Official title: A Long-Term extension study to demonstrate safety of Tildrakizumab in subjects with Psoriatic Arthritis who have previously completed study with Tildrakizumab.

Document: Clinical Study Protocol

NCT number: NCT03552276

Document date: 22-Jul-2020

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A Long-Term Extension Study to Demonstrate Safety of Tildrakizumab in Subjects with Psoriatic Arthritis who Have Previously Completed Study with Tildrakizumab

Protocol No.: CLR_18_07	EUDRACT Number: 2018-001060-35
Test Product:	Tildrakizumab
Indication:	Psoriatic Arthritis
Sponsor:	Sun Pharma Global FZE [redacted]
Development Phase:	Phase 2b/3
Sponsor Signatory:	[redacted]
Sponsor Medical Expert:	[redacted]
Date of the Protocol:	22 July 2020

Version of the Protocol: Protocol version 01, Amendment 1

[redacted]

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Long-Term Extension Study to Demonstrate Safety of Tildrakizumab in Subjects with Psoriatic Arthritis who Have Previously Completed Study with Tildrakizumab

PROTOCOL NUMBER: CLR_18_07

[redacted]

[redacted]

3 GENERAL INFORMATION

A Long-Term Extension Study to Demonstrate Safety of Tildrakizumab in Subjects with Psoriatic Arthritis Who Have Previously Completed Study with Tildrakizumab

Protocol No.:	CLR_18_07
Date of the Protocol:	15 Mar 2018
Date and Number of Amendment(s):	Amendment 1, 22 July 2020
Sponsor:	[redacted]
[redacted]	[redacted]
[redacted]	
Sponsor Signatory:	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[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		
Name of Active Ingredient: Tildrakizumab	**Volume:**	
	Page:	

Title of Study:
A Long-Term Extension Study to Demonstrate Safety of Tildrakizumab in Subjects with Psoriatic Arthritis who Have Previously Completed Study with Tildrakizumab

Study Sites:
It is planned that at least 70 sites will be initiated for this study in at least 8 countries. All study sites used in the parent study can enter subjects to this long-term extension study, based on subject eligibility.

Publication(s):
None.

Planned Study Period:	**Development Phase:**
Approximately June 2018 to an anticipated date of approximately 4 years after last subject entered from contributing parent study.	Phase 2b/3

Objectives:

Primary Safety Objectives

To assess the long-term safety of tildrakizumab given to psoriatic arthritis (PsA) subjects by evaluation of:

- Incidence and intensity of all adverse events (AEs),
- Changes in vital signs, laboratory assessments, electrocardiograms (ECGs), and Columbia-Suicide Severity Rating Scale (C-SSRS),
- Immunogenicity of multiple-dose administration of tildrakizumab in these subjects.

[redacted]

Methodology:

This is a long-term extension study of tildrakizumab in subjects with PsA who have previously completed the treatment period of study with tildrakizumab. The eligible subjects will continue to be administered one of the following dose regimens – 200 mg Q4W, 200 mg Q12W or 100 mg Q12W to maintain the blind of the ongoing parent study to at least Week 52. Thereafter, all subjects begin migrating to receive 100 mg tildrakizumab SC injection Q12 weeks in an open-label fashion for up to an additional 4 years in this long-term extension study, provided that they meet clinical response criteria.

No randomization will occur for this long-term extension study. Treatment allocation will be based upon the dose regimen assigned at the end of the treatment period in the parent study with all subjects receiving tildrakizumab. With this amendment, all subjects shall receive 100 mg tildrakizumab, every (Q) 12 weeks in the long-term extension study. All subjects who meet the inclusion criteria and complete the parent study treatment (up to Week 48 for the parent Phase 2 study, with return for the End of Treatment [EoT] visit at Week 52), and who meet defined clinical response criteria will receive 100 mg tildrakizumab, Q12 weeks for up to an additional 4 years. Subjects who completed the treatment period of their parent study and entered the parent study wash-out phase prior to study site activation of the long-term extension protocol will also be eligible for inclusion in the long-term study (when available) provided all eligibility criteria are met.

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The study will consist of a Baseline visit (Week 0) which will be the same as Week 52 of the parent study 12-weekly visits (from Week 8) up to approximately 2 years from the start of the extension study, followed by 24-weekly visits thereafter (from Week 104) up until approximately 4 years after the start of the study (approximately 5 years from the start of the parent study).

The parent Phase 2 study will retain a blind status at the time of the initiation of the extension study (double-blind for the PsA study, i.e., only the Sponsor and designated contract research organization [CRO] team members not directly related to the clinical conduct of the study will have been unblinded). Safety assessments will be conducted at the 12 weekly or 24-weekly visits in accordance with the Schedule of Assessments.

All scheduled visits will occur at the study site. However, should unusual circumstances such as public health emergency (i.e. pandemic with an infectious agent) or natural disasters arise, video conference or teleconference between the subject and site investigator will be permitted as deemed appropriate by the Sponsor provided no physical examination is needed for the visit. In this unusual circumstance, self-injection made by the subject at subject's home is allowed in order to guarantee treatment continuity.

When all subjects have completed the PsA parent Phase 2 study, the blind will no longer need to be maintained for the cohort, and this long-term extension study will have the option to become open-label for those subjects. Note: the timing of switch to an open-label design may differ across the cohorts of subjects entered, depending on the parent study. If other studies are also included in the long-term extension study, similar considerations for maintenance of blind will be necessary. Those subjects will be entered as separate cohorts and procedures such as continued double-dummy dosing regimens will be utilized, even after other parent Phase 2 cohorts have the option to switch to open-label.

Subjects not deriving sufficient clinical benefit in the opinion of the Investigator at any time after the initiation of this long-term extension study should be discontinued from investigational medicinal product (IMP), and receive clinical care as determined by the Investigator.

With the exception of those who withdraw informed consent, subjects who withdraw from IMP during the long-term extension study will undergo the EoT assessments approximately 4 weeks after their last administration of IMP. Subjects who complete treatment to Week 200 will return for a Follow-up assessment at Week 208 (4 years).

No independent assessor is needed to assess efficacy measurements. There will be no efficacy assessments during the LTE study. The Principal Investigator (PI)/designee will be responsible for performing safety evaluations.

Clinical Adjudication Committee will be established to evaluate cardiovascular events.

End of study is defined as the last visit of the 4-year treatment period (Week 208, EoT/Follow-up) for the last global subject.

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[redacted]

1 Subjects from parent Phase 2 study who do not meet inclusion/exclusion criteria at Wk 52 of parent study (using laboratory data from Wk 48 for efficacy response criteria), or who in the opinion of the Investigator would not benefit from continued treatment with Tildrakizunmab, will enter the 20-Wk wash-out phase in accordance with the parent protocol (Not shown). All eligible subjects will continue to long-term extension study, commencing at Wk 52 of parent study (B/L) and receive tildrakizumab 100 mg q12 wks (Week 0 of long-term extension study). Subjects who completed the treatment period of their parent study and entered the wash-out phase prior to study site activation of the long-term extension protocol will also be eligible for inclusion in the long-term study (when available) provided they meet eligibility criteria.

2 B/L = Wk 0 of the long-term extension study, and will be the same as Wk 52 of the parent study.

3 The long-term extension study will remain double-blind for all subjects from the parent Phase 2 PsA study until such point that the PsA study is complete with database locked. At that time, the long-term study will have the option to become open-label for subjects entering from Phase 2 parent study. Note the timing of the switch to open-label may differ across the cohorts of subjects, dependent on the parent study. The IMP administration will continue Q12 weeks, while the safety assessments will be Q12 weeks in the first two years, followed by Q24 weeks in the last 2 years.

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Number of Subjects:
Up to 286 subjects with PsA could be enrolled from the parent Phase 2 study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

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

1. Subject has provided written informed consent for this long-term extension study.
2. Subjects with PsA who met the inclusion criteria of the parent study and completed the parent study treatment period (e.g., up to Week 48 for the parent Phase 2 study, with return for the EoT assessment at Week 52).
3. PsA subjects who achieved a 20% reduction from Baseline in American College of Rheumatology (ACR)20 response criteria at Week 52, AND the subject has received sufficient clinical benefit, in the opinion of the Investigator, to support continued treatment with tildrakizumab.

   This criterion using response criteria at Week 52 will apply to all subjects, including those subjects who enter the study from the wash-out phase of their parent study (after Week 52) due to the timing of study site activation of the long-term extension study.
4. No concomitant use of both leflunomide and methotrexate simultaneously.
5. No history of active tuberculosis (TB) or symptoms of TB.

Exclusion Criteria:

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

1. New onset during the parent study of arthritic conditions other than the subject's original condition.
2. Female subjects of childbearing potential who do not agree to abstain from heterosexual activity or practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo-progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy). Contraceptive methods must be practiced upon entering the study and through 16 weeks after the last dose of IMP. If a subject discontinues prematurely, the contraceptive method must be practiced for 16 weeks following final administration of IMP.
3. Female is pregnant or breastfeeding, or planning to become pregnant or initiate breastfeeding while enrolled in the study or up to 16 weeks after the last dose of IMP.
4. Subject has previously been enrolled in this long-term extension study.
5. Any condition that in the opinion of the Investigator represents an obstacle for study conduct and/or represents a potential unacceptable risk for the subject.
6. Subject has an active infection or history of infections as follows:
   - a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first IMP dose of the extension study, with the last dose having been received within 7 days of start of the extension study,
   - recurrent or chronic infections, e.g., chronic pyelonephritis, chronic osteomyelitis, bronchiectasis, or other active infection that, in the opinion of the Investigator, might cause this extension study to be detrimental to the subject.

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7. Major chronic inflammatory or connective tissue disease other than PsA (e.g., rheumatoid arthritis, systemic lupus erythematosus, Lyme disease, gout, Crohn's disease, etc).
8. Known diagnosis of fibromyalgia, regional pain syndromes or active uveitis/symptomatic inflammatory bowel disease requiring therapy.
9. Subject has any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, or anemia) that, in the opinion of the Investigator, could cause continued treatment to be detrimental to the subject.
10. Subject has a known history of infection with hepatitis B, hepatitis C, or human immunodeficiency virus during the parent study.
11. Subject had myocardial infarction, unstable angina pectoris, or ischemic stroke within the past 6 months prior to the first IMP dose for this extension study.
12. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
13. Subject has a history of malignancy EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, *in situ* cervical carcinoma, OR *in situ* breast ductal carcinoma.
14. Subjects with a history of alcohol or drug abuse during the parent study.
15. Significant risk of suicidality at the Baseline assessment of this extension study based on the Investigator's judgment or, if appropriate, as indicated by a response of "yes" since the last visit to question 4 or 5 in the suicidal section, or any response in the behavioral section of the C-SSRS.
16. Subject has a need for use of a live vaccine within 10 weeks of final anticipated dose of IMP for the long-term extension study.
17. Concomitant use of prohibited medications or use of commercially available or investigational biologic therapies (other than tildrakizumab) for psoriasis or PsA.

General

18. Subjects who have been placed in an institution on official or judicial orders.
19. Subjects who are related to or dependent on the Investigator, Sponsor, or study site such that a conflict of interest may arise.

Test Product, Dose and Mode of Administration:

The IMP will be supplied as a [redacted] and administered subcutaneously (SC). All subjects will be dosed at the same time points with 100 mg tildrakizumab Q12 weeks (one 1-mL injection of 100 mg/mL) at Weeks 0, 8, 20, 32, 44, 56, etc and all subsequent 12-weekly time points to Week 200.

Reference Therapy, Dose and Duration of Administration:

There will be no placebo comparator in this study.

Investigational [redacted] and administered SC. Self-administration made by the subject at the subject's home is contemplated only if unusual circumstances, such as public health emergency (i.e. pandemic with an infectious agent) or natural disasters, arise.

Duration of Treatment:

Up to 200 weeks of continued tildrakizumab treatment from the parent study, followed by an EoT/Follow-up assessment at Week 208 (4 years), or approximately 4 weeks after last dose of IMP for those withdrawing early.

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Concomitant Medications, Supportive Care, and Study Restrictions:

Permitted medications include:

- Acetaminophen, except within 24 hours before a scheduled study efficacy evaluation,
- Non-steroidal anti-inflammatory drugs or low potency opioids,
- Methotrexate or leflunomide. Subjects may not be receiving both treatments concomitantly,
- Oral corticosteroids (no more than 10 mg for maintenance dose),
- Non-drug therapy (including but not limited to physical therapy, massage, diet, exercise, emollients, and joint taping).

Use of and adjustment of permitted medication is permitted throughout the study per Investigator discretion and therapeutic needs of the subject.

In accordance with the parent study, subjects are prohibited from use of the following at the time of written informed consent for and during the long-term extension study:

- High potency opioid analgesics (e.g., methadone, hydromorphone, or morphine) for the treatment of arthritis (allowed for treatment of other conditions for periods of up to 2 weeks),
- Sulfasalazine,
- Systemically administered calcineurin inhibitors (e.g., cyclosporine, tacrolimus),
- Azathioprine,
- Parenteral corticosteroids including intramuscular or intra-articular administration (topical, ophthalmic, intra-nasal, and inhaled corticosteroids are permitted) for the treatment of arthritis (allowed for treatment of other conditions for periods of up to 2 weeks),
- Live vaccines.

Any prohibited treatments must be discontinued prior to IMP initiation for the long-term extension study.

Additionally, subjects must not use systemic immunosuppressive therapies including commercially available or investigational therapies for psoriasis (PsO) and/or PsA such as:

- Use of all anti-tumor necrosis factor agents, including etanercept,
- Use of B-cell and T-cell depleting/inhibiting agents,
- Use of any other commercially available or investigational biologic therapies (other than tildrakizumab) for PsO and/or PsA within 3 months or 5 half-lives (whichever is longer) prior to or during IMP in the long-term extension study,
- Use of apremilast, or other approved or investigational medications for the treatment of current condition which are not identified as permitted therapies,
- Use of secukinumab, ustekinumab, ixekizumab, brodalumab, or any drug targeting interleukin (IL)-17, IL-23, or the IL-12/IL-23-shared p40 molecule.

Variables:

All endpoints will be presented for the measured time points indicated in the flow diagram of the study design.

Pharmacokinetics: Serum tildrakizumab concentration data.

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

- AEs.

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- AEs of special interest (AESIs).
- Laboratory assessments.
- Suicidal ideation and behavior (C-SSRS).
- Vital signs.
- Electrocardiogram.
- Physical examination.
- ADA to tildrakizumab.

Statistical Methods:

The All Subjects as Treated (ASaT) population consists of all subjects who entered the long-term extension study. The ASaT is the primary population for safety/tolerability and PK analyses. The analysis will be based on the treatment subjects actually received.

Safety endpoints will be analyzed descriptively.

Serum tildrakizumab concentration data will be listed by individual subject and summarized by visit and tildrakizumab dose group.

For all endpoints, the subjects in the parent PsA study will be summarized separately, by study and indication. [redacted]

Date of the Protocol: 22 July 2020

5 TABLE OF CONTENTS

5.1 List of Tables

5.2 List of Figures

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR(20/50/70)	The proportion of subjects achieving a 20/50/70% reduction from Baseline in American College of Rheumatology response criteria
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
[redacted]	[redacted]
ASaT	All Subjects as Treated
AUC	area under the curve
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAC	Clinical Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CPMP	Committee for Proprietary Medicinal Products
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EoT	End of Treatment
ESR	erythrocyte sedimentation rate
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
EUQPPV	European Union Qualified Person for Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
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
IgG1	immunoglobulin G1
IL	Interleukin
IMP	investigational medicinal product

IRB	Institutional Review Board
IV	Intravenous
IVRS	interactive voice response service
LTE	Long-term Extension
MACE	Major Adverse Cardiovascular Events
NOAEL	no-observed-adverse-effect-level
[redacted]	[redacted]
PASI75	proportion of subjects achieving a 75% reduction from Baseline in Psoriasis Area and Severity Index
[redacted]	[redacted]
PGA	Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
PQC	product quality complaint
PsA	psoriatic arthritis
PsO	Psoriasis
PT	preferred term
PtGA	Patient Global Assessment
Q	Every
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to the Fridericia formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
SF-36	36-item Short Form
SJC44	swollen joint count of 44 joints
SOP	Standard Operating Procedure
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC46	tender joint count of 46 joints
VAS	Visual Analog Scale

7 INTRODUCTION

7.1 Background

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

From animal studies and human disease association studies, there is significant evidence that IL-23 is a key pro-inflammatory cytokine in psoriasis (PsO), psoriatic arthritis (PsA), [redacted] Strong support for the relevance of the IL-23 pathway in PsO, PsA, and AS has come from genome-wide association studies identifying a specific hypomorphic polymorphism in the gene coding for IL-23R (rs11209026) to be less frequent in patients with these conditions.[1]

Tildrakizumab is being developed for chronic plaque PsO, and Phase 3 studies have been unblinded, with subjects continuing in a long-term open-label extension phase. In addition, a Phase 2 study for subjects with PsA has been completed. Tildrakizumab is anticipated to demonstrate efficacy in subjects with these conditions due to the relevance of the IL-23 pathway in these diseases. 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.[2]

Efficacy data are available from completed Phase 2 PsA study, and Phase 2 Study P05495 for subjects with moderate-to-severe chronic plaque PsO. Overall, all 4 doses of tildrakizumab (5 mg, 25 mg, 100 mg, and 200 mg dose levels administered at Weeks 0 and 4, then every [q] 12 weeks thereafter) were demonstrated to be safe and more efficacious than placebo (primary endpoint of proportion of subject achieving a 75% reduction from Baseline in Psoriasis Area and Severity Index [PASI75] at Week 16).

Efficacy data from the completed base portion of the Phase 3 studies (P010 and P011, both with tildrakizumab 100 mg or 200 mg doses administered at Weeks 0 and 4, then Q12 weeks thereafter to Week 52) also showed that treatment with each tildrakizumab dose demonstrated statistically significant efficacy compared to placebo. The analyses for P010, a 3-part, 64-week, randomized, double-blind, placebo-controlled, parallel-group, multi-site study, showed that tildrakizumab was generally well tolerated with a low incidence of drug -related adverse events (AEs) and AEs leading to discontinuation of investigational medicinal product (IMP). Similarly, the evaluation of the base portion of P011, a 52-week, randomized, double-blind, active -comparator and placebo-controlled, parallel-group, multi-site study also showed superiority of both doses of tildrakizumab (100 mg and 200 mg) over placebo on both co-primary endpoints (proportion of subjects achieving PASI75 and proportion of subjects with

a Physician Global Assessment [PGA] score of "clear" or "minimal", with at least a 2-grade reduction from Baseline at Week 12).[1]

The completed Phase 2 study for PsA subjects included the tildrakizumab dose regimens of 200 mg Q4 weeks, 200 mg Q12 weeks, 100 mg Q12 weeks, 20 mg Q12 weeks. In this Phase 2b study on PsA (Protocol SUN_CLR_16_23) involving 391 subjects from eight [redacted] an interim analysis demonstrated that all four tildrakizumab dosing regimens tested (200 mg, q4 weeks; 200 mg, q12 weeks; 100 mg, q12 weeks; and 20 mg, q12 weeks) were more efficacious than placebo as measured by ACR20 at Week 24 (primary endpoint). In addition, at Week 24, all four dosing regimens of tildrakizumab demonstrated benefit over placebo in ACR50 response, while only three dosing regimens (200 mg, q4 weeks; 200 mg, q12 weeks, 100 mg, q12 weeks) demonstrated benefit over placebo in ACR70. As of the database lock date of 05 Nov 2019 for PsA Phase 2 study, there have been no reported serious unexpected suspected adverse reactions in the study.

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

7.2 Rationale

7.2.1 Rationale for Dose

In this long-term extension study for subjects with PsA, the treatment regimen of tildrakizumab used will be one of the regimens that subjects are receiving at completion of the treatment phase of their parent study. No subjects will be receiving placebo as an assigned treatment group at completion of Phase 2 treatment in the parent study (Protocol number CLR_16_23), and all eligible subjects will have the opportunity to receive tildrakizumab in the long-term extension. The tildrakizumab treatment groups for subjects from the parent Phase 2 study will include 100 mg subcutaneous (SC) Q12 weeks, 200 mg SC Q12 weeks, and 200 mg SC Q4 weeks. The eligible subjects will continue to be administered one of the following dose regimens – 200 mg Q4W, 200 mg Q12W or 100 mg Q12W to maintain the blind of the ongoing parent study to at least Week 52. Thereafter, all subjects began migrating to receive 100 mg tildrakizumab SC injection Q12 weeks in an open-label fashion for up to an additional 4 years. These dose regimens are anticipated to provide robust suppression of the IL-23 pathway, and allow investigation of safe treatment of patients with the chronic condition PsA for prolonged periods of time.

[redacted] he estimated safety margin was derived from the systemic exposure at the no-observed-adverse-effect-level (NOAEL) dose (100 mg/kg given q14 days) in the 9-month repeat-dose primate toxicology study, and the

human exposures obtained from the Phase 1 studies. [redacted]. The human exposure at steady-state for the Phase 2/3 dosing paradigm (once Q12 weeks) was estimated by the observed exposure of $AUC0_{-\infty}$ (1130 and 1280 µg*day/mL) following a SC single-dose of 200 mg in Phase 1 clinical studies (P05776 and P06303), respectively. [redacted]

To date, tildrakizumab has been well tolerated at doses up to 200 mg Q12 weeks and no dose -related toxicities have been observed. The available accrued safety data from Phase 1 to Phase 3 studies in subjects with PsO supports the continued conduct of the long-term extension studies in PsO, and further study of tildrakizumab in subjects with moderate-to-severe chronic plaque PsO at doses up to and including 200 mg SC. In PsA Phase 2 study, there was no statistical advantage of therapeutic efficacy observed in a higher dose of tildrakizumab 200 mg over tildrakizumab 100 mg. Therefore, the dose regimen of tildrakizumab 100 mg, Q12 weeks was chosen for the long-term extension study. The current data also support the conduct of clinical studies in-patient populations where IL-23 is anticipated to play a pathogenic role in inflammatory disease such as PsA, AS, and related conditions.

7.2.2 Rationale for Study

The parent Phase 2 study is the first to be conducted with tildrakizumab in subjects exclusively with PsA, and the first to include a dosing regimen of 200 mg SC Q4 weeks. As tildrakizumab is in development for the PsO indication (Phase 3 completed, long-term safety studies ongoing), and substantial pharmacokinetic (PK) and pharmacodynamics data exist that can inform dose selection used in the parent studies, evaluation of long-term safety, tolerability, and efficacy is necessary in these disease areas where suppression of the IL-23 pathway is relevant, and where patients may require life-long treatment options. The study will include subjects with PsA from the Phase 2 study evaluating these subject population (e.g., future Phase 3 studies). The study will provide this patient population with the opportunity for continued use of a treatment that has afforded clinical benefit across an approximate 52-week period during their parent study.

8 STUDY OBJECTIVES

8.1 Primary Safety Objectives

To assess the long-term safety of tildrakizumab when administered to PsA subjects by evaluation of:

- Incidence and intensity of all AEs,
- Changes in vital signs, laboratory assessments, electrocardiograms (ECGs), and Columbia-Suicide Severity Rating Scale (C-SSRS),
- Immunogenicity of multiple-dose administration of tildrakizumab in these subjects.

8.2 Exploratory Objectives

- [redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a long-term extension study of tildrakizumab in subjects with PsA who have previously completed the treatment period of studies with tildrakizumab. Eligible PsA subjects who have previously completed the treatment period of Phase 2b study (CLR_16_23) will be entered into this long-term extension study.

The study will be multinational and conducted in approximately 70 study sites. All study sites used in the parent study can enter subjects to this long-term extension study, based on subject eligibility. Up to 286 subjects with PsA could be enrolled from the parent Phase 2 study. Treatment allocation will be based upon the dose regimen assigned at the end of the treatment period in the parent study, with all subjects receiving tildrakizumab in the long-term extension study. All subjects who meet the inclusion criteria and have completed the parent study treatment period (up to Week 48 for the parent Phase 2 study will return for the End of Treatment [EoT] visit at Week 52 of the parent study). The eligible subjects will continue to be administered one of the following dose regimens – 200 mg Q4W, 200 mg Q12W or 100 mg Q12W to maintain the blind of the ongoing parent study to at least Week 52 of the parent study. Thereafter, all subjects began migrating to receive 100 mg tildrakizumab SC injection Q12 weeks in an open-label fashion for up to an additional 4 years provided that they meet clinical response criteria (as defined in Section 9.3.1).

Note: eligibility for the long-term extension study will be based on response criteria at Week 52 of the parent study [using Week 48 laboratory data from the parent study where relevant for calculations] regardless of timing of subject entry. Subject eligibility for continuation to the long-term extension study based on the clinical response criterion will be determined by the interactive voice response service (IVRS). A flow diagram of the study design is presented in Figure 9-1 below.

The study will consist of a Baseline visit (Week 0) which will be the same as Week 52 of the parent study, 12-weekly visits (from Week 12) up to approximately 2 years from the start of the extension study, followed by 24-weekly visits thereafter (from Week 108) up until approximately 4 years after the start of the study (approximately 5 years from the start of the parent study).

The parent Phase 2 study blind status will be retained at the time of the initiation of the extension study). The eligible subjects will continue to be administered one of the following dose regimens – 200 mg Q4W, 200 mg Q12W or 100 mg Q12W to maintain the blind of the ongoing parent study to at least Week 52 of the parent study. Thereafter, all subjects begin migrating to receive 100 mg tildrakizumab SC injection Q12 weeks in an open-label fashion

for up to an additional 4 years. Safety assessments will be conducted at the 12-weekly or 24-weekly visits in accordance with Table 9-1.

All scheduled visits will occur at the study site. However, should unusual circumstances such as public health emergency (i.e. pandemic with an infectious agent) or natural disasters arise, video conference or teleconference between the subject and site investigator will be permitted as deemed appropriate by the Sponsor provided no physical examination is needed for the visit. In this unusual circumstance, self-injection made by the subject at the subject's home A decision to remove one or more treatment arms from the long-term extension study may occur as information from parent study becomes available. Subjects already enrolled in the long-term extension study may be switched to selected dose regimens for continued evaluation at that time. This decision is anticipated to occur approximately 1 year after the start of the long-term study.

When all subjects have completed the PsA Phase 2 parent study, [redacted] Note: the timing of switch to an open-label design may differ across the cohorts of subjects entered, dependent on the parent study. If other studies are also included in the long-term extension study, similar considerations for maintenance of blind will be necessary. Those subjects will be entered as separate cohorts and procedures such as continued double-dummy dosing regimens will be utilized, even after other parent Phase 2 cohorts have the option to switch to open-label.

In PsA Phase 2 study [CLR_16_23 PsA study], both tildrakizumab, 200 mg q12 weeks and tildrakizumab 100 mg, q12 weeks provided similar efficacies in the ACR20, ACR50, and ACR70 at Week 24. The lowest dose of 20 mg q12 weeks, did not demonstrate superiority over placebo in ACR70 and had numerically lowest ACR 50 response among the active doses tested. The highest dose of tildrakizumab 200 mg q4 weeks, did not provide significant benefit over tildrakizumab 200 mg, q12 weeks. Therefore, the dose regimen of tildrakizumab 100 mg, q12 weeks is chosen for the long-term extension study going forward.

Subjects not deriving sufficient clinical benefit in the opinion of the Investigator at any time after the initiation of this long-term extension study should be discontinued from IMP as described in Section 9.3.5, and receive clinical care as determined by the Investigator.

With the exception of those who withdraw informed consent, subjects who withdraw from IMP during the long-term extension study, will undergo the EoT assessments approximately

4 weeks after their last administration of IMP. Subjects who complete treatment to Week 200 will return for a Follow-up assessment at Week 208 (4 years).

The primary safety objectives of this study include assessment of the long-term safety of tildrakizumab by evaluation of incidence and intensity of AEs, and changes in vital signs, laboratory assessments, ECGs, C-SSRS, and immunogenicity data.

No independent assessor is needed to assess efficacy measurements. There will be no efficacy assessments during the LTE study. The Principal Investigator (PI)/designee will be responsible for performing safety evaluations.

Clinical Adjudication Committee (CAC) will be established to evaluate cardiovascular events (Section 13.3.6).

End of study is defined as the last visit of the 4-year treatment period (Week 208, EoT/Follow-up) for the last global subject.

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

[redacted]

1 Subjects from the parent Phase 2 study who do not meet inclusion/exclusion criteria at Wk 52 of the parent study (using laboratory data from Wk 48 for efficacy response criteria), or who in the opinion of the Investigator would not benefit from continued treatment with tildrakizumab, will enter the 20-Wk wash-out phase in accordance with the parent protocol (Not shown). All eligible subjects will enter the long-term extension study, commencing at Wk 52 of the parent study (B/L) and receive tildrakizumab 100 mg Q12 wks regimen (Week 0). Subjects who completed the treatment period of their parent study and entered the wash-out phase prior to study site activation of the long-term extension protocol will also be eligible for inclusion in the long-term study (when available) provided they meet eligibility criteria.

2 B/L = Wk 0 of the long-term extension study, and will be the same as Wk 52 of the parent study.

3 The long-term extension study will remain double-blind for all subjects from the parent Phase 2 PsA study until such point that the PsA study is complete with database locked. At that time, the long-term study will have the option to become open-label for subjects entering from Phase 2 parent study. Note the timing of the switch to open-label may differ across the cohorts of subjects, dependent on the parent study. The IMP administration will continue Q12 weeks, while the safety assessments will be Q12 weeks in the first 2 years, followed by Q24 weeks in the last 2 years.

9.1.2 Schedule of Assessments

The Schedule of Assessments for subjects from the PsA parent study are presented in Table 9-1.

Table 9-1 Schedule of Assessments for PsA Subjects

Visit[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	1Y BL					2Y				3Y					4Y				EoT/ FU
Week (± 7D)	0[b]	8	20	32	44	56	68	80	92	104	116	128	140	152	164	176	188	200	208[c]
Written informed consent	X																		
Inclusion/Exclusion criteria	X																		
Demographic information[d]	X																		
Physical examination	X					X				X				X				X	X
Vital signs	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X
AEs/Concomitant medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/Medication history[e]	X																		
ECG	X					X				X				X					X
IMP administration[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/chemistry/urinalysis[g]	X		X			X				X				X				X	X
Lipids[h]	X		X			X				X				X				X	X
Urine pregnancy test[i]	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X
hsCRP and ESR[i]	X		X			X				X				X				X	X
Anti-drug antibodies	X		X			X				X				X				X	X[j]
PK sample[h]	X		X			X				X				X				X	X
C-SSRS[k]	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X

Abbreviations: AE = adverse event; BL = Baseline; C-SSRS = Columbia-Suicide Severity Rating Scale; D = days; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; EoT = End of Treatment; FU = Follow-up; hsCRP = high sensitivity C-reactive protein; IMP = investigational medicinal product; M = months; PK = pharmacokinetic; PsA = psoriatic arthritis; W = weeks; Y = year(s).

a Visits will be scheduled every 12 weeks in the first two years, followed by every 24 weeks in the last two years. Collection of AEs and concomitant medications, as well as any unscheduled safety assessment deemed appropriate in the opinion of the Investigator to ensure subject safety, will be performed at each visit. In addition, following completion and database lock of the parent PsA Phase 2 study, the long-term extension study will have the option to become open-label for these subjects.

b The BL visit of the study Visit 1 (Week 0, Day 1) will be the same as Visit 16, Week 52 of parent PsA study (or later for subjects who entered the wash-out phase from the parent study due to the timing of study site activation of the long-term extension study).

c Subjects who withdraw from IMP at any time will complete the EoT/FU assessments approximately 4 weeks after administration of the last dose of IMP.

d To include body weight and height only. Other demographic data including date of birth, sex, and ethnicity will be obtained from the parent study.

e Report all AEs, SAEs, and concomitant medications that occur after signing of the Informed Consent Form for the long-term study. Any occurring prior to signing the Informed Consent Form for the long-term study should be recorded under Medical/Medication history.

f IMP administration will occur on Day 1 of Week 0; followed by subsequent dosing Q12 weeks.

g Blood samples are to be collected (pre-dose where applicable), after ECG and vital sign measurements.

h At visits where lipids are assessed, the blood samples are to be collected (pre-dose where applicable) after 12 hours fasting, following ECG and vital sign measurements.

i Urine pregnancy tests will be performed by using a urine dip stick. ESR will be performed at the site using materials supplied by the central laboratory. hsCRP samples will be sent to the central lab and analyzed by central lab.

j A final anti-drug antibodies sample needs to be collected after 20 weeks from last dose.

k Evaluations will continue from the parent study using the version with questions referring to ‘since the last visit’. No lifetime version will be repeated at BL.

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 Table 9-1. 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 (Pharmacokinetics)

A sample of blood to obtain sufficient serum for tildrakizumab levels and PK assessment will be collected prior to IMP administration at the specified time points indicated in Table 9-1. 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.

9.1.3 Study Assessments

The schedule of study assessments is presented in Table 9-1 and details of the study procedures are provided in Section 11 and Section 12. The Sponsor or designated Clinical Research Organization (CRO) will be notified immediately of any critical deviation from study procedures. All protocol deviations will be routinely examined by the Sponsor and the designated CRO.

The study will consist of a Baseline assessment (Week 52 for the parent Phase 2 study, or later for subjects who entered the wash-out phase from the parent study due to the timing of study site activation of the long-term extension study) followed by a continued long-term treatment period using the same dosing regimen received in the parent study.

No independent assessor is needed to assess efficacy measurements as there will be no efficacy assessments during the LTE study. The PI/designee will be responsible for performing safety evaluations.

9.1.3.1 All Study Subjects

9.1.3.1.1 Baseline Assessments (Day 1)

Baseline (Day 1) for this long-term extension study is defined in Section 9.1.1.

Prior to IMP administration, the assessments and procedures listed in Table 9-1 will be performed and include:

- Obtain and document written informed consent.
- Check inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2).

  Discontinue IMP for subjects who fail to show clinical response to treatment (as defined in Section 9.3.1 for PsA subjects), in accordance with the IVRS instruction (see Section 9.3.5).
- Demographics to include body weight and height only. Date of birth, sex, and ethnicity will be obtained from the parent study.
- Record physical examination findings.
- Record medical and medication history (including any AEs or concomitant medications that remain ongoing from the parent study or any relevant observations made at the Baseline visit prior to signing the Informed Consent Form (ICF) for this long-term extension study [including laboratory test results from Week 48 of the parent study] are to be recorded).
- Perform a urine pregnancy test by urine dip stick (at the site using materials supplied by the central laboratory).
- Perform safety assessments including:
  - 12-lead ECG,
  - vital signs,
  - C-SSRS,
  - routine safety laboratory assessments (hematology, chemistry, and urinalysis.). Blood samples are to be collected (pre-dose) after ECG and vital sign measurements,
  - lipids (blood samples are to be collected [pre-dose] after 12 hours fasting and after ECG and vital sign measurements),
  - erythrocyte sedimentation rate (ESR) will be performed at the site using materials supplied by the central laboratory. High sensitivity C-reactive protein (hsCRP) samples will be sent to the central lab and analyzed by central lab.

    These hsCRP/ESR measures will be used for determination of potential AEs should they rise unexpectedly.
- Obtain a PK sample for drug concentration.
- Obtain a blood sample for ADA testing.

Following completion of all assessments and providing all study criteria are met, administer the first dose of IMP for the long-term extension study (Baseline, Day 1). Following IMP administration, complete the following assessments:

- AEs,
- Record concomitant medications.

9.1.3.1.2 Treatment Period (Week 0 through Week 200)

During the 4-year long-term extension treatment period, subjects will receive 100 mg tildrakizumab, SC, Q12 weeks dosing regimen as described in Section 9.1. The assessments and procedures listed in Table 9-1 will be performed at 12-weekly intervals to Week 104 then 24-weekly intervals to Week 200 and include:

- Record physical examination findings (annually at Weeks 56, 104, 152, and 200 only).
- Perform a urine pregnancy test by urine dip stick (at the site using materials supplied by the central laboratory).
- Perform safety assessments including:
  - perform a 12-lead ECG (annually at Weeks 56, 104, 152, and 200 only),
  - vital signs (all visits except Week 116, 140, 164, and 188),
  - C-SSRS (all visits except Week 140, 164, and 188),
  - routine safety laboratory assessments (hematology, chemistry, and urinalysis, Weeks 20, 56, 104, 152, and 200 only). Blood samples are to be collected (pre-dose) after ECG and vital sign measurements,
  - lipids (Weeks 20, 56, 104, 152, and 200 only),
  - hsCRP and ESR measures at Week 8, 20, 56, 104, 152, and 200 only, to be used for determination of potent AEs should they rise unexpectedly (ESR will be performed at the site using materials supplied by the central laboratory. hsCRP samples will be sent to the central lab and analyzed by central lab),
  - AEs (all visits),
  - record concomitant medications(all visits),
- Obtain a PK sample (Weeks 20, 56, 104, 152, and 200 only).
- Obtain a blood sample for ADA assessments (Weeks 20, 56, 104, 152, and 200 only).
- Administer IMP (Weeks 0, 8, 20, 32, 44, 56, 68, 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, and 200).

9.1.3.1.3 End of Treatment/Follow-Up (Week 208 or Approximately 4 Weeks after Last Investigational Medicinal Product Administration)

Subjects who complete the study and receive the last scheduled IMP administration at Week 200 will return for a final Follow-up assessment at Week 208 (4 years). In addition,

subjects who withdraw from IMP at any time during this long-term extension study will return for the EoT/Follow-up assessment approximately 4 weeks after administration of their last dose of IMP.

The assessments and procedures listed in Table 9-1 will be performed and include:

- Record physical examination findings.
- Perform a urine pregnancy test by urine dip stick (at the site using materials supplied by the central laboratory).
- Perform safety assessments including:
  - 12-lead ECG,
  - vital signs,
  - C-SSRS,
  - routine safety laboratory assessments (hematology, chemistry, and urinalysis),
  - lipids,

    hsCRP and ESR measures, to be used for determination of potential AEs should they rise unexpectedly (ESR will be performed at the site using materials supplied by the central laboratory. CRP samples will be sent to the central lab and analyzed by central lab),
  - AEs,
  - record concomitant medications.
- Obtain a PK sample.
- Obtain a blood sample for ADA assessments. A final ADA sample needs to be collected after 20 weeks from last dose.

9.2 Discussion of Study Design

Subjects with PsA will be eligible for this long-term extension study if they have completed approximately 1 year of treatment in the parent study. At the time of the first subjects entering the long-term extension study, other subjects may still be continuing in the parent Phase 2 study.

The study has been developed based on design features used in the ongoing parent Phase 2 study for PsA subjects as well as ongoing Phase 3 studies for subjects with psoriasis. No efficacy endpoints will be assessed for the study.

The study has been designed to provide an immediate entry into the long-term phase from the end of the parent study with the last assessment from the parent study becoming the Baseline

assessment of the long-term extension. This enables scientific evaluation of safety at all measured time points beyond completion of treatment in the parent study and comparison back to the original Baseline of the parent study. Subjects who entered the wash-out phase of their parent study prior to study site activation of this long-term extension protocol will also be eligible for inclusion and will re-initiate the tildrakizumab dose last received in the parent study. The duration of time in the wash-out phase of the parent study prior to entry to the long-term extension is anticipated to be short, thus enabling continued efficacy assessment across the long-term extension 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

This extension study will provide subjects from parent Phase 2 study who receive clinical benefit from treatment after approximately 1 year, as determined by eligibility criteria and Investigator opinion, opportunity to receive continued long-term tildrakizumab treatment for up to a further 4 years. Subjects from other studies may also be eligible for entry to this long-term extension study, hence offering extended use of effective dosing regimens.

Subjects will only be eligible for continuation into this long-term extension study if they complete the treatment period of the parent study (Week 48 for parent Phase 2 studies, with return for the EoT assessment at Week 52), meet defined clinical response criteria and, in the opinion of the Investigator, would gain clinical benefit from long-term continuation of tildrakizumab.

The study has also been designed to minimize potential risks to subjects; all subjects will undergo Screening procedures at the start of their parent study aimed at reducing the likelihood and impact of any such risks. In addition, regular safety monitoring during the treatment period of the parent study and this long-term extension study for all subjects will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately. The design also allows withdrawal of subjects from tildrakizumab at the end of the parent study (in accordance with the current parent protocol wash-out phase) and at any time thereafter during the extension study if, in the opinion of the Investigator, the subject is no longer obtaining sufficient clinical benefit, thus enabling subjects to receive other treatment in accordance with local clinical practice.

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.

9.2.2 Early Termination

This study may be terminated at any time by the Sponsor if serious side effects should occur, if the Investigator does not adhere to the protocol or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In this event, the Sponsor will inform the study Investigators, institutions and all regulatory authorities.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

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

1. Subject has provided written informed consent for this long-term extension study.
2. Subjects with PsA who met the inclusion criteria of the parent study and completed the parent study treatment period (e.g., up to Week 48 for the parent Phase 2 study, with return for the EoT assessment at Week 52).
3. PsA subjects who achieved a 20% reduction from Baseline in American College of Rheumatology (ACR)20 response criteria at Week 52 (for details see Appendix 22.2), AND the subject has received sufficient clinical benefit, in the opinion of the Investigator, to support continued treatment with tildrakizumab.

   Note: This criterion using response criteria at Week 52 of the parent study will apply to all subjects, including those subjects who enter the study from the wash-out phase of their parent study (after Week 52) due to the timing of study site activation of the long-term extension study.
4. No concomitant use of both leflunomide and methotrexate,
5. No history of active tuberculosis (TB) or symptoms of TB.

9.3.2 Exclusion Criteria

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

1. New onset during the parent study of arthritic conditions other than the subject’s original condition.
2. Female subjects of childbearing potential who do not agree to abstain from heterosexual activity or practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo-progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy). Contraceptive methods must be practiced upon entering the study and through 16 weeks after the last dose

of IMP. If a subject discontinues prematurely, the contraceptive method must be practiced for 16 weeks following final administration of IMP.

3. Female is pregnant or breastfeeding, or planning to become pregnant or initiate breastfeeding while enrolled in the study or up to 16 weeks after the last dose of IMP.
4. Subject has previously been enrolled in this long-term extension study.
5. Any condition that in the opinion of the Investigator represents an obstacle for study conduct and/or represents a potential unacceptable risk for the subject.
6. Subject has an active infection or history of infections as follows:
   - a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first IMP dose of the extension study, with the last dose having been received within 7 days of start of the extension study,
   - recurrent or chronic infections, e.g., chronic pyelonephritis, chronic osteomyelitis, bronchiectasis, or other active infection that, in the opinion of the Investigator, might cause this extension study to be detrimental to the subject.
7. Major chronic inflammatory or connective tissue disease other than PsA (e.g., rheumatoid arthritis, systemic lupus erythematosus, Lyme disease, or gout, Crohn's disease, etc).
8. Known diagnosis of fibromyalgia, regional pain syndromes or active uveitis/symptomatic inflammatory bowel disease requiring therapy.
9. Subject has any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, or anemia) that, in the opinion of the Investigator, could cause continued treatment to be detrimental to the subject.
10. Subject has a known history of infection with hepatitis B, hepatitis C, or human immunodeficiency virus during the parent study.
11. Subject had myocardial infarction, unstable angina pectoris, or ischemic stroke within the past 6 months prior to the first IMP dose for this extension study.
12. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
13. Subject has a history of malignancy EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, *in situ* cervical carcinoma, OR *in situ* breast ductal carcinoma.
14. Subjects with a history of alcohol or drug abuse during the parent study.
15. Significant risk of suicidality at the Baseline assessment (Section 9.1.1) of this extension study based on the Investigator's judgment or, if appropriate, as indicated by a response of

"yes" since the last visit to question 4 or 5 in the suicidal section, or any response in the behavioral section of the C-SSRS.

16. Subject has a need for use of a live vaccine within 10 weeks of final anticipated dose of IMP for the long-term extension study.
17. Concomitant use of prohibited medications or use of commercially available or investigational biologic therapies (other than tildrakizumab) for PsO and/or PsA (see Section 10.6).

General

18. Subjects who have been placed in an institution on official or judicial orders.
19. Subjects who are related to or dependent on the Investigator, Sponsor, or study site such that a conflict of interest may arise.

9.3.3 Strategies for Subject Recruitment and Retention

Subject recruitment will be according to satisfaction of eligibility criteria at the end of parent study. The protocol requirements 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 long-term extension 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.

For safety reasons, and particularly following an AE, Week 208 (EoT/Follow-up) assessments should be conducted if the withdrawn subject is willing to undergo the assessments. Subjects who discontinue the study due to an AE considered related to study drug should be followed as described in Section 12.1.1.1.

The appropriate personnel from the study site and designated CRO will assess whether IMP should be discontinued for any subject whose treatment code has been broken inadvertently.

The Investigator must also contact the IVRS 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, or completely withdraw from the study (see Section 9.3.4). Subjects who consent will undergo the EoT/Follow-up assessment approximately 4 weeks after administration of the last dose of IMP.

At any time during this long-term extension study, subjects not deriving sufficient clinical benefit in the opinion of the Investigator should be discontinued from IMP. Investigators should monitor the clinical benefit of each subject in an ongoing manner throughout the study in order to make the determination as to whether it is appropriate for them to continue to participate.

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

- A serious adverse event (SAE), drug reaction or complication, or an unacceptable AE, whether attributed to IMP or not, that precludes continuation of treatment with IMP. This includes the development of allergic reactions or the development of other potentially serious drug reactions to medication required by the protocol,
- Diagnosis of malignancy (except basal or squamous cell carcinoma) during study (treatment may be continued at the discretion of the subject and Investigator, and in consultation with the medical monitor),
- Subjects who develop suicidal behavior (Section 12.4),
- Evidence of pregnancy,
- Withdrawal of informed consent,
- Lost to follow-up,
- Significant non-compliance of the subject with study procedures,
- Decision of the Sponsor to terminate the subject, site, or the study.

The derivation of clinical response (at Week 52 for the Phase 2 parent study) will be made within the IVRS system using information provided by the study site. The IVRS system will determine the subject's eligibility to continue into the long-term extension study. Subjects who fail to meet eligibility criteria at the end of their parent study will not be eligible to continue to the long-term extension study in accordance with the IVRS instruction, and would continue in the Follow-up period of their parent study.

Reasons for Temporary Discontinuation of Investigational Medicinal Product

Investigational medicinal product may be temporarily suspended in the event of:

- Clinically important laboratory abnormalities,
- Subjects who develop suicidal ideation (Section 12.4),
- Other intercurrent illnesses or major surgery,
- Use of prohibited treatment (according to inclusion criteria of the parent study, Section 9.3.1 and Section 9.3.2),
- Any other protocol deviation that results in a significant risk to the subject's safety,
- Sponsor decision.

After a laboratory abnormality leading to suspension of dosing normalizes sufficiently, IMP may resume at the discretion of the PI in consultation with the medical monitor. Similarly, IMP may resume after a prohibited medication leading to suspension of dosing is discontinued. A decision to discontinue IMP and/or to reinstitute IMP should be discussed with the medical monitor. The Investigator may suspend IMP 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 IMP after temporary discontinuation should always be discussed with the medical monitor.

9.3.6 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 a registered mail letter. All attempts should be documented in the subject’s medical records. If it is determined that the subject has died, the study 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.

9.3.7 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. Sun Pharma Global FZE or designee may also discontinue the study site or study country should there be a change in the personnel (or structure) of the site or political (or economic) environment of the country such that

continuation of the study in the site or country may negatively impact the study or no longer serves the primary objective of the study.

9.3.8 Discontinuation of Study

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

10 TREATMENT OF SUBJECTS

10.1 Identity of Investigational Medicinal product

10.1.1 Administration of Investigational Medicinal Product

Investigational medicinal product will be supplied as [redacted] and administered SC. All subjects will be dosed at the same time points to maintain the study blind of the parent study where applicable (see Section 10.2.4). All subjects will be receiving tildrakizumab in accordance with their parent study dose regimen until at least Week 52 in the parent study and will transition to tildrakizumab 100 mg Q12 weeks thereafter there will be no placebo comparator group in this study.

If a subject misses a visit and/or a scheduled dose of IMP, the study site must reschedule a visit to ensure the dose of IMP is taken as soon as possible within the visit window. If after 2 attempts to reschedule 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.

10.2 Investigational Medicinal Product Packaging and Labeling

10.2.1 Packaging

Each [redacted] of IMP contains 1 mL of solution. A [redacted] of tildrakizumab contains 100 mg (100 mg/mL) of active drug.

10.2.2 Labeling

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

10.2.3 Storage

All drug supplies for this study must be stored under refrigerated conditions (2ºC to 8ºC) and 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. If a study nurse is selected to administer IMP in a home setting (Section 9.1.3.3), the study IMP should be stored and transported in accordance with the study recommendations. The IMP should not be stored at the subject's home and should accompany the study nurse on the day of the scheduled visit.

10.2.4 Blinding and Randomization of Investigational Medicinal Product

Subjects will be not be randomized and will enter the long-term extension study with one fixed dose regimen of tildrakizumab, 100 mg at Week 52 of the parent study. However, subject numbers based on allocation from an IVRS system will remain in place from the parent study until such time the blind is no longer required to be maintained.

A copy of the randomization code with true treatment allocations will be held by the designated CRO 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 treatment completion of the parent study (for Phase 2 parent study, this will be following completion and database lock of all PsA subjects).

The long-term extension study is designed initially to maintain as last dosing regimen in the parent study followed by a regimen of 100 mg Q12 week, in an open-label fashion as blinding of IMP is no longer necessary to maintain. If a subject does not receive the scheduled dose, every effort should be made to administer the dose as soon as possible (see Section 10.1.1).

All safety assessments will be administered by the study coordinator or PI/designee.

Should a situation arise where unblinding is required, the Investigator at that study site may perform immediate unblinding via the IVRS without the need for communication with the Sponsor. This can only occur in emergency situations (Section 10.3).

At the time of the first IA for this extension study, the Phase 2 parent study will have been unblinded and hence no considerations of maintenance of blind will be necessary for those cohorts of subjects.

10.3 Procedure for Breaking the Randomization Code

Subjects, study site personnel, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until such time the long-term study can become open-label for the relevant cohort of subjects (Section 9.1.1).

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 designated site monitor, medical monitor, and the project manager 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 case 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 IMP may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

Investigational medicinal product accountability and subject compliance will be documented throughout the treatment period using study-specific IMP 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 (Section 10.1.1).

Deviations from the intended regimen could occur due to:

- Receiving unscheduled IMP injections,
- Missing an injection,
- Receiving the incorrect IMP dose.

10.5 Investigational Medicinal Product Accountability

Records shall be maintained of the delivery of IMP to the study sites, the inventory at the study sites, 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 IMP 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 IMP received from the Sponsor is reconciled. All IMP must be returned to the Sponsor at the end of the study.

10.6 Concomitant Therapy

Subjects should abide by inclusion and exclusion restrictions for this long-term extension study.

Permitted medications include:

- Acetaminophen, except within 24 hours before a scheduled study efficacy evaluation,
- Non-steroidal anti-inflammatory drugs or low potency opioids (e.g., tramadol),
- Methotrexate or leflunomide,
- Oral corticosteroids (no more than daily 10 mg for maintenance dose),
- Non-drug therapy (including but not limited to physical therapy, massage, diet, exercise, emollients, and joint taping)..

Use of and adjustment of permitted medication is permitted throughout the study per Investigator discretion and therapeutic needs of the subject.

In accordance with the parent study, subjects are prohibited from use of the following at the time of written informed consent for and during the long-term extension study:

- High potency opioid analgesics (e.g., methadone, hydromorphone, or morphine) for the treatment of arthritis (allowed for treatment of other conditions for periods of up to 2 weeks),
- Sulfasalazine,
- Systemically administered calcineurin inhibitors (e.g., cyclosporine, tacrolimus),
- Azathioprine,
- Parenteral corticosteroids including intramuscular or intra-articular administration (topical, ophthalmic, intra-nasal, and inhaled corticosteroids are permitted) for the treatment of arthritis (allowed for treatment of other conditions for periods of up to 2 weeks),
- Live vaccines.

Any prohibited treatments must be discontinued prior to IMP initiation for the long-term extension study.

During this long-term extension study, subjects must not use systemic immunosuppressive therapies including commercially available or investigational therapies for PsO or PsA such as:

- Use of all anti-tumor necrosis factor agents, including etanercept,
- Use of B-cell and T-cell depleting/inhibiting agents,
- Use of any other commercially available or investigational biologic therapies (other than tildrakizumab) for PsO and/or PsA within 3 months or 5 half-lives (whichever is longer) prior to or during IMP in the long-term extension study,
- Use of apremilast, or other approved or investigational medications for the treatment of current condition which are not identified as permitted therapies,
- Use of secukinumab, ustekinumab, ixekizumab, brodalumab, or any drug targeting interleukin (IL) 17, IL 23, or the IL-12/IL-23-shared p40 molecule.

11 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 9.1.2 and Section 9.1.3.

11.1 Adverse Events

The definitions for AEs and SAEs are provided in Section 11.1.1. The PI is responsible for ensuring all personnel involved in the study are familiar with the content of this section.

11.1.1 Definitions

11.1.1.1 Adverse Event

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 Baseline visit (including laboratory test results, and until the ICF is signed) are to be recorded on the AE eCRF, but will not be considered treatment-emergent AEs (TEAEs) for the long-term extension study, and will be reported separately from TEAEs. A TEAE includes any relevant observations following signing of the ICF for the long-term extension study, and 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 or ongoing at the start of the long-term extension study will only be recorded as a TEAE if there is a worsening of the pre-existing condition during the long-term study conduct with regard to nature, intensity 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. Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant.

11.1.1.2 Serious Adverse Event

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

- 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.

- 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.

- 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.

- 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.

- Is a congenital anomaly/birth defect,

- Is an important medical event.

  Important medical events that may 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 one of the outcomes listed in this definition.

11.1.1.3 Adverse Events of Special Interest

The events of severe infections (defined as any infection meeting the regulatory definition of a SAE or requiring intravenous antibiotics whether or not reported as a serious event), malignancies (including non-melanoma and melanoma skin cancer), confirmed Major Adverse Cardiovascular Events (MACE), and drug-related hypersensitivity reactions) will each be

identified a priori as an AE of special interest (AESI) for summarizing in this study. Major Adverse Cardiovascular Events include non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death. All MACE events will be evaluated and adjudicated by a CAC (Section 12.3.4). An AESI must be reported as if it were an SAE (Section 11.1.2)

11.1.1.4 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 the designated pharmacovigilance/safety services within 24 hours of awareness, 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 (Section 10.1.1). 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.

11.1.1.5 Product Quality Complaint

A product quality complaint (PQC) is related to a potential quality issue during manufacturing, release testing, stability monitoring, dose preparation, storage, or distribution of the product or delivery system. In addition, it includes any reports in which a suspicion of counterfeit/tampering exists. It is important to note that not all PQCs involve a subject. A PQC should be reported within 24 hours, using the details provided in Section 11.1.2.

11.1.1.6 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.

11.1.1.7 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 [redacted] for this study. The incident should be reported within 24 hours, using the details provided in Section 11.1.2.

11.1.1.8 Recording of Adverse Events

Any relevant observations made before the end of the Baseline visit (prior to signing the ICF for this long-term extension study) 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 signing the ICF will be recorded as an AE in the subject's AE eCRF (see Section 11.1.1.1).

For the purposes of this study, any detrimental change in the subject's condition, after the first dose of IMP for the long-term extension study and up to completion of the EoT/Follow-up visit, should be considered an AE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, intensity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome. A new AE must be recorded if the intensity 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 (awareness of sign or symptom, but easily tolerated),
- Moderate (discomfort sufficient to cause interference with normal activities),
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 11.1.1.2.

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.

11.1.1.9 Causal Assessment

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

Term	Definition	Clarification
Unrelated	Those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)	
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from administration of the drug. 2. It could also be explained by subject's concurrent disease, environmental factors, medical history, and other concomitant drugs or chemicals including food-drug interactions.
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	1. It follows a reasonable temporal sequence from administration of the drug. 2. It could also be explained by subject's concurrent disease, environmental factors, medical history, and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.	1. It follows a reasonable temporal sequence from administration of the drug. 2. It could not be readily explained (unlikely) by the subject's concurrent disease, environmental factors, medical history, and other concomitant drugs or chemicals including food-drug interactions. 3. It disappears or decreases in intensity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. 4. No re-challenge information is available or possible.
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.	1. It follows a plausible time sequence to drug intake; this means that there is a positive argument in sufficient detail to support the view that the drug is causally involved, pharmacologically or pathologically e.g., pharmacokinetics and type of reaction. 2. It could not be explained by subject's concurrent disease, environmental factors, medical history, and other concomitant drugs or chemicals including food-drug interactions (i.e., no alternative causes). 3. It disappears or decreases in intensity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance ‘grey baby syndrome’ and chloramphenicol or anaphylaxis immediately after the administration of a

Term	Definition	Clarification
		drug that had been given previously. This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive re-challenge observation). 5. It reappears on re-administration of the drug (only if ethically correct i.e. in case of non-serious and easily treatable AEs).

Abbreviations: AE(s) = adverse event(s).

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,
- IMP,
- Mechanism of action of IMP,
- Class effect,
- Concomitant treatments in use,
- Withdrawal of IMP,
- Lack of efficacy/worsening of existing condition,
- Erroneous treatment with IMP or concomitant medication,
- Protocol-related process.

Action taken with IMP due to the AE:

- None,
- Drug permanently discontinued,
- Drug temporarily discontinued,
- Unknown/not applicable.

Other action taken:

- Specific therapy/medication,
- Surgical medical procedure,

- (Prolonged) hospitalization.

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

- Recovered/resolved,
- Recovering/resolving,
- Not recovered/not resolved,
- Recovered with sequelae/resolved with sequelae,
- Fatal,
- Unknown.

11.1.1.10 Abnormal Laboratory Values/Vital Signs/12-Lead Electrocardiograms

Laboratory/vital signs/12-Lead ECG abnormalities should be reported as AEs/SAEs if it is clinically significant and any of the following criteria are 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.

11.1.1.11 Anaphylaxis

The clinical criteria for diagnosing anaphylaxis are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, or swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING:* a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, or hypoxemia), b) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, or incontinence).
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that subject* (minutes to several hours): a) Involvement of the skin-mucosal tissue (e.g. generalized hives, pruritus or flushing, or swollen lips-tongue-uvula), b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, or hypoxemia), c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, or incontinence), d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, or vomiting).
3. Reduced BP after exposure *to known allergen for that subject* (minutes to several hours): a) Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP, b) Adults: systolic BP of <90 mm Hg or >30% decrease from that person's Baseline.

Abbreviations: BP = blood pressure; PEF = peak expiratory flow

Data source: Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117(2):391-7.

11.1.1.12 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 IMP in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to the designated pharmacovigilance/safety services using the reporting details provided in Section 11.1.2 within 24 hours of awareness.

11.1.2 Reporting of Serious Adverse Events

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

Investigators and other site personnel must inform the designated pharmacovigilance/safety services of any SAE that occurs during the course of the study (from the time of written informed consent until 30 days after the last EoT/Follow-up visit), whether or not it is considered causally related to the IMP or to the study procedure(s), and within 24 hours of when he/she becomes aware of it. An SAE with an onset day greater than 30 days from the EoT/Follow-up visit will be recorded only for fatal SAEs and those deemed by the Investigator to be drug-related or AESIs (Section 11.1.1.3). The Investigator should make every effort to obtain follow-up information on the outcome until the event is considered resolved, chronic and/or stable.

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

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

Paper SAE forms should be completed at the site and faxed/emailed to the designated pharmacovigilance/safety services or emailed to the global email distribution list within 24 hours of awareness of the event.

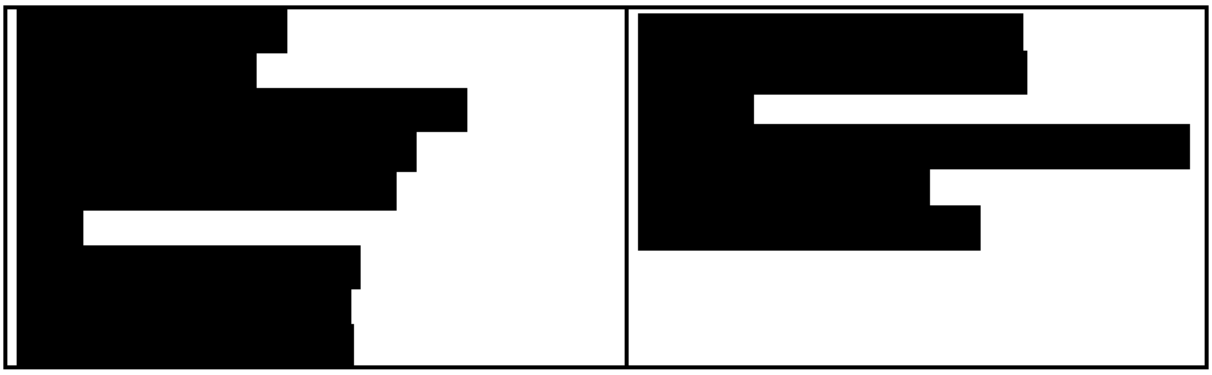
SAE and AESI reports should be sent or faxed to the designated pharmacovigilance/safety services provided in Section 3.

There may be situations when an SAE (or AESI) 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.

11.1.2.1 Safety Reporting to Sponsor

The designated pharmacovigilance/safety services will forward the SAE and Pregnancy report to the following Sponsor's safety representatives within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.



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

The designated CRO will notify the Sponsor of any SAE and will perform follow-up activities with the concerned study 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 designated pharmacovigilance/safety services.

In accordance with ICH GCP, the designated pharmacovigilance/safety services will inform the Investigators of findings that could adversely affect the safety of subjects, 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, the designated pharmacovigilance/safety services will inform the Investigators of SAEs. The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the designated pharmacovigilance/safety services will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be

responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the designated pharmacovigilance/safety services and of filing copies of all related correspondence in the Investigator Site File.

11.2 Safety Endpoints

All safety endpoints are listed in Section 12.3.1.

11.3 Laboratory Assessments

Laboratory measurements for blood chemistry, hematology, and urinalysis will be performed according to Table 9-1. 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 (see Table 9-1), blood samples are to be collected (pre-dose where applicable) after 12 hours fasting, and after ECG and vital sign measurements.

11.3.1 Clinical Laboratory Tests

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

Laboratory Testing Profile	Tests Included
Blood Chemistry	Sodium, potassium, chloride, bicarbonate/CO_2, blood urea nitrogen, serum creatinine, fasting glucose, albumin, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin, total protein, calcium, gamma-glutamyl transferase, creatine kinase
Hematology	Hemoglobin, hematocrit, WBC with differentials (monocytes, eosinophils, basophils, neutrophils, lymphocytes) as an absolute value, RBC count, platelet count, ESR[a]
Urinalysis	Specific gravity, pH, semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, blood Microscopy and/or culture to be performed if clinically indicated or if urinalysis results positive (blood, protein or leukocyte esterase/WBC). Urine hCG pregnancy testing for women of childbearing potential[a]; may be repeated more frequently than indicated if required by local practice, if a menstrual cycle is missed, or if potential pregnancy is suspected.

Lipid Panel	Total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, apolipoprotein A-1, B
Acute-phase Reactants	hsCRP

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CO_2 = carbon dioxide; ESR = erythrocyte sedimentation rate; hCG = human chorionic gonadotropin; hsCRP = high sensitivity C-reactive protein; RBC = red blood cells; WBC = white blood cells.

a Urine pregnancy tests and ESR will be performed at the study site using materials supplied by the central laboratory.

11.3.2 Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening visit of the parent study only. Urine pregnancy test with sensitivity of at least 25 mIU/mL, will be performed according to the Schedule of Assessments (Table 9-1). If at any point during the study there is a case of a positive urine human chorionic gonadotropin test, the subject will have IMP stopped and will be withdrawn from the study.

Pregnancy tests will also be performed whenever 1 menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected), to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IECs/ IRBs or if required by local regulations.

11.4 Assessment of Suicidal Ideation and Behavior

Subjects will be assessed for suicidal ideation and behavior at Baseline (Section 9.1.1) 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 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.

11.5 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 Fridericia formula (QTcF), is the observed QT interval (the time from the beginning of the Q-wave to the end of the T-wave) divided by the cubed root of the R-R interval (interval from the peak of a QRS-complex to the peak of the next) in seconds:

$$QTcF = {QT}/{\sqrt[3]{RR}}$$

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

$$QTcB = {QT}/{\sqrt{RR}}$$

11.6 Physical Examination

A standard complete physical examination will be performed at the weeks specified in Table 9-1. The following parameters and body systems will be examined and any abnormalities described: height, weight, general appearance, skin (presence of rash), head, ears, eyes, nose, throat, lungs (auscultation), heart (auscultation for presence of murmurs, gallops, or rubs), lower extremity examination, abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, and coordination), and lymph nodes. Any clinically significant changes from Baseline (after signing of the ICF for the long-term extension study) should be recorded as AEs.

11.7 Vital Signs

Body temperature (oral/tympanic or axillary), systolic and diastolic cuff blood pressure (measured after at least 5 minutes in the supine position), and pulse rate (measured after at least 5 minutes in the supine position) will be recorded according to the Schedule of Assessments (Table 9-1). 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.

11.8 Anti-Drug Antibodies

The presence of ADA for tildrakizumab will be assessed at the time points specified in Table 9-1. Samples will be collected as detailed in Section 9.1.2.1. Sample testing will be conducted as specified in the laboratory manual.

11.9 24/7 Medical Emergency Coverage for Urgent Protocol-related Medical Questions

In a study-related health emergency, when assigned medical monitors for a study cannot be reached by a caller, for discussion of urgent medical related questions an on-call physician can be reached 24 hours per day, 7 days per week via an [redacted]

- [redacted]

(Chargeable telephone number allowing global reach from both landlines and mobile phones)

- [redacted]

On this internet page, a list of country specific toll-free telephone numbers are provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, there may be restrictions when dialing toll-free numbers from a mobile phone.

12 STATISTICAL EVALUATION

12.1 Sample Size and Power

The sample size of this study is determined by the number of subjects who rollover from the parent PsA study. No power is calculated because the primary objective is to assess the long-term safety of tildrakizumab.

12.2 Statistical Methods

The All Subjects as Treated (ASaT) population consists of all subjects who entered the extension study. The ASaT is the primary population for safety/tolerability, efficacy, and PK analyses. The analysis will be based on the treatment subjects actually received.

All endpoints will be presented for the measured time points provided in Table 9-1. In addition, all data collected for subjects who entered the wash-out period of the parent study (whilst awaiting start of the long-term extension study at their study site) will be valid for data presentation. This includes data collected at visits beyond Week 52 of the parent study and prior to the Baseline visit of the long-term extension study.

12.2.1 Study Subject Data

Subject disposition and demographic data for subjects in the extension study will be summarized descriptively.

Exposure and compliance with IMP will be summarized descriptively.

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

12.2.2 Efficacy Endpoints

No efficacy endpoints will be measured.

12.2.3 Safety Endpoints

The following data will be collected for assessment of safety:

- AEs,
- AESI,
- Laboratory assessments,
- Suicidal ideation and behavior (C-SSRS),
- Vital signs,
- ECG,

- Physical examination,
- ADA to tildrakizumab.

12.3 Description of Statistical Analyses

All the safety and efficacy data will be summarized descriptively through appropriate data tabulations and descriptive statistics. 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.

The last value of a variable taken before the first dose of IMP in parent study will be used as the original Baseline value. The last value before the first dose of IMP in the long-term extension study will be used as the LTE 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).

12.3.1 Safety Analysis

The subjects in this long-term extension study will be summarized separately according to parent PsA studies and indication. Any additional summaries including pooling of indications, common dosing regimens, or studies will be provided in the SAP.

The subjects will be summarized based on the actual treatment received at specific time points when applicable.

Adverse Events

AEs will be coded using the most recent version available of the Medical Dictionary for Regulatory Activities (MedDRA).

Due to the various durations of exposure to a treatment, the exposure-adjusted AE incidence rate (per 100 subject-years) will be summarized by treatment group. The incidence of AEs will be summarized by system organ class and PT. If a subject experiences the same PT multiple times then the event will be counted only once for the greatest intensity during a treatment period. Separate tables will be presented by intensity; AEs considered to be related to IMP by the Investigator will be summarized similarly.

AEs of special interest will be summarized descriptively.

All AEs will be presented in full in a comprehensive listing including subject number, treatment (or sequence) received, intensity, seriousness, action taken, outcome, relationship to treatment, treatment received at AE onset, onset/stop and duration. Details of SAEs and AEs leading to

withdrawal will be listed separately. A more detailed description regarding presentation of AE data will be provided in the SAP.

Clinical Laboratory

Clinical laboratory parameters will have observed values and changes from Baseline summarized at each scheduled visit by treatment group.

Values outside the normal range will be categorized as above the normal range (H) or below the normal range (L) based on the laboratory's reference range and these will be flagged in the listings of individual subject data.

Vital Signs

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

ECG

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

ECG parameters (e.g., QTcF) will have observed values and changes from Baseline summarized at each scheduled visit by treatment group.

Physical Examination

Physical examination results will be summarized with incidence of "Normal" and "Abnormal" by body system at each scheduled visit by treatment group.

Assessment of Suicidal Ideation and Behavior

Subjects will be assessed for suicidal ideation and behavior using C-SSRS.

The C-SSRS consists of 2 major aspects: Suicidal Ideation and Suicidal Behavior. The following endpoints will be used to analyze C-SSRS data:

- Presence of Suicidal Ideation: Set to 1 if any ideation is present and 0 otherwise,
- Presence of Suicidal Behavior: Set to 1 if any type of suicidal behavior is present and 0 otherwise,
- Suicidal ideation score: Defined as the maximum suicidal ideation category (1-5) present on the C-SSRS at the assessment. A score of 0 is assigned if no ideation is present.

The number (%) of subjects with presence of suicidal ideation and behavior will be summarized at each assessment time. The C-SSRS data will be summarized using worst-case shift from baseline tables.

ADA to Tildrakizumab

For each subject, tildrakizumab serum concentrations and ADA sample results are matched to actual sampling times and treatment. Subjects are grouped based on the actual treatment received. The anti-tildrakizumab immunogenicity status of evaluable subjects, along with titer will be summarized by dose level.

[redacted]

12.3.2 Pharmacokinetic Analysis

Serum tildrakizumab concentration data will be listed by individual subject and summarized by visit. The subjects will be summarized based on the ASaT population with the actual treatment received at a specific visit. All samples for PK and ADA studies will also be saved for future safety or biomarkers analysis as deemed appropriate by Sun Pharmaceuticals. A list of biomarkers is provided in Appendix 22.3.

PK parameters may be used to refine previous PK models.

12.3.3 Interim Analysis

An IA to review safety data will be performed at one year of this long-term extension study. Additional IAs may be performed as needed to support reporting requirements or as needed for internal decision-making.

12.3.4 Data Safety Monitoring Board

According to FDA Guideline "Establishment and Operation of Clinical Trial Data Monitoring Committees"[3], March 2006, a Data Safety Monitoring Board is not required for this extension study.

12.3.5 Clinical Adjudication Committee

A CAC will evaluate an extensive set of cardiovascular events and all deaths to determine which of these meet pre-specified endpoint criteria. Cardiovascular events for adjudication

will be identified based on Investigator reports with specific AE terms. Instructions for obtaining source documentation for all events to be adjudicated will be provided to the Investigator study sites in a separate document. All personnel involved in the adjudication process will remain blinded to treatment allocation throughout this long-term extension study until such time the study may become open-label. Specific details regarding the cardiovascular endpoints to be analyzed, including the endpoint definitions and criteria can be found in the Adjudication Committee Charter.

13 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.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Conduct of the Study

The designated CRO and 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)[4], United States Food and Drug Administration (FDA, Code of Federal Regulations [CFR], Sections 312.50 and 312.56), European Union (Annex 1, Directive 2001/83/EC) and United Kingdom regulations (The Medicines for Human Use [Clinical Trials] Regulations 2004 [No. 1031]), and with ICH GCP (Committee for Proprietary Medicinal Products [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.

14.2 Study Monitoring

The Investigator shall permit the designated CRO site monitor 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 to medical records for the designated CRO site 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 the designated CRO in ensuring that the study adheres to GCP requirements.

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

15 ETHICS

15.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and ICF 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.

15.2 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.

15.3 Data Safety Monitoring Board

According to FDA Guideline “Establishment and Operation of Clinical Trial Data Monitoring Committees” [3], Mach 2006, a Data Safety Monitoring Board is not required for this extension study.

16 DATA HANDLING AND RECORD KEEPING

16.1 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 study 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 designated CRO and external investigational study 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 study 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. It is essential that all samples be analyzed at the central 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.

16.2 Retention of Essential Documents

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

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

17 FINANCING AND INSURANCE

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

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

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

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

18 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 final 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 conform 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 the United States. In addition, upon study completion and finalization of the clinical study report, the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical study results.

19 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(s) 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.

20 SIGNATURE OF INVESTIGATOR

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

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

21 REFERENCE LIST

1. MK-3222 (SCH 900222) Investigator's Brochure, Edition 8, 06 October 2017.
2. Randomized, Double-Blinded, Placebo-Controlled, Parallel-Design, Dose-Range Finding Study of Subcutaneous SCH 900222 in Subjects with Moderate-to-Severe Chronic Plaque Psoriasis (Protocol No. P05495). 16 July 2010.
3. Guidance for Clinical Trial Sponsors; Establishment and Operation of Clinical Trial Data Monitoring Committees. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), March 2006.
4. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/en/20activities/10ethics/10helsinki/DoH-Oct2013-JAMA.pdf. Accessed 07 October 2016.
5. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis. *Arthritis Rheum.* 1995;38(6):727-35.

22 APPENDICES

All subjects in this long-term study were required to meet the following criteria relating to a diagnosis of PsA, in accordance with the parent study inclusion criteria.

22.1 CASPAR (Classification criteria for Psoriatic ARthritis) Criteria

A subject must have inflammatory articular disease (joint, spine or entheseal) and ≥ 3 points from the following categories:

Category	Description	Points
Current psoriasis or personal or family history of psoriasis	Current psoriasis: skin or plaque disease confirmed by rheumatologist or dermatologist Personal history: obtained from subject, family physician, dermatologist, rheumatologist, or other qualified healthcare provider Family history: presence of psoriasis in 1° or 2° relative as reported by subject	2 (current) OR 1 (history)
Psoriatic nail dystrophy on current examination	Onycholysis, pitting, hyperkeratosis	1
Negative rheumatoid factor	Any method except latex, but preferably Enzyme-linked immunosorbent assay (ELISA) or nephelometry, using local laboratory reference range	1
Dactylitis (current or on history as recorded by rheumatologist)	Swelling of an entire digit	1
Radiographic evidence of juxta-articular new-bone formation	Ill-defined ossification near joint margins but excluding osteocyte formation on plain X-rays of the hand or foot	1

Sensitivity 91.4%; Specificity 98.7%

Data source: Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification Criteria for Psoriatic Arthritis: development of new criteria from a large international study. Arth Rheum. 2006;54:2665-2673.

22.2 American College of Rheumatology 20/50/70 Response Criteria

The ACR20/50/70 response measures the percentage of subjects with at least a 20/50/70% improvement from Baseline in both tender joints (68) and swollen joints (66) along with associated percentage improvements in 3 of 5 other items: 1) the PGA of disease activity (as measured using a Visual Analog Scale [VAS]), 2) the Patient Global Assessment (PtGA) of disease activity (as measured using a VAS), 3) patient pain assessment (as measured using a VAS), 4) patient self-assessed disability (as measured using the HAQ-DI), and 5) acute-phase C-reactive protein (CRP)[5]. A sensitivity analysis will be performed by evaluating ACR20/50/70 response calculated using ESR.

22.2.1 Joint Counts

In accordance with the parent studies, the measure used is the ACR joint count initially developed for the assessment of patients with rheumatoid arthritis. The ACR joint count of 68 tender and 66 swollen joints count will continue to be used in this long-term study and includes the majority of joints affected in PsA subjects. It includes the temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist (including the carpometacarpal and intercarpal joints as 1 unit), metacarpophalangeal, proximal interphalangeal, distal interphalangeal, 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).

22.2.2 Physician Global Assessment of Disease Activity

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

22.2.3 Patient Global Assessment of Disease Activity

The subject will assess their current global status of PsA by means of a VAS ("Considering all the ways your disease affects you, on average, how have you been doing today?"), anchored with verbal descriptors of "very well" to "very poorly".

22.2.4 Patient Pain Assessment

The subject will assess their level of present pain ("How much pain due to your arthritis are you currently experiencing?") 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 "no pain" to "worst possible pain".

22.2.5 Health Assessment Questionnaire - Disability Index (HAQ-DI)

The subject will assess their general disability over the past week using the HAQ-DI questionnaire.

The HAQ-DI is designed to assess subjects' usual abilities using their usual equipment. Subjects usually find the HAQ-DI self-explanatory, and clarifications are seldom required. There are 8 categories assessed by the HAQ-DI: 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. For each of these categories, subjects report the amount of difficulty they have in performing 2 or 3 specific activities. The time frame for the disability questions is the PAST WEEK and each question can be scored as 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty) or 3 (unable to do). The use of aids and devices for these activities is also recorded. Use of any device or aid will result in a minimum score of 2 for that category. The score for the disability index is the mean of the 8 category scores. If >2 of the categories, or 25%, are

missing, the scale is not scored. If <2 of the categories are missing, the sum of the categories is divided by the number of answered categories. A higher score indicates greater disability.

22.3 Biomarkers

The Sponsor, SUN Pharma Global FZE (SUN) would like to perform additional analysis on the following remaining blood samples:

- Samples collected to measure anti-drug antibodies (ADA)
- Samples collected to measure how much study medicine is in your blood (pharmacokinetics, PK)

Upon completion of ADA and PK analysis, samples will be used to analyze additional biomarkers [redacted]

Taking part in this optional biomarkers research is voluntary and subjects who sign amended informed consent will participate in Biomarker research. Samples will be destroyed once all the biomarkers tests have been completed.

[redacted]

[redacted]