjects into the study until such time that a visit, or with the agreement of the Sponsor, attendance at the Investigator meeting, has been made by a [redacted] to conduct a detailed review of the protocol and eCRF.

16 ETHICS

16.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH GCP and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, IB, available safety information, information about payment and compensation available to subjects, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

16.2 Written Informed Consent

The nature and purpose of the study shall be fully explained to each subject (or their legally responsible guardian).

Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed. The process of obtaining informed consent must be documented in the subject source documents.

The consent documents to be used for the study shall include all the elements of informed consent as outlined in accordance with FDA, ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate IEC/IRB prior to use.

16.3 Data Monitoring Committee

An independent DSMB will be established to periodically review safety results. The DSMB will have access to unblinded data. Based on the [redacted] review the DSMB will submit its recommendations in written form to the Sponsor who is responsible for responding to the recommendations of the DSMB and to take appropriate action. The Investigators will only be informed by the Sponsor in case of stopping the study. The DSMB may choose to request additional evaluations at any time if they feel this is warranted from the standpoint of safety.

The DSMB will act according to its own written SOP described in a charter and will prepare written minutes of its meetings.

In order not to disseminate unblinded data and to ensure that all staff involved in the conduct and final analysis of the study remains blind to the results of the safety review, only the [redacted].

At each planned safety review, the [redacted] of the subjects to be included in the analysis will be unblinded. Before unblinding, a SAP will be prepared for the safety review and approved by the Sponsor. The results will be sent confidentially to the DSMB by the [redacted]

17 DATA HANDLING AND RECORD KEEPING

17.1 Case Report Forms/Source Data Handling

All required study data must be entered in the eCRF created for the study. This data collection tool is a validated electronic data capture (EDC) system that contains a system generated audit trail. Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based EDC software system. The Investigator shall ensure that all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded. All internal [redacted] and external investigational site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the Investigator on CD-ROM for archiving at the investigational site.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory, unless otherwise specified (e.g., ESR).

The Investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the subject's file.

17.2 Retention of Essential Documents

The Investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least [redacted] 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 [redacted] have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, 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.

18 FINANCING AND INSURANCE

The Sponsor shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. If a subject incurs a study-related injury, the subject may be treated (and other necessary measures taken) at the study site and/or another medical institution. If it is necessary to compensate for the treatment, the Sponsor will cover the cost. The Sponsor shall not impose on the subject the burden of proving the causal relation between the study and the injury.

If any of the following is confirmed, the Sponsor may refuse or restrict the payment of the compensation:

- A serious GCP or protocol deviation by the Investigator or Sub-Investigator (except deviation medically necessary to avoid an immediate hazard to the study subjects)
- Intentional act or negligence on the part of the Investigator or Sub-Investigator or malpractice thereby
- Injury caused by unlawful act or delinquency of a third party
- Injury caused by intentional act or negligence of the subject.

If compensation becomes necessary for a study-related injury, the site will promptly notify the Sponsor and will co-operate with the Sponsor and its insurer (or their legal representatives) in their handling thereof.

19 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical study results.

20 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the Sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

21 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

((Type name and job title))	Date (day/month/year)

22 REFERENCE LIST

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4. Zochling J, Braun J. Assessment of ankylosing spondylitis. Clin Exp Rheumatol. 2005;23(Suppl.39):S133-S141.
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   Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm. Accessed October 11, 2016.
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   Available at: http://www.wma.net/en/20activities/10ethics/10helsinki/DoH-Oct2013-JAMA.pdf. Accessed October 07, 2016.
10. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arth Rheum. 1984;27(4):361 368.

23 APPENDIX 1