Study title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis

Document: Clinical Study Protocol

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1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis

Protocol No.: CLR_16_23	EUDRACT No.: 2016-003937-62
Test Product:	Tildrakizumab
Indication:	Treatment of Adult Subjects with Active Psoriatic Arthritis
Sponsor:	Sun Pharma Global FZE Office at #43, Block Y SAIF Zone Sharjah, 122304 United Arab Emirates
Development Phase:	Phase 2b
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:	16 Mar 2018
Version of the Protocol:	[redacted]

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis

PROTOCOL NUMBER: CLR_16_23

Sun Pharma Global FZE

[redacted]

3 GENERAL INFORMATION

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis

Protocol No.:	CLR_16_23
Date of the Protocol:	[redacted]
Date and Number of Amendment(s):	[redacted]
Sponsor:	Sun Pharma Global FZE Office at #43, Block Y SAIF Zone Sharjah, 122304 United Arab Emirates
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[redacted]	[redacted]
Sponsor Medical Expert:	Patrick Burnett, M.D., Ph.D. 2 Independence Way Princeton NJ 08540 Tel No.: +1 (609) 480 2902
[redacted]	[redacted]

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)**
Name of Product: Tildrakizumab		
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Title of Study:
A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis

Study Centers:
The study will be multinational and performed in approximately 100 study centers.

Publication(s):
None.

Planned Study Period:	**Development Phase:**
Apr 2017 to Sep 2019	Phase 2b

Objectives:

Primary Efficacy Objective:

Parts 1 and 2

- To evaluate the optimal dose regimen of tildrakizumab in subjects with psoriatic arthritis (PsA) as measured by the proportion of subjects achieving a [redacted] from Baseline in American College of Rheumatology response criteria [ACR[redacted]]) at [redacted]

Primary Safety Objective:

Parts 1 and 2

- To assess the safety/tolerability and immunogenicity of multiple-dose administration of tildrakizumab in subjects with PsA.

Secondary Objectives:

Parts 1 and 2

- To evaluate the effect of tildrakizumab on ACR[redacted] at [redacted]; and ACR[redacted], ACR[redacted], the components of ACR, Disease Activity Score (DAS)28(joints)-C-reactive protein (DAS28-CRP), minimal disease activity (MDA), dactylitis and enthesitis, and the Health Assessment Questionnaire Disability Index (HAQ-DI) at [redacted]
- To characterize the pharmacokinetics (PK) of tildrakizumab in subjects with PsA.

Exploratory Objectives:

Parts 1 and 2

- To develop a mechanistic-based exposure-response (i.e. indirect) PK/pharmacodynamics (PD) model to explore the relationship of tildrakizumab exposure and ACR response.
- To evaluate the effect of tildrakizumab on Psoriasis Area and Severity Index (PASI) 75/90/100 response rates at measured time points for subjects with moderate disease [redacted]
- To assess the effect of tildrakizumab on the 36-item Short Form (SF-36) health survey at measured time points.

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- To evaluate the effect of tildrakizumab on the PsA Impact of Disease (PsAID) questionnaire at measured time points.
- To assess the effect of tildrakizumab on ACR[redacted], ACR[redacted], ACR[redacted], the components of ACR, DAS28-CRP, MDA, Leeds Dactylitis Index (LDI), and Leeds Enthesitis Index (LEI) at other measured time points.

Part 3

- Assess the effect of the investigational medicinal product (IMP) discontinuation on ACR[redacted], ACR[redacted], ACR[redacted], the components of ACR, LDI, LEI, PASI, and HAQ-DI
- Evaluate immunogenicity following IMP discontinuation
- Determine population PK parameters following IMP discontinuation

Methodology:

This is a randomized, double-blind, placebo-controlled, multiple-dose, Phase 2b study. The study will be multinational and performed in approximately [redacted] study centers. At least [redacted] On completion of [redacted] subjects may enter the [redacted] providing they meet the inclusion/exclusion criteria for the [redacted] and the Investigator deems they would benefit from continued treatment with tildrakizumab. In circumstances where the LTE study site activation has not occurred at the time the subject reaches the end of Part 2, they may enter from Part 3 if the required eligibility conditions are met.

Randomization will be stratified by prior anti-tumor-necrosis factor (TNF) use [redacted] and Baseline body weight [redacted] Subjects with prior anti-TNF use will be [redacted] of the total number of subjects.

Subjects who fail to show minimal response to treatment [redacted] 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. Criteria for other endpoints are included in the statistical analysis plan (SAP).

Subjects who show clinical response to treatment [redacted] Subjects receiving tildrakizumab [redacted] during Part 1 who fail to show clinical response to treatment at [redacted] will be discontinued from the study drug and will enter Part 3 to receive treatment according to the Investigators' discretion. Subjects receiving [redacted] who fail to show clinical response to treatment at [redacted] will enter [redacted] Subjects in Part 2 who are not deriving sufficient clinical benefit in the opinion of the Investigator at any time after [redacted] should be

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discontinued from study drug and enter Part 3 so that they may receive additional treatment as determined by the Investigator.

Subjects discontinued from IMP at any time (apart from withdrawal of informed consent) will be required to complete the [redacted] assessment a [redacted] and e[redacted] Subjects who withdraw from the study during Part 3 will undergo the [redacted] assessments [redacted].

The primary endpoint is the ACR[redacted] response rate at [redacted] Secondary efficacy endpoints will include ACR[redacted], ACR[redacted] response rates, and the components of ACR response; proportion of subjects who require adjustment of background therapy; proportion of subjects who achieve a DAS28-CRP[redacted] proportion of subjects who achieve MDA criteria; LDI and LEI change from Baseline; and HAQ-DI change from Baseline. The PK and immunogenicity of tildrakizumab will also be evaluated.

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

Following the last subject's [redacted].

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

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 Registration of Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP).

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[redacted]		
Number of Subjects: [redacted]		

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Diagnosis and Main Criteria for Inclusion:

[redacted]

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[redacted]

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[redacted]

General

[redacted]

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Test Product, Dose and Mode of Administration:

[redacted]

Reference Therapy, Dose and Duration of Administration:

[redacted]

Concomitant Medications, Supportive Care, and Study Restrictions:

Concomitant medications limited throughout the study [redacted]

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

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

- NSAIDs or low-potency opioids: For subjects receiving NSAIDs or low-potency opioids (including PRN use): the subject must be on a stable dose for [redacted] prior to initiation 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 (including PRN use) is defined as subjects taking an NSAID or low-potency opioids on [redacted] per [redacted].
- Corticosteroids: Subjects taking oral corticosteroids (not to exceed the equivalent of [redacted] must remain on a stable dose. Subjects who were using topical corticosteroids when they enrolled under [redacted]
- Disease-modifying anti-rheumatic drugs (DMARDs): Subjects taking either MTX [redacted]) or leflunomide [redacted] must remain on a stable dose, unless a decrease in dose is required

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because of toxicity or intolerance. Oral MTX cannot be changed to parenteral dosing during the period of observation. Subjects may not use a combination of MTX and leflunomide.

Tapering of any of these concomitant medications during the study is allowed only if there is toxicity (accompanied by recording of an adverse event [AE] on the electronic Case Report Form); 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 [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 [redacted] prior to IMP initiation through to the end of Part 1.

Duration of Treatment:

[redacted].

Variables:

Efficacy:

[redacted]

– A [redacted]

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[redacted]

Pharmacodynamics:

Incidence of anti-drug antibodies (ADA) and correlations with safety and efficacy endpoints will be investigated ([redacted]

Safety: The following data will be collected for assessment of safety:

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

Statistical Methods:

Sample Size:

[redacted] Results are based on simulations incorporating the use of the [redacted] the composite hypothesis that the response rate for all [redacted] is not significantly different from placebo versus the alternative

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hypothesis that [redacted] has a response rate significantly greater than that of placebo. This is the primary hypothesis test for this study.

Statistical Analysis:

The primary efficacy analysis population will be the Full Analysis Set (FAS) defined as all randomized subjects who have received at [redacted] of IMP. The primary analysis will be based on the Cochran-Mantel-Haenszel test, incorporating prior anti-TNF use and Baseline weight as stratification factors, to compare response rates for the primary endpoint [redacted] between placebo and each of the respective active dose arms. In addition, the [redacted] In order to control for [redacted], the [redacted]. Should assumptions per the [redacted] not be satisfied, pairwise comparisons will be based on [redacted] In this case, [redacted] Early withdrawals with incomplete data will be classified as [redacted] for the primary endpoint (ACR[redacted]). Subjects who fail to show minimal response to treatment [redacted] Any subject requiring these adjustments will be counted as a non-responder for the primary analysis.

All secondary efficacy endpoints will be analyzed using the FAS. [redacted]

Exploratory endpoints up to [redacted] will be analyzed based on methods described for secondary endpoints using the FAS. [redacted] the effect of IMP discontinuation on ACR[redacted], ACR[redacted], ACR[redacted], the components of ACR, LDI, LEI, PASI, and HAQ-DI will be evaluated using summary statistics.

Safety endpoints will be analyzed descriptively based on the Safety Analysis Set, defined as all subjects who received [redacted]. 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 [redacted], an [redacted] will be conducted on all available data to evaluate the primary efficacy outcome.

Date of the Protocol: 16 Mar 2018

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[redacted]

[redacted]

[redacted]

[redacted]

5.1 List of Tables

5.2 List of Figures

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%CV	coefficient of variation
ACR[redacted]	American College of Rheumatology (the proportion of subjects achieving a [redacted] reduction from [redacted] in response criteria)
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
AUC	area under the curve
BSA	body surface area
β-hCG	beta human chorionic gonadotropin
CAC	Clinical Adjudication Committee
CASPAR	Classification of Psoriatic Arthritis
CI	confidence interval
CO_2	carbon dioxide
C_{max}	maximum concentration
C_{min}	minimum concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DAS(28-CRP)	Disease Activity Score(28 [joints]-C-reactive protein)
DIP	distal interphalangeal
DMARD	disease-modifying anti-rheumatic drug
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EC_{50}	effective concentration at 50% of E_{max}
ECI	events of clinical interest
EDC	electronic data capture
ED_{50}	median effective dose (for population)
E_{max}	maximum drug effect
EoS	End of Study
EoT	End of Treatment
ESR	erythrocyte sedimentation rate
EUDRACT	European Union Drug Regulatory Agency Clinical Trial

FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HLA	human leucocyte antigen
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
hsCRP	high sensitivity C-reactive protein
IA	interim analysis
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
kg	kilogram
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LTBI	latent tuberculosis infection
LTE	long-term extension
MACE	Major Adverse Cardiovascular Events
MCP	metacarpophalangeal
MDA	minimal disease activity
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMRM	mixed model repeated measure
MTX	methotrexate
NOAEL	no-observed-adverse-effect-level
NSAIDs	non-steroidal anti-inflammatory drugs
PA	posterior-anterior
PASE	Psoriatic Arthritis Screening and Evaluation

PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic
PFS	pre-filled syringe
PGA	Physician Global Assessment
PI	Principal Investigator
PIP	proximal interphalangeal
PK	pharmacokinetic
pM	picomolar
PPAS	Per Protocol Analysis Set
PQC	product quality complaint
PRN	as needed (pro re nata)
PsA	psoriatic arthritis
PsAID	PsA Impact of Disease
PsO	psoriasis
PT	prothrombin time
PtGA	Patient Global Assessment
q	every
QA	quality assurance
QTcB	QTc corrected according to Bazetts' formula
QTcF	QTc corrected according to the Fridericia formula
RA	rheumatoid arthritis
RBC	red blood cells
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SF-36	36-item Short Form
SIB	suicidal ideation and behavior
SOP	Standard Operating Procedure
$T_{1/2}$	half-life
TB	tuberculosis
TEAE	Treatment-emergent adverse event
T_{max}	time of maximal concentration
TNF	tumor necrosis factor
TU	tuberculin units
ULN	upper limit of normal

VAS	Visual Analog Scale
WBC	white blood cells
WHO	World Health Organization

7 INTRODUCTION

7.1 Background

Psoriasis (PsO) is a chronic inflammatory skin disorder affecting approximately [redacted] of people worldwide.[1] Psoriatic arthritis (PsA) has been defined as a unique inflammatory arthritis associated with PsO. The precise prevalence is unknown, but estimates vary from 0.3% to 1% of the population; among patients with PsO the observed prevalence of inflammatory arthritis varies from [redacted] The clinical features typically present as an oligoarticular and mild disease. However, with time PsA becomes polyarticular, and it is a severe disease in at least [redacted] of patients.[2] Symptoms include tenderness, pain and stiffness in and around the joints, dactylitis, spondylitis, pain and swelling in the heels, nail disfiguration (discoloration, splitting, or pitting), and generalized fatigue[redacted] Patients with PsA who present with polyarticular disease are at risk for disease progression. In addition to progression of clinical and radiological damage, health related quality of life is reduced among patients with PsA[redacted]

PsA is classified with the spondyloarthropathies because of the presence of spondylitis in up to [redacted], the occurrence of extra-articular features common to the spondyloarthropathies (mucous membrane lesions, iritis, urethritis, diarrhea, aortic root dilatation), and association with human leucocyte antigen [HLA]-B27. PsA may be distinguished from the other spondyloarthropathies by the presence of peripheral arthritis, asymmetrical distribution of the spinal involvement (both sacroiliac joints and syndesmophytes), lower level of pain, and limitation of movement. Several clinical features help distinguish PsA from rheumatoid arthritis (RA). Although RA is more common in women, PsA occurs just as frequently in both sexes. The specific clinical features of PsA include the involvement of distal joints. Joint distribution tends to occur in a ray pattern so that all the joints of a single digit are more likely to get affected than the same joints on both sides (which is typical of RA). The deformities that result from PsA lead to shortening of digits because of severe joint or bone lysis, with the most severe form being the telescoping of digits.[2]

Current treatment choices for PsA include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, topical treatments (for skin), light therapy (for skin), physiotherapy, and disease-modifying anti-rheumatic drug (DMARDs).[3,5] [redacted] ethotrexate (MTX) is approved by the U.S. Food and Drug Administration (FDA) for the skin condition PsO, but it is frequently used off-label for PsA. Methotrexate has been reported as providing symptomatic relief to some patients with multiple joint involvement and PsO but there is little scientific evidence to support the use as a disease-modifying agent for PsA.[5]

From animal studies and human disease association studies, there is significant evidence that IL-23 is a key pro-inflammatory cytokine in PsO and some other inflammatory diseases. Strong support for the relevance of the IL-23 pathway in PsO and some other inflammatory diseases has come from recent genome-wide association studies identifying a certain single nucleotide polymorphism in the gene coding for IL-23R to be less frequent in patients with PsO and some other inflammatory diseases.[1]

[redacted]

7.2 Rationale

Tildrakizumab is being developed for chronic plaque PsO, and Phase 3 studies have recently been unblinded, with subjects continuing in the long-term open-label extension. In the Phase 2b study [redacted] for PsO, all [redacted] were demonstrated to be safe and more efficacious than placebo [redacted] These data are considered relevant to the PsA development program considering PsO and PsA are highly related conditions with a shared pathophysiology, and the 2 conditions commonly present in the same patient. [redacted] Arthritis Screening and Evaluation (PASE), and Health Assessment Questionnaire (HAQ). [redacted]

Further information relating to efficacy and safety data from clinical trials of tildrakizumab is available in the Investigator's Brochure.[1]

7.2.1 Rationale for Dose

[redacted]

[redacted]

The dosing regimens in this study cover approximately a [redacted] from a suboptimal dose [redacted] to the anticipated maximally effective dose [redacted]) based on pharmacokinetic (PK) and pharmacodynamic (PD) modeling.

Data from Phase 1 studies and the Phase 2b study in PsO patients were incorporated into a population PK model. The Phase 1 study [redacted]) had PK data available from [redacted] with [redacted]

The PK model that describes tildrakizumab after SC administration is 1-compartmental, with first-order absorption and elimination. Significant covariates were an effect of weight on clearance and volume of distribution and an age effect on clearance. Using the individual Bayesian estimates, the simulated mean plasma concentrations of tildrakizumab at the proposed doses were determined. From these simulated profiles, a dose-dependent relationship with tildrakizumab exposure is anticipated. Therefore, the [redacted] separation between each of the doses is anticipated to result in appropriate separation of the observed exposures.

A PK-PD model was subsequently developed, incorporating an indirect-effect maximum drug effect (E_{max}) model. Sequential PK-PD analysis of the clinical response data from [redacted] yielded estimates of the PD parameters including the effective concentration at [redacted] Utilizing the individual subject PK parameters yielded the predicted [redacted] The longitudinal model of PASI reduction utilized an exposure-related suppression of plaque formation in an indirect-effect model, together with a placebo-effect on plaque degradation that represented the healing process. [redacted] The simulations incorporated PK variability, within- and between-subject variability in PASI response, and model uncertainty. Per arm, the percentage of PASI75 responders was tabulated. [redacted]

[redacted]

[redacted].

Based on the predicted ED_{50}, the proposed doses are selected to cover the relevant range spanning from a low dose ([redacted]

Considering the significant overlap in effective doses for PsO and PsA observed with tildrakizumab and related monoclonal antibodies (e.g., ustekinumab, secukinumab, etanercept, and adalimumab), these dose-response curves may be predictive of the clinical response in PsA subjects. [redacted]. Together, these doses cover a roughly [redacted] and are anticipated to define the critical areas of the dose-response curve, thereby enabling selection of a dose with the optimal benefit:risk profile to be carried into Phase 3 studies in subjects with PsA.

[redacted]

7.2.2 Rationale for Study

The IL-23/IL-17 axis has been studied in PsA and both cytokines are implicated in PsA disease activity. In view of the efficacy of ustekinumab [redacted] in PsA [redacted] 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.

This will be the first study conducted with tildrakizumab exclusively in subjects with PsA. As tildrakizumab is in development (Phase 3 ongoing) for the related PsO indication, substantial PK and PD data exist that can inform dose selection in PsA, as described. Under these circumstances, the next step for development is to confirm efficacy in the PsA population and understand the relationship between dose and clinical response. Therefore, this Phase 2b study will [redacted]. The tildrakizumab arms and a placebo arm will be analyzed at [redacted] for the primary endpoint (the proportion of subjects achieving a [redacted] reduction from Baseline in American College of Rheumatology response criteria [redacted]).

8 STUDY OBJECTIVES

8.1 Primary Efficacy Objective

[redacted]

8.2 Primary Safety Objective

[redacted]

8.3 Secondary Objectives

[redacted]

[redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a randomized, double-blind, placebo-controlled, multiple-dose, Phase 2b study [redacted] The study will be multinational and performed in approximately [redacted]. [redacted] All subjects will [redacted] During the wash-out period, subjects will no longer receive tildrakizumab and will be treated according to the Investigators' discretion. [redacted]

[redacted]

Subjects who fail to show minimal response to treatment [redacted] Any subject requiring these adjustments will be counted as a non-responder for the primary analysis. Criteria for other endpoints are included in the statistical analysis plan (SAP).

[redacted]

discontinued from the study drug and will enter Part 3 to receive treatment according to the Investigators' discretion. [redacted] should be discontinued from study drug as described in [redacted] and enter [redacted] so that they may receive additional treatment as determined by the Investigator.

Subjects discontinued from IMP at any time (apart from withdrawal of informed consent) will complete the [redacted]. Subjects who withdraw from the study during Part 3 will undergo the [redacted]

The primary endpoint is the ACR[redacted] response rate [redacted]. Secondary efficacy endpoints will include ACR[redacted], ACR[redacted] response rates, and the components of ACR response; proportion of subjects who require adjustment of background therapy; proportion of subjects who achieve a DAS28-CRP[redacted] proportion of subjects who achieve MDA criteria; LDI and LEI change from Baseline; and HAQ-DI change from Baseline. 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 would not be involved in the care of subjects and would not discuss disease activity or the treatment with subjects or the Principal Investigator (PI)/designee responsible for performing other efficacy and safety evaluations.

Following the last subject's [redacted] visit (or early termination prior to [redacted]), an interim analysis (IA) will be conducted on all available data to evaluate the primary efficacy outcome ([redacted]

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

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).

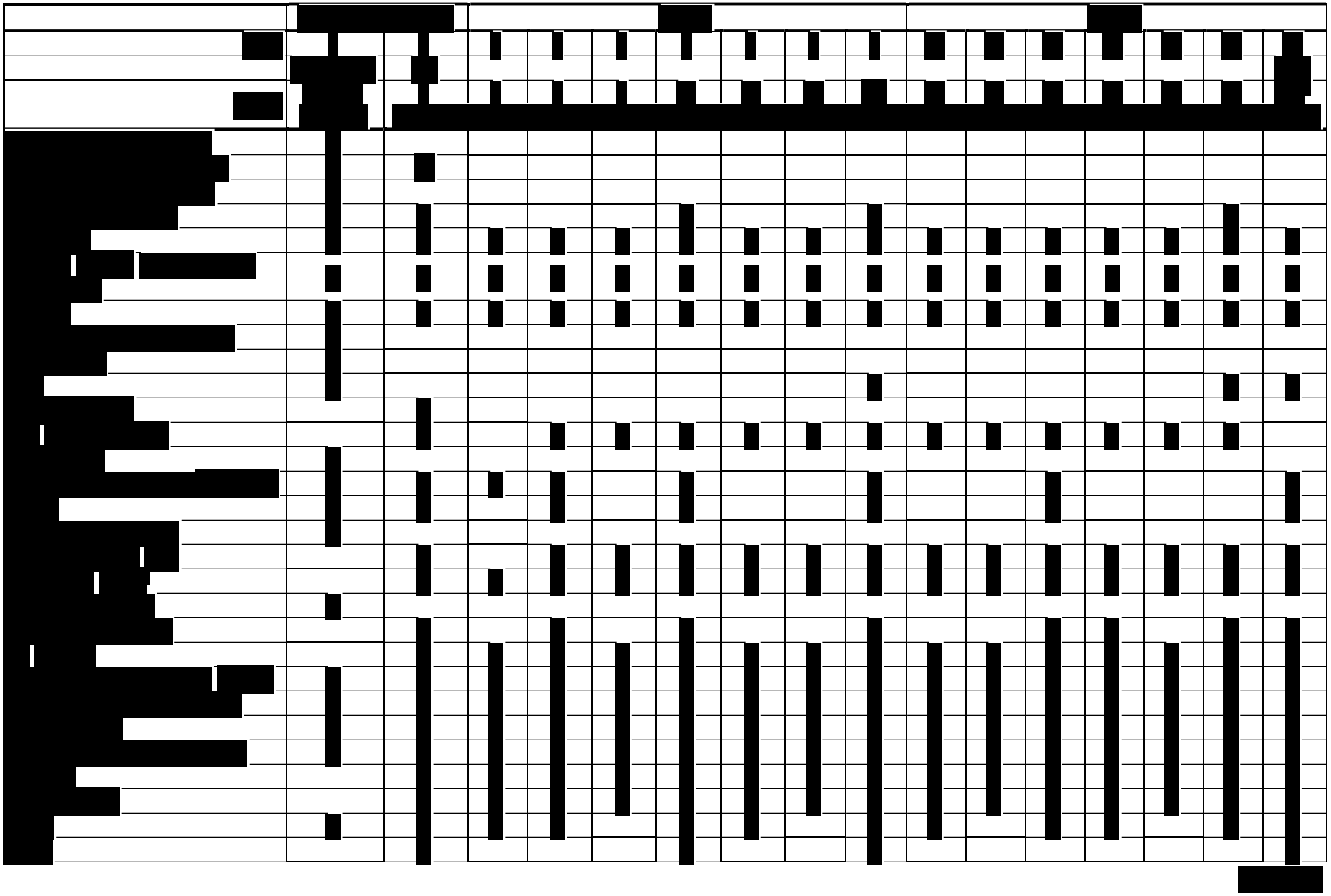
[redacted]

[redacted]

9.1.2 Schedule of Assessments

[redacted]

[redacted]



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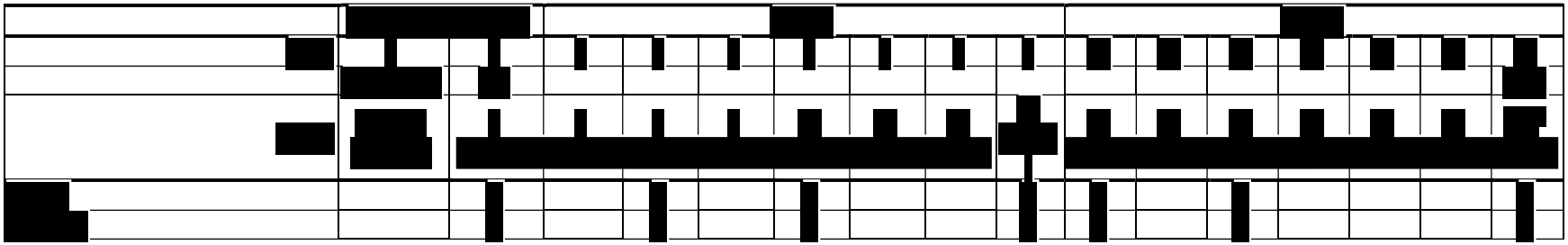

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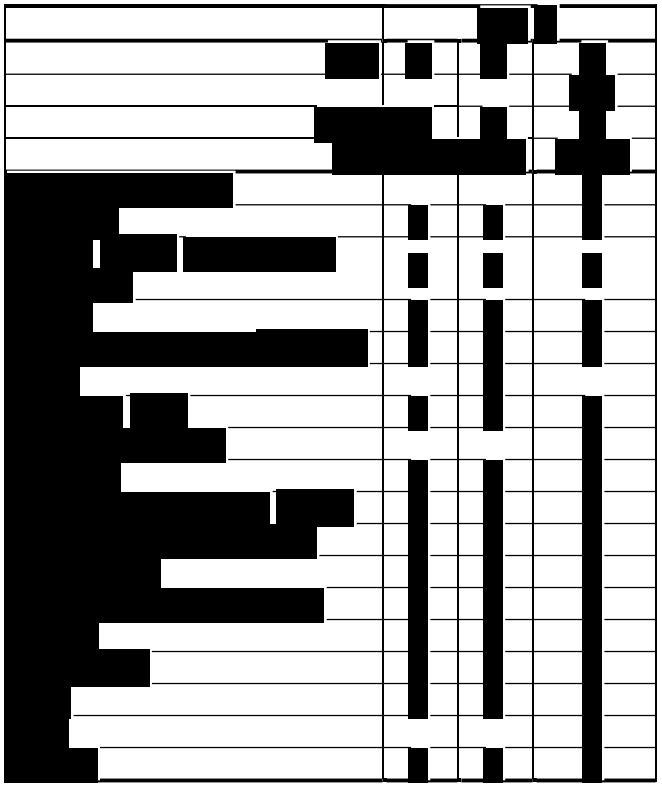

[redacted]

9.1.2.1 Blood Samples for Determination of Anti-Drug Antibodies

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

alysis),

aterials supplied by

9.1.3.5 Unscheduled Visits

An unscheduled visit is defined as any visit to the Investigator site where the subject is seen by study personnel outside of the protocol-specified time points, due to safety reasons or when a

repeated measurement is required [redacted]

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, multiple-dose, Phase 2b study to evaluate the efficacy of 4 dose groups of tildrakizumab administered by SC injection in subjects with active PsA. The study has been developed based on design features used in the completed [redacted] as well as [redacted] The primary efficacy endpoint is based on the proportion of subjects achieving ACR[redacted] response criteria at [redacted] which has been well established for the evaluation of clinical outcome. Secondary efficacy endpoints are based on evaluation of other measures of ACR (ACR[redacted] and ACR[redacted]), the proportion of subjects requiring adjustment of background medication, DAS28-CRP, MDA, dactylitis and enthesitis, and HAQ-DI, which are all accepted measures for the evaluation of clinical outcome.

The study has been designed with 4 distinct phases (Screening, double-blind treatment period, double-blind follow-up, and a wash-out period). This enables scientific evaluation of efficacy at [redacted] longer term evaluation of efficacy and safety through [redacted] and ensures subject safety via a monitored wash-out period for subjects who do not enter the LTE study. All safety measures are consistent with evaluations used in clinical studies and previous studies with tildrakizumab.

9.2.1 Risk/Benefit and Ethical Assessment

Given that efficacy benefits were reported for subjects with concurrent PsA in the completed Phase 2b study in [redacted] there is an expectation that subjects treated with tildrakizumab will improve PsA disease activity and measures of quality of life (HAQ) at [redacted] 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 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. 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 who do not enter the LTE study will continue to be monitored throughout a [redacted] following the EoT visit, during which no active IMP will be administered.

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

[redacted]

[redacted]

6. Subject had myocardial infarction, unstable angina pectoris, or ischemic stroke within the past 6 months prior to the first IMP dose.

[redacted]

[redacted]

[redacted]

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. The IMP 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 Part 1 or 2, if the withdrawn subject is willing to undergo the assessments. For subjects withdrawing during Part 3 and willing to undergo final assessments, the [redacted] should be conducted at [redacted] after their last visit.

The appropriate personnel from the site and [redacted] will assess whether IMP 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 to register the subject's discontinuation from IMP.

9.3.5 Investigational Medicinal Product Discontinuation

Subjects may voluntarily discontinue IMP for any reason at any time and enter the 20-week wash-out period, or completely withdraw from the study [redacted]). Subjects who consent to enter the wash-out period will undergo the [redacted]

At any time during Part 1 or Part 2 of the study, the Investigator should discontinue IMP of a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being. [redacted]

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

[redacted]

Note: the derivation of clinical response [redacted] will be made within the IVRS system using information provided by the site. The IVRS system will determine the subject's eligibility to continue based on treatment received during Part 1 of the study.

Reasons for Temporary Discontinuation of Study Drug

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

1. Clinically important laboratory abnormalities
2. Subjects who develop suicidal ideation

3. Other intercurrent illnesses or major surgery
4. Use of prohibited treatment
5. Any other protocol deviation that results in a significant risk to the subject's safety
6. Sponsor decision

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 IMP 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 IMP 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 IMP 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 study visits to [redacted] 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)

[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 [redacted] to reschedule or the visit window was missed and the subject still is not able to take the dose, the Sponsor should be contacted to determine if the subject should be discontinued from the study.

[redacted]

10.2 Study Treatment Packaging and Labeling

10.2.1 Packaging

[redacted]

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

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 [redacted] conditions [redacted] according to labeled storage conditions. Until dispensed for administration to subjects, the IMP will be stored in a securely locked area, accessible to authorized personnel only

10.2.4 Blinding and Randomization of Study Treatment(s)

This study will be performed as a randomized, double-blind study including 2 stratification factors [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 [redacted] is considered potentially unblinding information, it will be known to the Study Biostatistician only.

An IVRS 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]

A copy of the randomization code with true treatment allocations will be held by [redacted] during the study. Another randomization list (containing kit number and treatment) 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 IVRS without the need for communication with the Sponsor. This can only occur in emergency situations ([redacted]

Blinding of study medication and dose regimens will be maintained by using a double-dummy double-blind design, where all subjects receive medication (active or placebo) at all scheduled dosing visits. If a subject does not receive the scheduled dose, every effort should be made to administer the dose as soon as possible ([redacted]

To ensure validity of assessments, the following assessments will be performed by an independent assessor:

- Joint count
- PASI
- LDI/LEI

The PGA of disease activity will be assessed by the treating physician (using the full 68/66 tender/swollen joint count assessment [redacted]] performed by the independent assessor). All other assessments will be administered by the study co-ordinator or PI/designee [redacted] For the DAS28-CRP score [redacted] the subset of 28 joints (from the full counts) will be transcribed to the appropriate page of the eCRF by site staff, and the score will be calculated during data reporting using the eCRF data and the central CRP laboratory result.

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

10.3 Procedure for Breaking the Randomization Code

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 all subjects complete their double-blind treatment [redacted] and wash-out period.

Following last subject completion of the [redacted] visit (or earlier withdrawal from study treatment), an IA using unblinded data will be performed for the placebo-controlled double-blind treatment period [redacted]

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, IMP 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 IVRS. 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 IMP 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] r that the code 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 IVRS 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, IMP 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 (Part 1 and Part 2) using study-specific study medication dispensing 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

Concomitant Medications, Supportive Care, and Study Restrictions:

The following restrictions will apply to all subjects during the study. Subjects should abide by inclusion and exclusion restrictions.

Concomitant medications limited throughout the study [redacted]

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

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

- [redacted]

subjects taking an NSAID or low-potency opioids on average [redacted].

- Corticosteroids: Subjects taking oral corticosteroids (not to exceed the equivalent of [redacted] must remain on a stable dose. Subjects who were using topical corticosteroids when they enrolled under [redacted] may continue using them in line with the inclusion and exclusion criteria in [redacted]
- DMARDs: Subjects taking either MTX [redacted] dose, unless a decrease in dose is required because of toxicity or intolerance. Oral MTX cannot be changed to parenteral dosing during the period of observation. Subjects may not use a combination of MTX and leflunomide.

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 [redacted] per Investigator discretion and therapeutic needs of the subject, or if the subject does not show minimal response to treatment [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 [redacted] 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 Joint Counts

Five clinical patterns have been described among patients with PsA: distal interphalangeal (DIP), asymmetrical oligoarticular, symmetric polyarticular, spondylitis, and arthritis mutilans. Peripheral joints are assessed for tenderness and swelling. There is no validated measure to assess peripheral joints in PsA; the measure used is the ACR joint count initially developed for the assessment of patients with RA. The ACR joint count ranges from [redacted] for tenderness, and [redacted] he ACR joint count of [redacted] count includes the majority of joints affected in PsA, and it can be readily performed in a clinic visit. It includes the temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist (including the carpometacarpal and intercarpal joints as 1 unit), metacarpophalangeal (MCP), proximal interphalangeal (PIP), DIP, hip, knee, talotibial, midtarsal (including subtalar), metatarsophalangeal, and interphalangeal joints of the toes (proximal and distal joints of each toe is counted as 1 unit).

11.1.2 American College of Rheumatology [redacted] Response Criteria

The ACR[redacted] response measures the percentage of subjects with at least a [redacted] improvement from Baseline in both tender joints [redacted] and swollen joints [redacted] along with associated percentage improvements in [redacted] A sensitivity analysis will be performed by evaluating ACR[redacted] response calculated using ESR.

11.1.2.1 Physician Global Assessment of Disease Activity

The treating physician will evaluate the status of the subject's PsA by means of a [redacted]S. The subject will be assessed according to how their current arthritis is. The VAS will be anchored with verbal descriptors of [redacted]

11.1.2.2 Patient Global Assessment of Disease Activity

The subject will assess their current global status of PsA by means of a VAS [redacted]), anchored with verbal descriptors of [redacted]

11.1.2.3 Patient Pain Assessment

The subject will assess their level of present pain [redacted] using a VAS. The subject will be asked to rate their pain at that time on the scale that is anchored with verbal descriptors of [redacted]".

11.1.2.4 Patient Self-assessed Disability

The subject will assess their general disability over the past week using the HAQ-DI questionnaire ([redacted]

11.1.3 Health Assessment Questionnaire – Disability Index

The HAQ-DI is designed to assess patients' usual abilities using their usual equipment. Patients usually find the HAQ-DI self-explanatory, and clarifications are seldom required. There are [redacted] assessed by the HAQ-DI: [redacted] For each of these categories, patients report the amount of difficulty they have in performing 2 or 3 specific activities. The time frame for the disability questions is the [redacted] and each question can be scored as [redacted] The use of aids and devices for these activities is also recorded. Use of any device or aid will result in a [redacted] for that category. The score for the disability index [redacted]. If more than [redacted], [redacted], [redacted]. If [redacted] of the categories are missing, the sum of the categories is divided by the number of answered categories. A [redacted].

11.1.4 Disease Activity Score 28-item C-Reactive Protein

The DAS28-CRP is a measure of disease activity as assessed across [redacted] including the shoulder, elbow, wrist, MCP (1 through 5), PIP (1 through 5), and knee, with all 14 joints assessed for each side of the body. It is a [redacted] of the [redacted]

11.1.5 Leeds Dactylitis Index and Leeds Enthesitis Index

The Leeds dactylometer is a validated tool for assessing dactylitis. The dactylometer is used to measure the circumference of the base of the affected digit and is compared to the contralateral digit. The LDI is a measure of this comparison along with a tenderness score [redacted] for joints deemed to have dactylitis [redacted] The LEI examines tenderness at 6 sites: 2 [redacted] For each entheseal site, assessment is made of the adjacent joint in terms of tenderness and soft-tissue swelling, with a [redacted] if present. The LEI score range is [redacted]

11.2 Exploratory Assessments

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

11.2.1 Psoriasis Area and Severity Index

A subject's PASI is a measure of overall PsO severity and coverage. It is a commonly used measure in clinical studies for PsO treatments. PASI consists of 2 major steps: [redacted].
The PASI combines the assessment of the severity of lesions and the area affected into a single score [redacted] Every effort will be made to ensure that the Investigator or designee who performed the PASI Screening /Baseline evaluation will also perform the PASI for the subject at all subsequent visits. All PASI evaluation will be performed prior to study medication administration. The PASI evaluation will only be conducted for subjects with [redacted] disease [redacted]

11.2.2 36-item Short Form

The SF-36 v2 is a multi-purpose survey that measures 8 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.

11.2.3 Psoriatic Arthritis Impact of Disease

The PsAID questionnaire is a self-reported tool that assesses the impact of PsA on people's lives. The questionnaire assesses 9 items: pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, and anxiety, fear and uncertainty [redacted]

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in [redacted] and [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 PI 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 Screening and Baseline visit (including Screening laboratory test results, and until the first dose of IMP) 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 that:

1. Results in death

   Death is not an AE in itself, but an outcome. The cause of the death is the AE which resulted in death.

2. Is life-threatening

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it had been more severe.

3. Requires in-patient hospitalization or prolongs existing hospitalization

   Hospitalization is defined as at least 1 overnight formal admission into hospital, usually in order to perform additional tests, provide treatment which it is not possible to provide at home and/or due to an unstable medical condition which requires specific monitoring of the subject. Pre-planned hospitalizations (known already prior to signing the ICF) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalization due to unplanned complications. "Social" hospitalization whereby it is administratively impossible to release the subject home is not necessarily an SAE. Complications that occur during hospitalizations are AEs unless they would qualify as an SAE for any of the above criteria. If the complication delays subject release from hospital then the AE becomes an SAE. Hospitalizations which are not performed due to an AE are not regarded as SAEs.

4. Results in persistent or significant disability/incapacity

   The term significant disability refers to any condition that impairs physical/physiological well-being to the extent that the subject is unable to function normally. Physical disability may include, but is not limited to, permanent disability of locomotion or motility, but also systemic permanent dysfunction including heart failure, liver insufficiency or pulmonary fibrosis.

5. Is a congenital anomaly/birth defect

6. Is an important medical event

   Important medical events that my not result in death, be life-threatening or require hospitalization may be considered as an SAE when, based on appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent [redacted] listed in this definition.

12.1.1.3 [redacted]

[redacted]

12.1.1.4 [redacted]

[redacted]

12.1.1.5 Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of 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] within [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.

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.

12.1.2 Recording of Adverse Events

Any relevant observations made before the end of the Screening and Baseline visit (prior to first dose of IMP) are to be recorded on the AE eCRF, but will not be 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] following the EoT visit. For the purposes of this study, any detrimental change in the subject's condition, after the 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 wash-out period, at least 2 attempts should be made to collect AEs.

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 IMP, he/she should promptly notify the Sponsor.

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

- Mild [redacted]
- Moderate [redacted]
- Severe [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 serious. 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 a reasonable possibility of a causal 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 [redacted] 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]

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

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

- Time relationship between IMP intake and event's onset
- De-challenge
- Re-challenge
- Medical history
- Study treatment
- Mechanism of action of IMP
- Class effect
- Concomitant treatments in use
- Withdrawal of study treatment
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study medication or concomitant medication
- Protocol-related process.

Action taken with IMP due to the AE:

[redacted]

Other action taken:

[redacted]

Each single AE must be rated by choosing 1 of the following outcomes:

[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

[redacted]

12.1.6 Pregnancy

Pregnancy itself is not regarded as an AE unless there is suspicion that the IMP 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] using the reporting details provided in [redacted].

12.1.7 [redacted]

[redacted] **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.

[redacted]

If the [redacted] 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 [redacted] 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] will forward the SAE and Pregnancy report to the following Sponsor's safety representatives [redacted] (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.

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]

In accordance with ICH GCP, [redacted] 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] 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] 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] 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 [redacted] and [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 [redacted] r 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]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

12.3.2 Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening visit. A urine pregnancy test with sensitivity of at [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 beta human chorionic gonadotropin (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 [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] 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 Since Last Visit version. There are 5 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] in the suicidal ideation section, or any positive 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 temporarily discontinued 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 12-lead ECG recordings will be obtained at scheduled study visits after the subject has rested for at least 5 minutes 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 12-lead 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 12-lead 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 [redacted]

QTcB (QTc corrected according to Bazetts' 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 (Screening only), weight, general appearance, skin (presence of rash), 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 should be recorded as AEs.

12.7 Vital Signs

Body temperature (oral), systolic and diastolic cuff blood pressure [redacted] and pulse rate [redacted] 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 active infection with TB. The subject must have a [redacted], defined as a [redacted].

Subjects with a [redacted] are allowed if they have [redacted] If there is evidence of prior LTBI, subjects must have

history of adequate prophylaxis per local standard of care. If presence of LTBI is established, treatment according to local country guidelines must have been followed for at [redacted] prior to inclusion in the study.

12.8.1 QuantiFERON®-TB Gold In-Tube Test

QuantiFERON®-TB Gold In-Tube[9] is an in vitro diagnostic test using a peptide cocktail simulating [redacted]. Detection of interferon by [redacted] is used to identify in vitro responses to these [redacted]. QuantiFERON®-TB Gold In-Tube is an indirect test for TB 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 [redacted]. A maximum of [redacted] are allowed. [redacted]

12.9 Chest Radiograph

A chest radiograph will be obtained at the [redacted] in subjects with [redacted] unless it has been taken and documented within the [redacted] There must be no evidence of [redacted] for the subject to be considered eligible for the study.

12.10 Anti-drug Antibodies

The presence of ADA for tildrakizumab will be assessed at the time points specified in [redacted] and [redacted] Samples will be collected as detailed in [redacted] Sample testing will be conducted as specified in the laboratory manual.

12.11 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 [redacted]

13 STATISTICAL EVALUATION

13.1 Sample Size and Power

The study will randomize [redacted] for prior anti-TNF use [redacted]) and Baseline body weight [redacted] This sample size is based on an assumed active treatment effect in ACR[redacted] of up to [redacted] (ACR[redacted] response rate under placebo [redacted], and [redacted] in each of the remaining groups); a [redacted], and a [redacted] dropout rate. Results are based on simulations incorporating the use of the Simes method for testing the composite hypothesis that the response rate for all [redacted] active treatment groups is not significantly different from placebo versus the alternative hypothesis that at least one of the [redacted] active treatment groups has a response rate significantly greater than that of placebo. This is the primary hypothesis test for this study. Note that [redacted] per group also yields [redacted] power for testing that an individual treatment group response rate exceeds that of the placebo group assuming the true ACR[redacted] rate is [redacted] for the active group and [redacted] for placebo.

13.2 Randomization

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

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

Randomization will be performed by the [redacted]. Subjects will be stratified by prior anti-TNF use [redacted] and Baseline body weight [redacted]). [redacted]

13.3 Analysis Sets

The primary evaluation of the primary efficacy endpoint will be performed using the [redacted] Results for the [redacted] will be considered supportive. Safety endpoints will be analyzed using the Safety Analysis Set.

PK data will be analyzed using the PK Analysis Set.

13.3.1 Full Analysis Set

[redacted]

13.3.2 Per Protocol Analysis Set

[redacted] The deviations can include but are 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 at least 1 dose of IMP. Analyses will be based on the actual treatment received.

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 tildrakizumab concentration data to obtain reliable estimates of the key PK parameters.

13.4 Endpoints

13.4.1 Study Subject Data

Demographic data and subject characteristics at Baseline will be summarized descriptively.

Exposure and compliance with IMP will be summarized descriptively.

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

13.4.2 Primary Efficacy Endpoint

The primary endpoint is:

<u>Part 1:</u>

- The proportion of subjects who achieve ACR[redacted] at [redacted] as defined in [redacted].

13.4.3 Secondary Efficacy Endpoints [redacted]

The secondary efficacy endpoints are as follows:

Parts 1 and 2

- The proportion of subjects who achieve ACR[redacted] at [redacted]
- The proportion of subjects who achieve ACR[redacted] at [redacted]
- The proportion of subjects who achieve ACR[redacted] at [redacted]
- Change from Baseline in the individual components of ACR response at [redacted]
  - Tender joint counts [redacted]
  - Swollen joint counts [redacted]
  - PGA of disease activity (VAS)
  - PtGA of disease activity (VAS)
  - Patient's pain assessment (VAS)
  - Patient's self-assessed disability
  - Acute-phase hsCRP
  - ESR
- The proportion of subjects who require adjustment of background therapy.
- Change from Baseline in HAQ-DI [redacted]
- The proportion of subjects who achieve a DAS28-CRP [redacted]
- The proportion of subjects who achieve MDA criteria at [redacted].
  - [redacted]
- Change from Baseline in LDI and LEI [redacted]

13.4.4 Exploratory Efficacy Endpoints

Exploratory endpoints include:

Parts 1 and 2:

- PASI 75/90/100 response rates at measured time points for subjects with moderate disease [redacted]
- SF-36 at measured time points
- PsAID questionnaire at measured time points

- ACR[redacted], the components of ACR, DAS28-CRP, MDA, LDI, and LEI at other measured time points

Part 3:

- ACR[redacted], the components of ACR, LDI, LEI, PASI, and HAQ-DI at measured time points

13.4.5 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

These safety parameters will be assessed using the Safety Population.

13.4.6 Pharmacokinetic Endpoints

Secondary PK endpoints include:

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

Exploratory PK endpoints will be based on a mechanistic-based exposure-response (i.e., indirect) PK/PD model to explore the relationship of tildrakizumab exposure and PD endpoints.

These parameters will be assessed using the PK Analysis Set.

13.4.7 Anti-Drug Antibodies Endpoints

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

13.5 Description of Statistical Analyses

13.5.1 General Considerations

The statistical evaluation will be performed by [redacted] using SAS®, [redacted].

13.5.2 General Statistical Methods

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation (SD), median, and range will be provided. For categorical 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 last value of a variable taken before the first dose of IMP will be used as the Baseline value. Unless otherwise specified, missing or dropout data 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], incorporating prior anti-TNF use and Baseline weight as stratification factors, to compare response rates for the primary endpoint (ACR[redacted] at [redacted] between placebo and each of the respective active dose arms. In addition, the [redacted] common risk (the response rate) difference between placebo and each of the respective active dose arms and the confidence interval (CI) will be estimated. In order to control for [redacted], the [redacted] will be used in the determination of dose level success against placebo. Should assumptions per the [redacted] not be satisfied, pairwise comparisons will be based on [redacted] following [redacted]. In this case, the [redacted] be based on [redacted] Early withdrawals and any other subjects with incomplete data at [redacted] will be classified as [redacted] for the primary endpoint (ACR[redacted]). Subjects who fail to show minimal response to treatment [redacted] 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.

Analysis of the primary endpoint will be based on the [redacted]. A sensitivity analysis will be performed based on [redacted].

Subgroup analysis on prior anti-TNF use [redacted] and Baseline weight [redacted] may be performed for the primary endpoint. [redacted].

13.5.4 Analysis of Secondary Endpoint(s)

All secondary analyses will be performed using the [redacted]. Binary secondary endpoints up to [redacted] will be analyzed based on the methods described for ACR[redacted] Continuous endpoints up to [redacted] will be analyzed based on a mixed model repeated measure (MMRM) analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, prior TNF use (yes/no), Baseline weight (≤ 90 kg, > 90 kg), and Baseline value.

Key secondary analyses will also be performed for the [redacted]S. A more detailed description of secondary endpoint analysis, including those considered key, will be presented in the SAP.

13.5.5 Analysis of Exploratory Endpoints

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

For [redacted] the effect of IMP discontinuation on ACR[redacted], ACR[redacted], ACR[redacted], the components of ACR, LDI, LEI, PASI, and HAQ-DI will be evaluated using summary statistics. Specifically, the proportions of subjects who achieve ACR[redacted], ACR[redacted], ACR[redacted], and PASI75/90/100 at each measured time point during [redacted] will be summarized [redacted] in the components of ACR, LDI, LEI, and HAQ-DI during [redacted] will be summarized descriptively by randomized treatment group.

13.5.6 Analysis of Pharmacokinetic Endpoints

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

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

The PK Analysis Set will be used for the analysis.

Exploratory analysis will be performed as below:

- [redacted]
- [redacted]

Exploratory PK analyses may be described in separate SAPs.

13.5.7 Analysis of Anti-Drug Antibodies

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

13.5.8 Safety Analyses

The analysis of safety parameters will be based on the Safety Analysis Set. 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 (MedDRA). 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.

[redacted]

Clinical Laboratory

Clinical laboratory parameters [redacted] will be summarized at each scheduled visit.

Values outside the normal range will be [redacted] 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 [redacted] will be summarized at each scheduled visit.

ECG

The overall ECG interpretation will be summarized by presenting the [redacted]

ECG parameter [redacted] 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.

13.5.9 Interim Analysis

[redacted].

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

Patients with PsA, especially those patients with severe disease, are at increased risk of atherosclerotic cardiovascular events and have high rates of comorbidities associated with cardiovascular risk (e.g., hypertension, obesity, diabetes). As such, 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 direct access 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)[11], 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 medical records 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]n 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 Sponsor/[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, Investigator's Brochure, 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.

16.2.1 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 results of the interim 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 members of the DSMB and the unblinded statistician will have access to these data.

At each planned safety review, the randomization codes 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 unblinded statistician.

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 [redacted] 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:

1. 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)
2. Intentional act or negligence on the part of the Investigator or Sub-Investigator or malpractice thereby
3. Injury caused by unlawful act or delinquency of a third party
4. 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

[redacted]

[redacted] [redacted]

22 REFERENCE LIST

1. MK-3222 (SCH 900222) Investigators Brochure. Edition 7. 10 October 2016.
2. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl II):ii14–ii17.
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23 APPENDIX 1

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