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AIN457

Clinical Trial Protocol CAIN457F2367 / NCT04711902

A phase III randomized, double-blind, placebo controlled, multicenter, bridging study of subcutaneous secukinumab, to demonstrate efficacy after sixteen weeks of treatment and to assess safety, tolerability and long-term efficacy follow-up to one year in Chinese subjects with active psoriatic arthritis

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	antinuclear antibody
anti-CCP	Anti-cyclic citrullinated peptide
anti-dsDNA	anti-double stranded DNA antibodies
AS	ankylosing spondylitis
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
β-hCG	Beta human chorionic gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
BSL	Baseline
BUN	Blood Urea Nitrogen
°C	degree Celsius
CASPAR	Classification of Psoriatic Arthritis
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulation
CI	confidence interval
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRP	C-Reactive Protein
csDMARDs	Conventional Synthetic Disease-Modifying Antirheumatic Drugs
CTLA4 Ig	Cytotoxic T lymphocyte associated antigen-4 immunoglobulin fusion proteins
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score for 28 joints - C reactive protein
DLT	Dose Limiting Toxicity
DMARDs	Disease modifying antirheumatic drug(s)
DNA	Deoxyribonucleic Acid
EC	Ethics committee
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	Electronic Data Capture

EDD	Estimated date of delivery
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EOS	End of study
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
°F	degree Fahrenheit
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	high-density lipoprotein
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
hs-CRP	high-sensitivity C-reactive protein
i.v.	intravenous
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
[redacted]	[redacted]
IL-17	Interleukin-17
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	intrauterine system
LDH	lactate dehydrogenase
[redacted]	[redacted]
LDL	low-density lipoprotein
[redacted]	[redacted]
LFT	Liver function test
LN	natural logarithm
LOCF	Last observation carried forward
MAP	Meta-Analytic-Predictive

MAR	missing at random
MCS	mental component score
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	mixed-effects model repeated measures
MRI	Magnetic resonance imaging
MTX	methotrexate
NSAIDs	Non-steroidal anti-inflammatory drugs
PaGA	Patient's Global Assessment of disease activity
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PCS	Physical component score
PFS	prefilled syringe
PhGA	Physician's global assessment of disease activity
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PoC	Proof of concept
PPD	purified protein derivative
PRN	pro re nata
PRO	Patient Reported Outcomes
PsA	Psoriatic arthritis
PsO	Psoriasis
PSW	Premature Study Withdrawal
PT	prothrombin time
PUVA	psoralen and ultraviolet A
q1w	every week
q4w	every 4 weeks
QMS	Quality Management System
RA	Rheumatoid arthritis
RANKL	Receptor activator of NF-kappaB ligand
RBC	red blood cell(s)
RF	Rheumatoid factor
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	serum creatinine
SD	standard deviation
SF36-PCS	Short form health survey -physical component summary
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SJC	Swollen Joint Count
SNP	Single nucleotide polymorphism
SUSAR	Suspected Unexpected Serious Adverse Reaction
t.i.d	3 times a day
TB	Tuberculosis
TBL	total bilirubin

TCM	Traditional Chinese medicine
TD	Study Treatment Discontinuation
TFQ	Trial feedback questionnaire
TJC	Tender Joint Count
TNF-IR	Tumor Necrosis Factor - Inadequate Response
TNFα	Tumor necrosis factor alpha
TP1	Treatment period 1
ULN	upper limit of normal
US	United States
UV	Ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VAS	Visual Analog Scale
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WoCBP	Women of Childbearing Potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
EOS	End of Study
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Protocol summary

Protocol number	CAIN457F2367
Full Title	A phase III randomized, double-blind, placebo controlled, multicenter, bridging study of subcutaneous secukinumab, to demonstrate efficacy after sixteen weeks of treatment and to assess safety, tolerability and long-term efficacy follow-up to one year in Chinese subjects with active psoriatic arthritis
Brief title	Study of efficacy and safety of secukinumab in Chinese subjects with active PsA compared to placebo
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this bridging study is to assess the efficacy and safety of secukinumab 150 mg subcutaneous (s.c.) in Chinese participants with active PsA compared to placebo to support registration in China. [redacted]
Primary Objective(s)	To demonstrate the treatment effect of secukinumab 150 mg s.c. [every week (q1w) ×4, followed by dosing every 4 weeks (q4w)] in Chinese subjects with active PsA is consistent with global population by assessing American College of Rheumatology 20 (ACR20) response rates in participants treated with secukinumab 150 mg s.c. compared to placebo s.c. at Week 16. The clinical question of interest is: What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ACR20 response at Week 16 and the completion of 16 week-treatment in Chinese patients with active PsA? The justification for targeting this treatment effect is to estimate the effect of the study drug for the full duration when administered without dose changes.
Secondary Objectives	● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the proportion of subjects achieving an ACR50 response. ● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from BSL in Disease Activity Score for 28 joints (DAS28-CRP) . ● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing change from BSL in Psoriatic Arthritis Disease Activity Score (PASDAS). ● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from BSL in medical outcome short form health survey (SF36-PCS) . ● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from BSL in Health Assessment Questionnaire - Disability Index (HAQ-DI©) . ● To evaluate the overall safety and tolerability of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w). The clinical questions of interest are: What is the effect of secukinumab 150 mg s.c. relative to placebo on ACR50 response after 16 week-treatment in Chinese participants with active PsA? What is the effect of secukinumab 150 mg s.c. relative to placebo on change from BSL in DAS28-CRP, PASDAS, SF36 PCS and HAQ-DI after 16 week-treatment in Chinese participants with active PsA?
Study design	Study CAIN457F2367 is a randomized, double-blind, placebo-controlled, parallel-group design. A screening period running up to 10 weeks before randomization will be used to assess participant eligibility followed by 52 weeks of treatment.

Key Inclusion criteria	● Chinese male or non-pregnant, non-lactating Chinese female participants at least 18 years of age ● Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have at BSL ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each) ● Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening ● Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis ● Participants with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to Non-steroidal anti-inflammatory drugs (NSAIDs) ● Participants taking methotrexate (MTX) (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 16 ● Participants who have been on a Tumor necrosis factor alpha (TNFα) inhibitor must have experienced an inadequate response to previous or current treatment with a TNFα inhibitor given at a dose in clinical use for at least 3 months or have stopped treatment due to safety/tolerability problems after at least one administration of a TNFα inhibitor.
Key Exclusion criteria	● Chest X-ray or chest (magnetic resonance imaging) MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician ● Participants taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine) ● Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor ● Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer ● Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization ● Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization ● Participants who have previously been treated with more than 3 different TNF-α inhibitors (investigational or approved).
Study treatment	Participants fulfilling the inclusion criteria will be randomized to one of the following two groups in a 1:1 ratio, with 20 participants in each of the two groups as depicted below: ● Group 1 : Secukinumab 150 mg s.c. at BSL, Week 1, 2, 3, 4, 8, and 12 ● Group 2 : Secukinumab Placebo s.c. at BSL, Week 1, 2, 3, 4, 8, and 12 **At Week 16,** the participants in Group 1 and Group 2 will be re-randomized in 1:1 ratio separately: ● **Group 1 will be re-randomized in 1:1 ratio to:** Secukinumab 150 mg s.c. regimen (1.0 mL prefilled syringe (PFS) of 150 mg dose + 1.0 mL PFS of placebo) OR secukinumab [redacted] s.c. regimen ([redacted] dose) every 4 weeks from Week 16 to Week 48. ● **Group 2 will be re-randomized in 1:1 ratio to:** Secukinumab 150 mg s.c. regimen (1.0 mL PFS of 150 mg dose + 1.0 mL PFS of placebo) OR secukinumab [redacted] s.c. regimen ([redacted]) every 4 weeks from Week 16 to Week 48.

Efficacy assessments	1. American College of Rheumatology (ACR) 20, 50 [redacted] responses ● Swollen Joint Count (SJC)/Tender Joint Count (TJC) ● Patient's global assessment of disease activity [(Visual Analog Scale(VAS)] ● Physician's global assessment of disease activity (VAS) ● Patient's assessment of PsA pain intensity (VAS) ● Health Assessment Questionnaire – Disability Index (HAQ-DI©) ● High sensitivity C-Reactive Protein (hs-CRP) and Erythrocyte Sedimentation Rate (ESR) 2. Disease Activity Score (DAS28) and European League Against Rheumatism (EULAR) response criteria 3. PASDAS [redacted]
Key safety assessments	Adverse event monitoring, Physical examination, Vital signs, Height and weight, QuantiFERON TB-Gold test or purified protein derivative (PPD) skin test, Electrocardiogram (ECG), Local tolerability (Injection site reactions), Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis), Pregnancy and assessment of fertility, Tolerability of secukinumab
Other assessments	Clinician Reported Outcomes (ClinRO) ● Swollen Joint Count (SJC)/Tender Joint Count (TJC) ● Physician's global assessment of disease activity (PhGA, VAS) [redacted] [redacted]Patient reported outcomes (PRO) [redacted] ● Medical Outcome Short Form Health Survey (SF-36 v2) version 2 (Acute form) ● HAQ-DI© ● Patient's Global Assessment of Disease Activity ● Patient's assessment of PsA Pain

Data analysis	The primary analysis of ACR20 at Week 16 in the Full analysis set (FAS) will be evaluated using a logistic regression with treatment as a factor and weight as a covariate. Difference in response proportions between secukinumab regimen and placebo regimen and the corresponding 95% confidence interval (CI) will be computed utilizing the logistic regression model fitted. The primary efficacy variable will be ACR20 response at Week 16. The analysis of the primary efficacy variable will be based on the FAS . Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing. Sensitivity analysis will be conducted in order to provide evidence that the results seen from the primary analysis are robust. These analyses will center on the deviations in model assumptions and the treatment of missing data. In order to determine the robustness of the logistic regression model used for the primary analysis, ACR20 response in active PsA participants at Week 16 will also be evaluated using a non-parametric regression model with the same independent variables as the logistic regression model. [redacted] The impact of missing data on the analysis results of ACR20 in active PsA participants will be assessed as well by repeating the logistic regression model using different ways to handle missing data. This may include, but are not limited to: ● Multiple imputation ● Observed data analysis The secondary efficacy variables are described below. Secondary efficacy variables will be analyzed using the FAS population. Handling of missing data for secondary variables will be the same as for the primary variable. Safety analysis will include summaries of Adverse Events (AEs), laboratory measurement, ECG , and vital signs Full details of data analysis will be specified in statistical analysis plan
Key words	Psoriatic Arthritis, PsA, subcutaneous, secukinumab in prefilled syringe, Secukinumab, AIN457

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondylarthritis (SpA). While the various SpA may be diverse in their clinical presentations, common environmental, immunologic as well as genetic factors associated with susceptibility to SpA are suspected Turkiewicz et al (2007). This latter notion was corroborated by findings in a large-scale single nucleotide polymorphism (SNP) scan study, where IL-23R variants that were previously linked to Crohn`s disease and psoriasis (diseases that may both co-exist with spondylarthritides) conferred risk to developing ankylosing spondylitis (AS) Barrett et al 2008. Together, a common pathway including the IL-23/IL-17 axis may play a role in seronegative SpAs including PsA. The prevalence of PsA varies from 1 to 420 per 100,000 across the world, with estimates of 20-420 per 100,000 in Europe and North America, 1 per 100,000 in Japan and 20 per 100,000 in China Li R et al 2012. However, the low prevalence of PsA in China may be due to underdiagnosis as suggested in a study Yang Q et al 2011.

Psoriatic arthritis is a chronic inflammatory musculoskeletal disease that has 5 disease domains: peripheral arthritis, axial disease, dactylitis, enthesitis, and skin and nail disease Ritchlin et al 2009. About 6-48% of patients with psoriasis suffer from PsA. It is not only more common but also more severe than previously thought Gladman 2004, Taylor et al 2006. Median follow up of 2 years of diagnosis, radiological erosions were developed in 47% of the participants Kane D et al 2003. Without proper monitoring and treatment, it will lead to significant structural damage and loss of physical function, and even arthritis mutilans, which is the most severe destructive form of PsA Acosta et al 2015. PsA is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden. Typically conventional synthetic diseases modifying antirheumatic drugs (DMARDs) are used for PsA including methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide, however, these are often inadequate because they only partially control established disease Mease et al 2008.

Several lines of evidence support the notion of prominent T cell involvement in the pathogenesis of PsA. Memory cluster of differentiation 4 (CD4+) and cluster of differentiation 8 (CD8+) cells are present in skin lesions as well as the inflamed synovium that express activation markers and have characteristics of oligoclonal expansion. Curran et al 2004; Tassiulas et al 1999 Clinical trials demonstrated efficacy of T cell targeted therapy in PsA (cyclosporine A, CTLA4 Ig, alefacept). TNF blocking therapy was successfully introduced to the treatment of participants with PsA Mease et al 2000. Despite these efforts, an unmet clinical need exists for participants with PsA for better disease control and long term prevention of structural damage beyond mere abrogation of inflammatory processes.

IL-17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant proinflammatory cytokine of the helper Th17 cell subset. Additional effects of anti-IL-17 on bone homoeostasis via RANKL and IL-1, upstream of TNFα, can be inferred from animal studies Koenders et al 2005. Assuming a potential role of IL-17 cells in the inflammatory infiltrate in PsA, it can be speculated that locally disturbed homeostasis of osteoclastogenic and

osteoblastogenic mechanisms characteristic of PsA might be affected by IL-17 blockade, thus, potentially providing a therapeutic advancement to prevent structural damage in PsA.

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that neutralizes IL-17A activity. IL-17A is the key cytokine in the newly discovered Th17 pathway which is thought to be an important mediator of autoimmunity. Neutralization of IL-17A has strong pre-clinical and clinical target validation and documentation of efficacy in a proof-of-concept study conducted in participants with PsA (CAIN457A2206) suggesting a clinically meaningful response for signs and symptoms up to Week 16. The safety and efficacy of secukinumab were further assessed in three randomized, double-blind, placebo-controlled phase III studies in participants with active psoriatic arthritis (≥3 swollen and ≥3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroids or disease-modifying anti-rheumatic drug (DMARD) therapy

The phase III studies CAIN457F2306 and CAIN457F2312 in PsA (McInnes 2013, Baeten 2013, Kavanaugh 2017, Strand 2017), CAIN457F2305 and CAIN457F2310 in AS (Baeten 2015, Deodhar 2016, Baraliakos 2017, Braun 2017, Marzo-Ortega 2017) and CAIN457H2315 in nr-axSpA (manuscript in review) demonstrated significant improvement with inhibition of IL-17A through secukinumab in measures of disease signs and symptoms, physical function, quality of life and objective markers of inflammation, thus confirming the pivotal role of IL-17A in both PsA and axSpA.

In a Phase III study (CAIN457F2306; N=606) employing an intravenous (i.v.) loading regimen with 10mg/kg i.v at Wk 0, 2, and 4, then 75 mg s.c. q4wk or 10 mg/kg i.v. at Wk 0, 2, and 4, then 150 mg s.c. q4wk, the efficacy of secukinumab in PsA participants is supported by positive results for signs and symptoms (i.e. ACR20/50, PASI75/90), resolution of dactilytis, enthesitis and inhibition of radiologic damage at Week 24

Another Phase III study (CAIN457F2312; N=397) employing a prefilled syringe (PFS) with 75 mg s.c./wk x 4 (75 mg loading regimen) then dosing q4wk, 150 mg s.c./ wk x 4 (150 mg loading regimen) then dosing q4wk, or 300 mg s.c./wk x 4 (300 mg loading regimen) then dosing q4wk. Secukinumab demonstrated positive efficacy results superior to placebo in participants with PsA through most components of the arthritic and skin measures of signs and symptoms and physical function in a population comprised of 65% naïve to TNF-α inhibitors and 35% participants who were inadequate responders to a TNF-α inhibitor.

In the third Phase III study (CAIN457F2342; N=996), employing a PFS with 150 mg s.c./q4w (150 mg no loading regimen), 150 mg s.c./wk x 4 (150 mg loading regimen) then dosing q4wk and 300 mg s.c./wk x 4 (300 mg loading regimen) then dosing q4wk. The secukinumab demonstrated a rapid onset of efficacy and were superior to placebo in the treatment of participants with PsA through all components of the disease including the arthritic and skin measure of signs and symptoms, radiographic endpoint and physical function in the overall population as well as in TNF-naïve participants and TNF-IR participants. Therefore, treatment with secukinumab can also reduce erosion of bone in PsA and can result in improvement of symptoms and functional joint manifestations in afflicted participants.

A total of 200 Asian patients from global pivotal studies (CAIN457F2306, CAIN457F2312, CAIN457F2318, CAIN457F2336, and CAIN457F2342) were included in a combined analysis.

Consistency of efficacy results was seen between Asian population and the overall PsA population. Both the 300 mg and 150 mg were efficacious in the Asian population.

As of 25 Jun 2020, over 26,000 participants have been enrolled in studies with secukinumab with over 22,000 having received active drug at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. Full safety results from all PsA, AS and psoriasis completed studies show that secukinumab generally is safe and well tolerated. Please refer to the Investigator Brochure (IB) for a more detailed review of the pre-clinical and clinical information on secukinumab. From the above combined analysis, the overall pattern of adverse events in the Asian patient was generally consistent with the overall PsA population , with no distinguishable trends or dose dependence for any particular types of AEs. Besides, a psoriasis phase 3 study (CAIN457A2318) and an AS phase 3 study (CAIN457F2308) have confirmed that use of secukinumab up to 1 year was safe and well-tolerated in Chinese patients with psoriasis with potential PsA comorbidities (n=441) or AS (n=327). Secukinumab is approved for the treatment of psoriasis and AS in China. All these favorable risk and benefit profile of secukinumab supports the clinical development for the treatment of PsA patients with secukinumab in China.

Secukinumab has been approved by Food and Drug Administration (FDA), European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of active PsA in adults. Secukinumab is one of the best options to control all domains of PsA and prevent radiographic progression. Unfortunately, the main treatment of PsA in China largely relies on NSAIDs and csDMARDs (conventional synthetic DMARDs) that have unsatisfied efficacy and safety concerns, with no biologics approved up to now. Thus there remains huge unmet medical needs in PsA for targeting of new mechanisms that can provide the clinical benefit on all clinical domains of PsA and good safety profile in Chinese population .

1.2 Purpose

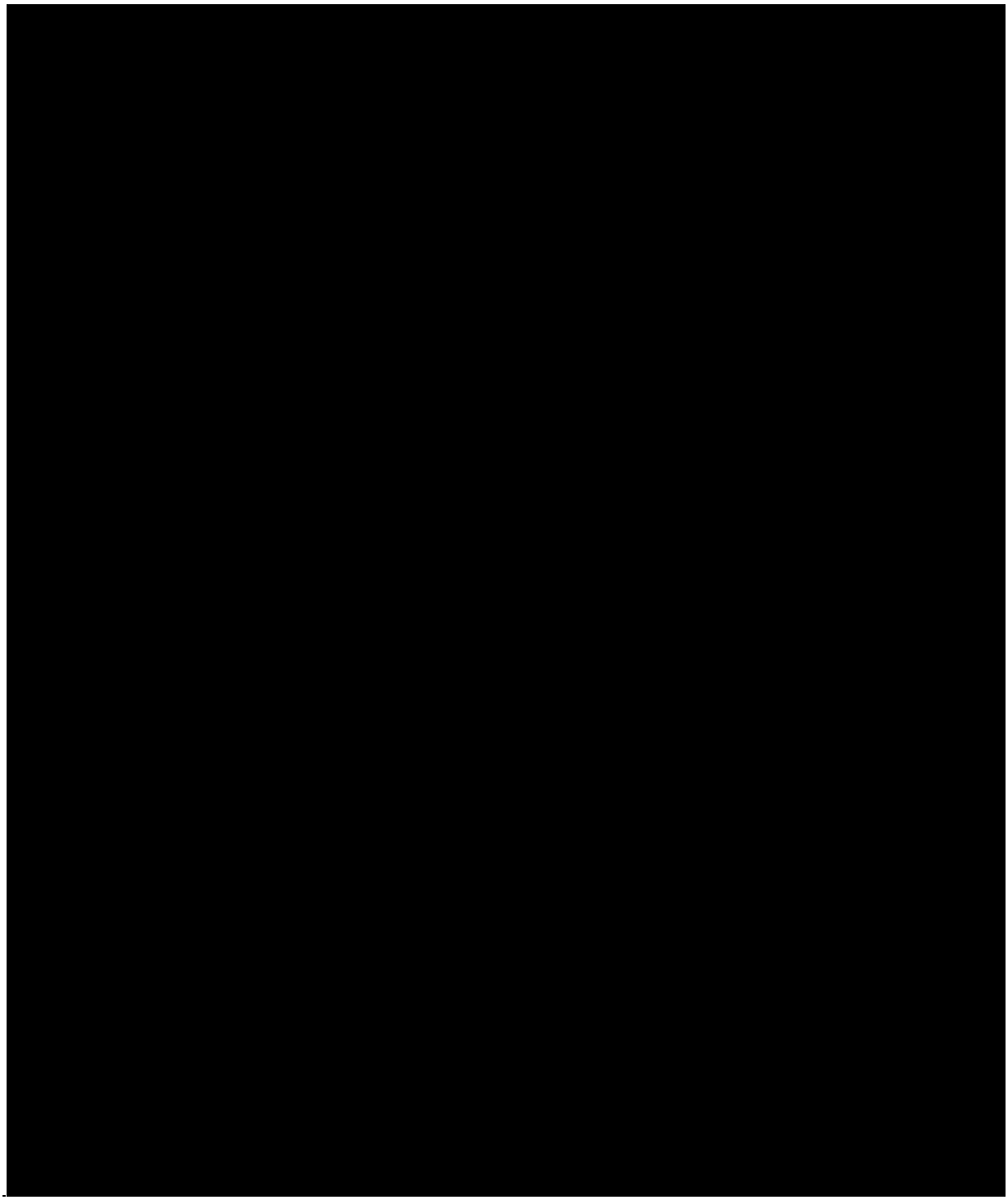
The purpose of this bridging study is to assess the efficacy and safety of secukinumab 150 mg s.c. in Chinese participants with active PsA compared to placebo to support registration in China. The clinical data in this study will be used for the extrapolation between Chinese population and global population by demonstrating that the treatment difference in ACR20 response rates between Secukinumab 150mg s.c. and placebo in Chinese participants at Week 16 is consistent with that observed in global studies.

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate the treatment effect of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) in Chinese subjects with active PsA is consistent with global population by assessing American College of Rheumatology 20 (ACR20) response rates in participants treated with secukinumab 150 mg s.c. compared to placebo s.c. at Week 16.	● ACR20 response at Week 16. A patient will be considered as improved according to the ACR20 criteria if he/she has at least 20% improvement in the three following measures: ● Tender joint count; ● Swollen joint count; ● and at least 3 of the following 5 domains: a. Patient's assessment of PsA pain b. Patient's global assessment of disease activity c. Physician's global assessment of disease activity d. Health Assessment Questionnaire – Disability Index (HAQ-DI©) score e. Acute phase reactant (hsCRP or ESR)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the proportion of subjects achieving an ACR50 response.	● ACR50 response rate at Week 16.
● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from BSL in Disease Activity Score for 28 joints - C reactive protein (DAS28-CRP) .	● Change from BSL in DAS28-CRP at Week 16.
● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing change from BSL in PASDAS	● Change from BSL in PASDAS at Week 16.
● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from BSL in medical outcome short form health survey - physical component summary(SF36-PCS).	● Change from BSL in SF36-PCS at Week 16.
● To evaluate the efficacy of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w) at Week 16 compared with placebo by assessing the changes from BSL in Health Assessment Questionnaire - Disability Index (HAQ-DI©) .	● Change from BSL in HAQ-DI© at Week 16.
● To evaluate the overall safety and tolerability of secukinumab 150 mg s.c. (q1w×4, followed by dosing q4w).	● Physical examination, vital signs, laboratory values, AEs/SAEs.
[redacted]	



2.1 Primary estimands

The clinical question of interest is: What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ACR20 response at Week 16 and the completion of 16 week-treatment in Chinese patients with active PsA?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

The primary estimand is described by the following attributes:

a. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted PsA population
b. Variable: composite of remaining on the study and on randomized treatment through 16 weeks and achieving ACR20 response at 16 weeks
c. Intercurrent event: the intercurrent event of discontinuation from treatment or study prior to Week 16 has been addressed via the composite variable definition
d. Population-level summary: difference in proportions of responders between secukinumab and placebo groups

2.2 Secondary estimands

The clinical questions of interest are:

- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ACR50 response at week 16 and the completion of 16 week-treatment in Chinese patients with active PsA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in DAS28-CRP at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in PASDAS at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in SF-36 PCS at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on change from BSL in HAQ-DI at week 16 in Chinese patients with active PsA had patients completed 16 week-treatment?

The justification for targeting the treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

The estimand definition of all secondary objectives related to response (e.g., ACR50, etc.) will have the same attributes as that for the primary estimand, except for the variable of interest.

Estimand definition for the secondary continuous variables (e.g., HAQ-DI©, etc.) is the following:

a. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted PsA population
b. Variable: change from BSL in the variable of interest
c. Intercurrent event: discontinuation from treatment or study prior to Week 16
d. Population-level summary: difference in variable means between secukinumab and placebo groups

3 Study design

This bridging study uses a randomized, double-blind, placebo-controlled, parallel-group design. A screening period running up to 10 weeks before randomization will be used to assess participant eligibility followed by 52 weeks of treatment.

At BSL, approximately 40 Chinese participants whose eligibility is confirmed will be randomized to one of two treatment groups in 1:1 ratio:

- Group 1 - secukinumab 150mg s.c. :

Secukinumab 150 mg (1.0 mL PFS of 150 mg dose) administered at BSL, Weeks 1, 2, and 3 followed by dosing every four weeks starting at Week 4.

- Group 2 - placebo s.c.

Placebo (1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4.

At Week 16, the participants in Group 1 and Group 2 will be re-randomized in a blinded manner in 1:1 ratio separately:

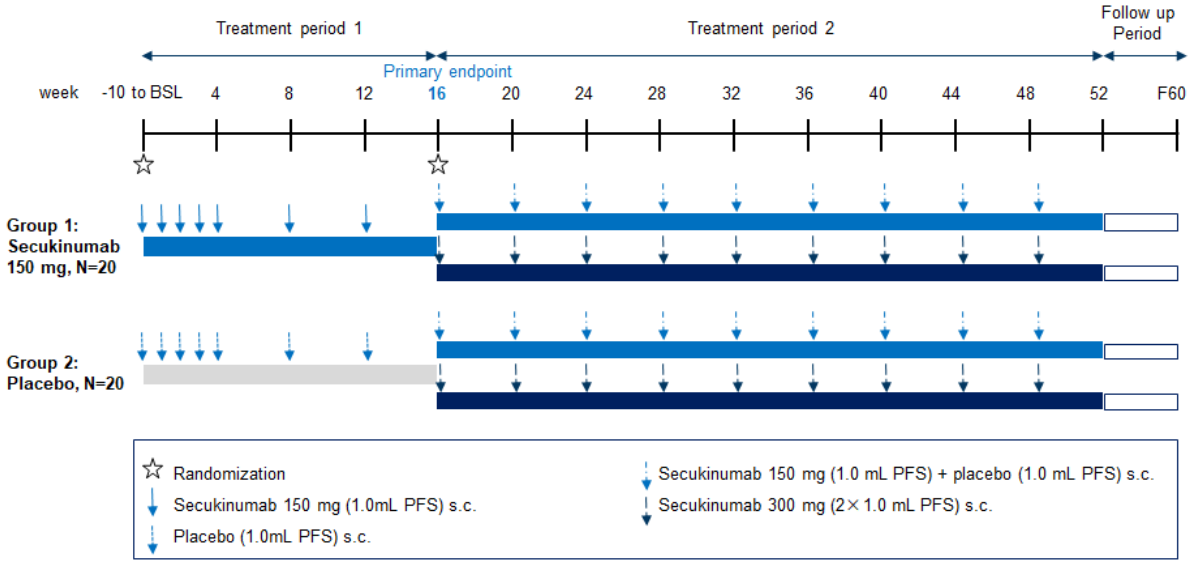
- The participants in Group 1 will be re-randomized in 1:1 ratio to secukinumab 150 mg s.c. q4w regimen (1.0 mL PFS of 150 mg dose + 1.0 mL PFS of placebo) [redacted]
- The participants in Group 2 will be re-randomized in 1:1 ratio to secukinumab 150 mg s.c. q4w regimen (1.0 mL PFS of 150mg dose + 1.0 mL PFS of placebo) or [redacted]

A primary endpoint analysis will be conducted after all participants complete Week 16 visit. Rescue medication will not be allowed before the completion of Week 16 assessments (Section 6.2.3). Although no participant will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in Section 6.2.2) occurs prior to completion of Week 16 assessments, participants will be discontinued from the study treatment and will enter into the follow-up period after an End of Study visit. Safety and efficacy will be assessed in detail at every study visit, and participants who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator, or for any reason of their own accord, are free to discontinue participation in the study at any time.

A follow-up visit will be done 12 weeks after last study treatment administration for all participants, regardless of whether they complete the entire study as planned or discontinue prematurely.

The total combined duration of treatment for this Phase III study is 52 weeks.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall (double-blind, randomized, parallel-group, placebo-controlled)	The double-blind, randomized, parallel-group, placebo-controlled design used in this study up to Week 16 is in alignment with Phase III trials of other biologics in this disease area and in compliance with the European Medicines (Evaluation) Agency (EMA/EMEA) guidelines (EMA 2006) and China Food and Drug Administration (CFDA) requirement in use of biologics drug. The design in this study up to Week 16 is similar with global PsA Phase III trials, to enable the evaluation of treatment effect of secukinumab 150 mg s.c. regimen compared to placebo in Chinese population.
Randomization (strata, allocation ratio)	At BSL, all eligible participants will be randomized via Interacive Response Technology (IRT) in a 1:1 ratio to one of the treatment arms. At Week 16,all participants will be re-randomized in a 1:1 ratio to secukinumab 150 mg s.c. [redacted] to enable to assess long-term efficacy and safety of secukinumab 150 mg s.c. regimen [redacted]
Blinding	Double-blinding is used in this study to minimize bias in the evaluation of safety and efficacy assessment. Blinding is maintained beyond the primary endpoint, to ensure reliable efficacy and safety measures over time.
Duration of study periods	Primary endpoint of the trial is assessed at Week 16, allowing for comparisons of efficacy at a point in time which is same as global PsA Phase III trials. The treatment duration in the placebo group is kept a minimum. The participants in placebo arm will start receiving active treatment at Week 16. The total study duration, including 52 weeks of treatment plus the follow-up period, will allow for the assessment of long term safety and efficacy.

4.2 Rationale for dose/regimen and duration of treatment

The dosing regimens in this study rely upon dose-efficacy relationships observed in a proof of concept (PoC) trial (CAIN457A2206) and two phase III trials (CAIN457F2312, CAIN457F2342) in PsA, as described below. The PoC trial in PsA (CAIN457A2206) suggested that after two i.v. secukinumab doses of 10 mg/kg given 3 weeks apart, secukinumab demonstrated high efficacy, achieving an ACR 20 response at Week 6 in 62% of the TNF-naïve subjects on secukinumab vs. 20% on placebo, and was well-tolerated .

A phase III study CAIN457F2312 assessed the efficacy of 75 mg, 150 mg and 300 mg s.c. at BSL, Weeks 1, 2, 3, then q4w starting at Week 4 , and CAIN457F2342 assessed the efficacy of 150 mg q4w s.c. starting at BSL, and 150 mg, 300 mg s.c. at BSL, Week 1, 2, 3 , then q4w starting at Week 4. The primary endpoint ACR 20 was assessed at Week 24 (study CAIN457F2312) or Week 16 (study CAIN457F2342). Given the similarity of the ACR 20 response seen at the Week 24/Week 16 primary endpoint for the 150 mg dose in each of these studies, 150 mg dose is a sufficient dose to provide clinically and statistically significant efficacy.

Refer current Secukinumab (AIN457) Investigator's Brochure (IB) for details.

The loading regimen is supported by model-based analyses using data from psoriasis studies, predicting significantly improved PASI75 response rate after 12 weeks of treatment, compared to the response rates with initial monthly dosing. A loading regimen with four weekly doses of either 150 mg s.c. is expected to sustain rapid onset and greater magnitude of the effect of secukinumab on PASI75 and PASI90 in participants with PsA and psoriasis.

Selecting secukinumab 150 mg dose in this study (CAIN457F2367) enables to evaluate the efficacy and safety of 150 mg in Chinese population and allow the extrapolation of clinical data between Chinese population and global overall population.

In Study CAIN457F2312 and CAIN457F2342, PASI75 and PASI90 response was assessed in the subgroup of participants who had ≥ 3% skin involvement with psoriasis at BSL. For both PASI75 and PASI90 response rates, the difference to placebo was statistically significant for the secukinumab 150 mg and 300 mg doses. The percentage of PASI 75/90 responders increased as secukinumab dose increased, with the secukinumab 300 mg dose demonstrating a meaningful improvement over the secukinumab 150 mg dose. [redacted]

Refer current Secukinumab (AIN457) Investigator's Brochure (IB) for details.

Of note, the 75 mg s.c. loading/s.c. maintenance regimen tested in CAIN457F2312 achieved a statistically significant but clinically lower effect size in ACR 20 response of 29.3% and did not achieve statistically significant improvements in any of the efficacy endpoints tested in a pre-defined testing hierarchy, including PASI75, PASI90 DAS28 CRP, SF36 PCS, HAQ-DI©, ACR 50, dactylitis and enthesitis.

The maintenance regimens with secukinumab 150 mg in this study aims at ensuringsustainable improvement for PsA signs and symptoms and enabling evaluation of long-term efficacy and safety. .

The selected doses are expected to be safe and well tolerated as the positive safety profile has been demonstrated across all approved indications (including safety data from PsO Phase III study and AS Phase III study in China).

Formulation to be used

This study (CAIN457F2367) will use secukinumab liquid in PFSs. Secukinumab at 150 mg s.c. administered in PFSs has been substantiated in China-central study CAIN457A2308 in the indication of PsO and in global PsA study CAIN457F2312, CAIN457F2336, and CAIN457F2342 in the indication of PsA.

4.3 Rationale for choice of control drugs (comparator/placebo)

A placebo group is included in this study up to the Week 16. Due to the nature of the disease and the primary outcome measure used (ACR20 response), a placebo group is necessary to obtain reliable efficacy measurements for comparison between the active treatment groups and placebo in a controlled fashion. It is necessary to maintain placebo up to Week 16 to evaluate secukinumab treatment effect at Week 16. The continuation of the placebo group up to Week 16 can be supported from an ethical standpoint. Firstly, treatment duration of the placebo group is kept to a minimum and the participants in placebo group will start receiving active treatment at the end of Week 16. Secondly, the regular assessments of disease activity ensures that participants experiencing worsening of their disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time. In addition, the inclusion of a placebo group is in accordance with health authority guidelines, including FDA 1999/EMA 2006, and the parallel-group, placebo controlled design is in alignment with phase III trials of other biologics in this therapeutic domain as outlined in EMA guidelines EMA 2006.

4.4 Purpose and timing of primary endpoint analysis/design adaptations

The primary endpoint analysis will be performed after all participants have completed Week16 visit (or discontinued earlier) to support health authority review on the new indication of PsA registration in China. The final analysis will be conducted after all participants have completed Week F60 visit. Additional analyses may be performed to support interactions with health authorities, as necessary.

Novartis Clinical Team will be unblinded after week 16 database lock to placebo versus secukinumab (Treatment Period 1), but will remain blinded on re-randomization (Treatment Period 2) until final database lock.

All investigators, site personnel, participants, and monitors will remain blinded to all treatments during the whole duration of study, until the Week F60 database lock has occurred.

4.5 Risks and benefits

The risks and benefits of secukinumab in psoriatic arthritis are based from the following completed studies:

Data from analyses of 2 pivotal phase III trials (CAIN457F2306 and CAIN457F2312) demonstrated s.c. secukinumab 150 mg s.c. weekly dose regimen for the first month, followed

by 150 mg monthly dose regimen significantly improved participant clinical signs and symptoms of arthritis and psoriasis, their quality of life including physical function and demonstrated radiographic evidence of delayed progression of joint damage. The participants with a history of an inadequate response for their arthritis to a TNFα-inhibitor and/or with moderate to severe PsO achieved the highest levels of clinical response with the 300 mg s.c. dose regimen. Secukinumab 150 mg and 300 mg demonstrated sustained efficacy in the treatment of participants with PsA throughout the 5-year treatment period for the disease domains including the arthritic, skin measures signs and symptoms, physical function, and quality of life measures. The safety profile of secukinumab 150 mg, and 300 mg showed no new or unexpected safety signals in PsA participants over a treatment period of up to 5 years.

Data from the CAIN457F2318 phase III trial with both secukinumab 150 mg and 300 mg s.c. doses demonstrated efficacy. For both secukinumab treatment groups, the responses achieved at Week 24 for the primary and secondary endpoints at the end of the placebo-controlled phase were generally maintained through Week 104. Study CAIN457F2336, a phase III trial, demonstrated that secukinumab s.c. 150 mg administered as a load or no load regimen had a rapid onset of efficacy and was superior to placebo in the treatment of participants with PsA through all components of the disease including the arthritic, skin signs and symptoms, and physical function measures. The safety profile of secukinumab 150 mg load and no load dose regimens up to Week 104 showed no new or unexpected safety signals.

CAIN457F2342, a phase III trial of s.c. secukinumab (150 mg with and without load and 300 mg) demonstrated that clinical responses reported at Week 16 were sustained through Week 104. Radiographic progression that was significantly inhibited at Week 24 in the overall population with all three secukinumab regimens vs. placebo was sustained up to Week 104. . There are no new or unexpected safety findings up to Week 104.

CAIN457F2366, a randomized, double-blind, active comparator phase IIIb trial in participants with active PsA naïve to biologic therapy for PsA or PsO, demonstrated that s.c. secukinumab 300 mg was associated with a higher treatment retention rate than s.c. adalimumab 40 mg and provided numerically higher clinical responses across musculoskeletal, skin endpoints, and composite indices at Week 52, despite narrowly missing statistical significance for superiority versus adalimumab in the primary endpoint of ACR20 response at Week 52. The safety profile of secukinumab showed no new or unexpected safety signals.

A combined analysis including a total of 200 Asian from global PsA Phase 3 studies, demonstrated higher ACR response rates at week 16 for both doses 150 mg and 300 mg compared to placebo. This was observed for all ACR response levels with p-values <0.05. And the safety results in Asian were consistent with gobal PsA pool and no dose dependence were noted for any particular type of SAEs in Asian subgroup.

CAIN457A2318, a randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to demonstrate efficacy after twelve weeks of treatment and to assess safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity, was conducted in mostly (441/543) Chinese patients, with 24 of these patients having active PsA at BSL. Similar trends of efficacy in Chinese patients with PsA treated by secukinumab 150mg and 300mg were observed as compared to the overall PsA patients studied in the global development program. The safety results observed in the 441 Chinese subjects was consistent

with the known safety profile of secukinumab in other pupulations and showed no new or unexpected safety signals.

Based on the currently available data, secukinumab 150 mg and 300 mg offers a favorable benefit risk profile for participants for the treatment of PsA. Refer current Secukinumab (AIN457) Investigator's Brochure (IB) for details.

5 Study Population

The study population will be comprised of the participants who have passed screening assessments and comply with eligibility criteria.

Participants can be re-screened only once and no re-screening study related procedures should be performed prior to written re-consent by the participant. Mis-randomized participants will not be re-screened.

This is a China stand-alone study and it is expected that approximately 40 Chinese participants will be randomized.

Enrollment will stop as soon as the target number of randomized participants is reached.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Participant must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed.
3. Chinese male or non-pregnant, non-lactating Chinese female participants at least 18 years of age.
4. Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have at BSL ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each).
5. Rheumatoid factor (RF) and anti-CCP antibodies negative at screening.
6. Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis.
7. Participants with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.
8. Participants who are regularly taking NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 16
9. Participants taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 16.

10. Participants taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 16.
11. Participants on MTX must be on folic acid supplementation at randomization.
12. Participants who are on a DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed.
13. Participants who have been on a TNFα inhibitor must have experienced an inadequate response to previous or current treatment with a TNFα inhibitor given at a dose in clinical use for at least 3 months or have stopped treatment due to safety/tolerability problems after at least one administration of a TNFα inhibitor.
14. Participants who have previously been treated with TNFα inhibitors (investigational or approved) will be allowed entry into study after appropriate wash-out period prior to randomization:
    - 4 weeks for Enbrel® (etanercept) or "Yi Sai Pu" (entanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route).
    - 8 weeks or longer for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion).
    - 10 weeks or longer for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route).
    - 10 weeks or longer for Simponi® (golimumab) – with a terminal half-life of 11-14 days.
    - 10 weeks or longer for Cimzia® (certolizumab) – with a terminal half-life of approx. 14 days .

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician.
2. Participants taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine).
3. Previous exposure to secukinumab or other biologic drug directly targeting interleukin-17 (IL-17) or IL-17 receptor.
4. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer.
5. Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. The following wash out periods need to be observed prior to the randomization:
    a. Oral or topical retinoids 4 weeks
    b. Photochemotherapy (e.g. PUVA) 4 weeks
    c. Phototherapy (UVA or UVB) 2 weeks
    d. Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks

6. History of hypersensitivity to drug of similar chemical classes as that of the study drug or its excipient.
7. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.
8. Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization.
9. Participants who have previously been treated with more than 3 different TNF-α inhibitors (investigational or approved).
10. Participants who have ever received biologic immunomodulating agents except for those targeting TNFα.
11. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., Campath, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective contraception during the entire study (during the entire study).

    Effective contraception is defined as either:

    - Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Spermicides alone are not a barrier method of contraception and should not be used alone.
    - Other more effective than the barrier method and are also acceptable:
        a. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject [Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
        b. Female sterilization: have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
        c. Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception women should have been stabile on the same pill for a minimum of 12 weeks before taking study treatment.

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

    NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

14. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy, including active IBD and active uveitis.
15. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy.
16. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes.
17. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine (Scr) level exceeding 1.5 mg/dL (132.6µmol/L).
18. Screening total white blood cell(s) (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85g/L).
19. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.
20. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive PPD skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
21. History or current infection with HIV, hepatitis B or hepatitis C.
22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial.
24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
25. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
26. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
27. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.
28. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The following drugs will be used in this study and will be administered in accordance with this protocol. Secukinumab 150 mg syringes for subcutaneous injection will be provided in 1.0 mL pre-filled syringe. Secukinumab placebo for subcutaneous injection will be provided as a 1.0 mL pre-filled syringe matching the appearance of 150 mg secukinumab syringe; each placebo pre-filled syringe contains a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose.

Participants will be instructed by site staff on how to self-administer the subcutaneous injection using the PFS, based on the Instructions for Use (IFU). The investigational drug will be administered by the participant into the appropriate injection site of the body under the supervision of the site staff. All injections through Week 48 will be performed at the study site. Site staff will administer the injection to those participants who are not able or unwilling to self-administer the PFS injection.

Home administration will be allowed under the situation as described in Section 16.9 .

NOTE: The PFS do not need to be prepared at the site. PFS will be packaged both as double-blind supplies.

The study medication will be labeled as follows:

- Double blind Secukinumab PFS will be labeled as AIN457 150mg/1.0 ml/Placebo

Novartis GCS will supply the following investigational products:

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Secukinumab 150 mg	PFS solution for injection	Subcutaneous Injection	Double Blind	Novartis Pharma AG (global)
Secukinumab Placebo	PFS solution for injection	Subcutaneous Injection	Double Blind	Novartis Pharma AG (global)

6.1.2 Additional study treatments

No additional treatment beyond investigational treatment described in Section 6.1.1 is used in this trial.

6.1.3 Treatment arms/group

Participants fulfilling the inclusion criteria will be randomized to one of the following two groups in a 1:1 ratio, with 20 participants in each of the two groups as depicted below:

- Group 1 : Secukinumab 150 mg s.c. at BSL, Week 1, 2, 3, 4, 8, and 12
- Group 2 : Secukinumab Placebo s.c. at BSL, Week 1, 2, 3, 4, 8, and 12

At Week 16, the participants in Group 1 and Group 2 will be re-randomized in 1:1 ratio separately:

- **Group 1 will be re-randomized in 1:1 ratio to:**

Secukinumab 150 mg s.c. regimen (1.0 mL PFS of 150 mg dose + 1.0 mL PFS of placebo) [redacted]

- **Group 2 will be re-randomized in 1:1 ratio to:**

Secukinumab 150 mg s.c. regimen (1.0 mL PFS of 150 mg dose + 1.0 mL PFS of placebo) [redacted]

6.1.4 Treatment duration

The overall planned duration of study treatment is 52 weeks, split between Treatment Period 1 (16 weeks) and Treatment Period 2 (36 weeks). Participants may voluntarily discontinue from the study treatment for any reason at any time. (see Section 9.1.1)

6.2 Other treatment(s)

Not applicable.

6.2.1 Concomitant therapy

The investigator should instruct the participant to notify the study site about any new medications (including over-the-counter drugs, calcium, vitamins, herbal medicines and tranditional Chinese medicines) administered after the participant is enrolled into the study. All medications (other than study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded on the Prior and Concomitant medications or Procedures and Significant Non Drug Therapy eCRF. The reason, name of the drug, procedure or non-drug therapy should be listed.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before reassigning treatment for a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Participants are permitted to use the medications as described below.

Methotrexate (MTX)

Participants taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 16.

Folic acid

Participants on MTX must be taking folic acid supplementation (at the dose permitted by local practice guideline) before randomization and during the trial to minimize the likelihood of MTX associated toxicity.

Cholestyramine for leflunomide wash out

In case of leflunomide treatment, a drug wash out of 8 weeks has to be performed. However, prior to randomization another wash out procedure might be considered. Cholestyramine could be given orally to wash out the drug at a dose of 8 g 3 times a day (t.i.d). Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in participants who require a drug elimination procedure. If a participant receives 8 g t.i.d. for 11 days, the wash out period could be 4 weeks (counting from the beginning of the 11 days treatment).

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization. The participant should remain on a stable dose until Week 16.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 16 assessment, although the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks.

Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding eCRF page.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization and up to Week 16. After Week 16 assessment, no more than 1 joint per 24-week period may be injected. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) .

Non-steroidal anti-inflammatory drugs (NSAIDs) [including cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) inhibitors], low strength opioids and acetaminophen/paracetamol

Participants on regular use of NSAIDs, low strength opioids, or paracetamol/acetaminophen as required (PRN) should be on stable dose for at least 2 weeks before randomization to allow inclusion. They should remain on a stable dose in the study up to Week 16, however, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment.

After Week 16 assessments are completed, a change in the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment regimen is permitted.

Any change of the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF page.

Note: Background and concomitant medications will not be provided by Novartis and must be supplied by the the study center.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after Screening (Visit 1). The minimum required period without prohibited treatment before Screening (Visit 1) is also listed in Table 6-2. Each concomitant drug must be individually assessed against all exclusion criteria and the table below to see if it is allowed. If in doubt, the investigator should contact Novartis or delegate before randomizing a participant or allowing a new medication to be started.

Live vaccines should not be given until 12 weeks after last study treatment administration.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Biological immunomodulating agents > 3 different TNFα	No prior use allowed	Discontinue from study
Other biological immunomodulating agents except for those targeting TNFα (such as Ustekinumab)	No prior use allowed	Discontinue from study
Etanercept [1]	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Discontinue study treatment c) Stop prohibited treatment
Infliximab [1]	a) 8 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 8-week wash out or discontinue from study b) Discontinue study treatment c) Stop prohibited treatment
Adalimumab, golimumab, certolizumab [1]	a) 10 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 10-week wash out or discontinue from study b) Discontinue study treatment c) Stop prohibited treatment
Unstable dose of MTX [2]	a) 4 weeks prior to randomization b) Treatment period up to Week 16	a) Delay randomization to achieve 4-week stable dose or discontinue from study b) Keep MTX at a stable permitted dose from at least 4 weeks before randomization up to Week 16, otherwise, discontinue study treatment
DMARDs (except MTX)	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Leflunomide	a) 8 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 8-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment

Medication	Prohibition period	Action taken
Leflunomide with Cholestyramine washout	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Apremilast	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Unstable dose of NSAIDs (including COX-1 or COX-2 inhibitors), low strength opioids and paracetamol/acetaminophen[2]	a) 2 weeks prior to randomization b) Treatment period up to Week 16	a) Delay randomization to achieve 2-week stable dose or discontinue from study b) Keep NSAIDs, low strength opioid and paracetamol/acetaminophen at a stable dose from at least 2 weeks before randomization up to Week 16, otherwise, discontinue study treatment
Unstable dose of systemic corticosteroids <= 10 mg prednisone equivalent [2]	a) 2 weeks prior to randomization b) Treatment period up to Week 16	a) Delay randomization to achieve 2-week stable dose or discontinue from study b) Keep systemic corticosteroids (<= 10 mg prednisone equivalent) from at least 2 weeks before randomization up to Week 16, otherwise, discontinue study treatment
Systemic corticosteroids > 10 mg prednisone equivalent [2]	a) 2 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 2-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Intra-articular injections [2]	a) 4 weeks prior to randomization b) Treatment period up to Week 16 c) Treatment period after Week 16 assessment to Week F60	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Discontinue study treatment c) No more than 1 joint per 24-week period is permitted after Week 16 assessment to Week F60
Intramuscular or intravenous corticosteroid treatment	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Any investigational treatment or participation in any interventional trial	a) 4 weeks or 5 half-lives (which is longer) prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve wash out or discontinue from study b) Discontinue study treatment c) Stop prohibited treatment

Medication	Prohibition period	Action taken
Live vaccinations	a) within 6 weeks preceding randomization randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve wash out or discontinue from study b) Interrupt study treatment for 12 weeks, or discontinue study treatment (see details in Section 6.5) c) Stop prohibited treatment
Oral or topical retinoids	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Photochemotherapy (e.g. PUVA)	a) 4 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Phototherapy [ultraviolet A (UVA) or ultraviolet B (UVB)]	a) 2 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 2-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency)	a) 2 weeks prior to randomization b) Treatment period c) Follow up period	a) Delay randomization to achieve 2-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment
Traditional Chinese medicine treatments of psoriasis and/or psoriatic arthritis [3]	a) 4 weeks prior to randomization b) Treatment period up to Week 16 c) Treatment period after Week 16 assessment to Week F60	a) Delay randomization to achieve 4-week wash out or discontinue from study b) Stop prohibited treatment or discontinue study treatment c) Stop prohibited treatment

1. These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation (see Section 9.1.1).
2. See details in Section 6.2.1
3. Traditional Chinese medicine (TCM) is defined as a compendium of methods popular in Chinese tradition for the treatment of a wide range of conditions. TCM practitioners use herbal remedies, acupuncture, massage, mind-body and dietary therapies, and other methods.

6.2.3 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a participant is experiencing either no benefit from participation in the trial or worsening / exacerbation of their disease.

Rescue medication must not be used before completion of Week 16 assessments (see Section 3). Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication (Table 6-2).

When in doubt the Investigator should contact the Novartis medical monitor before treatment reassignment or allowing a new medication to be started. If any of the medications listed in

Table 6-2 is deemed a necessary rescue therapy, the Investigator must follow the actions to be taken outlined in this section. Rescue treatment is to be provided by the study center or personal physician.

Please see Section 6.2.1 and Section 6.2.2 for details. Although no participant will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited treatments (as described in Table 6-2) occurs , participants will be discontinued from study treatment and continue to the follow-up visit . Efficacy will be assessed in detail at every study visit, and participants who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord are free to discontinue participation from the treatment at any time.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a participant Number (participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The participant No. consists of the Center Number (Center No.) as assigned by Novartis to the investigative site with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database.

Upon signing the informed consent form, the participant is assigned to the next sequential participant No. available. Once assigned to a participant the participant number will not re-used. The re-screened participant will receive a new participant Number.

Participants numbers are assigned when the site creates the first entry for the participant in the Case Report/Record Form (CRF), therefore CRF must be created prior to contacting the IRT system.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

At BSL, all eligible Chinese participants will be randomized via IRT to one of the two treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant. The randomization number will not be communicated to any of the site staff.

Based on enrollment target, the participants who are anti-TNFα inhibitor inadequate responder (TNF-IR) should not be more than 10% of Chinese randomized participants to ensure a representative population for the assessment of efficacy and safety.

Participants who complete the Treatment period 1 (BSL to Week16) will enter Treatment period 2 (Week 16 to Week 52). For this effect, after all **Week 16 assessments would have been completed, the investigator or his/her delegate must contact the IRT in order to re-randomize the participants.** The IRT will assign the medication number of PFS to be

administered. IRT will only communicate to the caller the medication numbers, not the randomization number.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis GCS using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Stratification is not applicable in the study

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is a double-blind randomized treatment trial. Participants, investigator staff, persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions of bioanalyst (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Unblinding of treatment dose or original randomized treatment assignment before the Week F60 database lock and analyses are completed will only occur in the case of participant emergencies Section 6.6.2.

The hsCRP lab results from samples collected during the treatment period will be revealed only after the Week F60 database lock and analyses are completed to maintain blinding.

The primary endpoint analysis will be performed when the database is locked (after all participants have completed Week 16 assessments). Summary results may be shared internally and externally; however, individual unblinded participant data will not be disclosed. A final database lock will occur when all participants have completed the study.

Unblinding will occur in the case of participant emergencies and at the conclusion of the study.

Novartis Clinical Team will be unblinded after week 16 database lock to placebo versus secukinumab (Treatment Period 1), but will remain blinded after re-randomization (Treatment Period 2) until final database lock.

All investigators, site personnel, participants, and monitors will remain blinded to all treatments during the whole duration of study, until the Week F60 database lock has occurred.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Dose modifications

Investigational treatment dose modifications are not permitted.

6.5.2 Dose interruptions

Study treatment interruption should be avoided with the following exceptions:

Study treatment interruption is only permitted if, in the opinion of the investigator, a participant is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks. Any study treatment interruption must be recorded on the corresponding eCRF page.

In all cases the **original visit schedule should be maintained** (no recalculation from the last visit).

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The site staff will provide the study treatment assigned by IRT to the participants. Kit numbers are collected in the IRT and the site staff will record study drug administration in the eCRF. The compliance will also be assessed by means of site and participant specific drug accountability by Novartis monitors during site monitoring visits using medication pack numbers, drug label information and information from IRT.

In this study, the compliance to the planned administration schedule is expected to be high since the study treatment will be administered onsite by self-administration by the participants or by the trained site staff.

All dates and times of study treatment administration will be recorded in the Drug Accountability Log.

Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the Investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient

to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying

information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken. Participants unblinded following an intentional emergency code breaking should be discontinued from the study.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label. All study treament kits assigned to the participant during the study will be recorded in the IRT.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of China. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The PFS (150 mg active/placebo) sealed in their outer box must be stored in a access controlled/locked refrigerator between 2 degree Celsius (°C) and 8°C [36 degree Fahrenheit (°F) and 46°F)] (Do Not Freeze) and protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate (according to local requirements) during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

Secukinumab solution for subcutaneous injection (150 mg in 1.0 mL active/placebo) will be provided in PFSs.

The study treatment solution **must** be injected into **non-affected** areas of the skin.

Although all doses of study treatment (secukinumab and placebo) will be administratered at the study site, it is preferred that participants self-administer. However, if the participant is not able or not willing to self-administer, administration will be performed by study site staff. The injections will be self-administered by the participant at the study site under the supervision of a site staff member after the study assessments for the visit have been completed. Participants will be instructed by the site staff on how to self-inject study treatment using a PFS, following the IFU.

At study visits requiring pre-dose blood samples, the study treatment will be injected only after the blood samples have been collected.

For each study visit at the site, all study assessments including completion of PROs should be completed prior to the administration/self-administration of the study treatment.

All dosages prescribed and dispensed to the participants and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Immediately before dispensing the package to the participant, site staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that participant's unique participant number.

The investigator should promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study.

Any PFS for which a defect or malfunction is noticed prior to or during the injection at any of the study visits, must be kept at the site until guidance is received from Novartis on whether it should be returned to Novartis for investigation or discarded. Devices identified as defective should be stored according to local guidelines, until specific instruction is discussed with

Novartis personnel. Additionally, from BSL onwards, any noticed defect, malfunction, problem during the injections or product complaints with the PFS should be recorded in the source document and the Use of Device eCRF. Sites should detail the issue, the date, the kit number and the visit number. Site will be asked to record based on their judgment whether the observed issue was primarily related to the device or to the user. Device malfunctions should also be immediately reported to Novartis personnel as a necessary replacement kit may need to be provided.

Administration

Single syringes will be packaged in individual boxes. The boxes containing the PFSs with study treatment solution should be kept at 2 to 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. Prior to administration the boxes containing the PFSs with study treatment solution should be allowed to come to room temperature **unopened** for 15-30 minutes prior to injection.

The injections will be administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least one inch from the previously used site. If participant chooses the abdomen, a 2 inch area around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where participant has scars or stretch marks.

Used safety syringes should be disposed immediately after use in a sharps container or according to the local regulatory requirements.

Table 6-3 Dose and treatment schedule (BSL to Week 12)

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Secukinumab 150 mg s.c (Group 1)	150 mg (1.0mL PFS)	BSL, Week 1,2,3, 4, 8 and 12
Secukinumab Placebo s.c (Group 2)	0 mg (1.0mL PFS)	BSL, Week 1, 2, 3, 4, 8 and 12

At BSL/randomization visit, the participants will be randomized to one of the above two groups in a 1:1 ratio

Table 6-4 Dose and treatment schedule (Group 1 & Group 2 participants- Week 16 to Week 48)

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Secukinumab 150 mg s.c and Placebo s.c.	150 mg (1.0mL PFS) 0 mg (1.0mL PFS)	**Q4W** (Week 16, 20, 24, 28,32, 36, 40, 44 and 48)

At Week 16, the participants in Group 1 and Group 2 will be re-randomized in 1:1 ratio to either Secukinumab 150 mg s.c. regimen (1.0 mL PFS of 150mg dose + 1.0mL PFS of placebo)

7 Informed consent procedures

The following informed consents are included in this study:

1. Main study consent
2. As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participants's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

It is permissible to re-screen a participant if she/he fails the initial screening. Participants can be rescreened only once, and no study-related re-screening procedure should be performed prior to written re-consent by the participant.

If a participant re-screens for the study, then the participant must sign a new ICF and be issued a new participant number prior to any screening assessment being conducted for the participant under the new screening participant number. For all participants, the investigator/qualified site staff will record if the participant was rescreened on the rescreening CRF and any applicable screening numbers the participant was issued prior to the current screening number.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) . This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements (see Section 5.2).

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule *(*Table 8-1*)* lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule *(*Table 8-1*)* or as close to the designated day/time as possible.

- For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration.
- For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration

Note: All efforts need to be made to maintain the actual duration of 52-week study treatment period. Therefore, a study visit subsequent to a visit, which has been delayed or brought forward needs to be planned as per original visit schedule. The original visit schedule should be maintained (no recalculation from the last visit).

Missed or rescheduled visits should not lead to automatic discontinuation of study treatment. Participants who prematurely discontinue from treatment during a specific treatment period should return for the final visit within that treatment period (4 weeks after the last study treatment), as well as return for the follow-up visit (Week F60), 12 weeks after the last study treatment. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

If participants refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. Documentation of attempts to contact the participant should be recorded in the source documentation.

Table 8-1 Assessment Schedule

Period	Screening[1]		Treatment Period 1 (TP1)								Treatment Period 2 (TP2)									Post-Treatment Follow-Up
Visit Name	**-10 to -4**	**≤-4 to BSL**	**Base line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16/ End of TP1/TD [2]**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52/ End of TP2/TD[2]**	**F60 (End of study/PSW)[2]**
Weeks	**-10 to -4**	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**
Days	**-70 to -28**	**-28 to 0**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Informed consent	X																			
Inclusion / Exclusion criteria	X	X	X																	
Medical history/current medical conditions		X	X																	
Washout evaluation/instruction[3,4]	S																			
Smoking history			X																	
Demography	X																			
Psoriasis/psoriatic arthritis medical history and previous therapies	X																			
PsA CASPAR Criteria		X																		

Period	**Screening**[1]		**Treatment Period 1 (TP1)**								**Treatment Period 2 (TP2)**									**Post-Treatment Follow-Up**
Visit Name	**-10 to -4**	**≤-4 to BSL**	**Base line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16/ End of TP1/TD** [2]	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52/ End of TP2/TD**[2]	**F60 (End of study/PSW)**[2]
Weeks	**-10 to -4**	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**
Days	**-70 to -28**	**-28 to 0**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Physical Examination[4]		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Body Height		X																		
Body Weight		X	X							X									X	X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test or QuantiFERON TB-Gold test [5]		X																		
HBV, HCV and HIV screen[4,6]		S																		
Chest X-ray/MRI[7]		S																		
Electrocardiogram (ECG)			X							X									X	X
Contact IRT			X	X	X	X	X	X	X	X[8]	X	X	X	X	X	X	X	X		
Administration of sc study treatment via PFS at study site			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Period	**Screening**[1]		**Treatment Period 1 (TP1)**								**Treatment Period 2 (TP2)**									**Post-Treatment Follow-Up**
Visit Name	**-10 to -4**	**≤-4 to BSL**	**Base line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16/ End of TP1/TD** [2]	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52/ End of TP2/TD**[2]	**F60 (End of study/PSW)**[2]
Weeks	**-10 to -4**	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**
Days	**-70 to -28**	**-28 to 0**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Prior/Concomitant medication/ Non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy (Serum)[4,6]		S																		S
Pregnancy Test [4,6,9]			S				S		S	S		S		S		S			S	S
Adverse Events/SAE (incl. injection site reaction & occurrence of injections)[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ANA			X							X									X	
anti-double stranded DNA antibodies (anti-dsDNA)			X							X									X	
Anti-CCP	X																			
Rheumatoid factor (RF)	X																			
Hematology		X	X						X	X			X			X			X	X
Blood chemistry		X	X						X	X			X			X			X	X

Period	**Screening**[1]		**Treatment Period 1 (TP1)**								**Treatment Period 2 (TP2)**									**Post-Treatment Follow-Up**
Visit Name	**-10 to -4**	**≤-4 to BSL**	**Base line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16/ End of TP1/TD** [2]	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52/ End of TP2/TD**[2]	**F60 (End of study/PSW)**[2]
Weeks	**-10 to -4**	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**
Days	**-70 to -28**	**-28 to 0**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Urinalysis		X	X						X	X			X			X			X	X
High sensitivity C-Reactive protein (hsCRP)[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Erythrocyte Sedimentation Rate (ESR)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tender and swollen joint counts (TJC78, SJC76)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's assessment of PsA pain (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Period	**Screening**[1]		**Treatment Period 1 (TP1)**								**Treatment Period 2 (TP2)**									**Post-Treatment Follow-Up**
Visit Name	**-10 to -4**	**≤-4 to BSL**	**Base line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16/ End of TP1/TD** [2]	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52/ End of TP2/TD**[2]	**F60 (End of study/PSW)**[2]
Weeks	**-10 to -4**	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**
Days	**-70 to -28**	**-28 to 0**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Physician's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health Assessment Questionnaire (HAQ-DI)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of psoriasis and arthritis disease activity (VAS)			X				X	X	X	X		X		X		X			X	
Body Surface Area (BSA) evaluation[12]			X																	

Period	**Screening**[1]		**Treatment Period 1 (TP1)**								**Treatment Period 2 (TP2)**									**Post-Treatment Follow-Up**
Visit Name	**-10 to -4**	**≤-4 to BSL**	**Base line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16/ End of TP1/TD** [2]	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52/ End of TP2/TD**[2]	**F60 (End of study/PSW)**[2]
Weeks	**-10 to -4**	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**
Days	**-70 to -28**	**-28 to 0**	**1**	**7**	**14**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
[redacted]																				
SF-36 v2			X				X	X	X	X		X							X	
[redacted]																				
Lipids[13]			X					X		X		X							X	X
Treatment period 1 completion form										X										
Treatment period 2 completion form																			X	
Trial feedback questionnaire																				X[14]

Period	Screening[1]		Treatment Period 1 (TP1)								Treatment Period 2 (TP2)									Post-Treatment Follow-Up
Visit Name	-10 to -4	≤-4 to BSL	Base line	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk16/ End of TP1/TD [2]	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk52/ End of TP2/TD[2]	F60 (End of study/PSW)[2]
Weeks	-10 to -4	-4 to 0	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	60
Days	-70 to -28	-28 to 0	1	7	14	21	28	56	84	112	140	168	196	224	252	280	308	336	364	420

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] If subject's washout period is ≤ 4 weeks, two screening visits can be performed on the same day.
[2] These assessments are also to be conducted for patients who discontinue from the treatment- Treatment Discontinuation (TD): Patients who prematurely discontinues during Treatment Period 1 has to return for assessments associated with End of TP1 visit (4 weeks after the last study treatment) and End of study visit (12 weeks after the last administration of the study treatment). Patients who prematurely discontinues during Treatment Period 2 has to return and complete assessments associated with End of TP2 visit (4 weeks after the last study treatment) and End of study visit (12 weeks after the last administration of the study treatment).
[3] To determine the duration of the washout period, and if the second screening visit will be performed (see Section 8.1).
[4] assessment to be recorded on source documentation only
[5] Either a QuantiFERON TB-Gold test or a PPD skin test must be performed at Screening. A QuantiFERON TB-Gold test is to be performed at the second screening visit. The PPD skin test can be performed at any time during the screening period but it has to be read within 72 hrs and before randomization.
[6] Sample will be analyzed locally
[7] If patients do not have a chest X-ray available within 3 months of screening, an X-ray is to be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation. The x-ray might be replaced by an MRI assessment.
[8] Patients will be re-randomized at Week 16.
[9] Recommended to perform urine pregnancy test at designated visits in local lab, if not feasible alternatively the serum pregnancy test should be performed. A positive urine test requires immediate interruption of study drug and needs to be confirmed with a serum Beta human chorionic gonadotropin (β-hCG test) (serum pregnancy test). If positive, the participant must be discontinued from the study treatment.
[10] AEs/SAEs occurring after the participant has signed the informed consent must be captured on the appropriate eCRF page.
[11] Since the results of this test may unblind study personnel, results from the central lab will be provided for SCR and BSL only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only
[12] BSA evaluation at BSL to determine if [redacted] should be done or not.
[13] Sample has to be obtained fasting.
[14] Optional

8.1 Screening

Screening

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have duration of 4-10 weeks, during which time the participant will sign the ICF, be evaluated for eligibility and allowed sufficient time for potential medication washout (see Table 6-2, in addition to all other assessments indicated in Table 8-1).

Screening will consist of two consecutive visits. During the first screening visit, initial assessments will be performed as outlined in Table 8-1. At that visit the duration of the washout period will be determined. The second screening visit will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to second screening visit on the same day and complete all assessments in the next 4 weeks prior to randomization.
- If the washout period is more than 4 weeks, the participant will be instructed to initiate necessary washout regimen and return for screening visit 2 at 4 weeks prior to randomization.

The rationale is that in all cases second screening visit must occur within the 4 weeks prior to randomization.

If participants do not have a chest X-ray obtained within 3 months preceding the screening visit, a chest X-ray should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the participant meets all inclusion/exclusion criteria. In some sites selected by Novartis, the X-ray assessment may be replaced by MRI assessment.

All participants evaluated at both screening visits for eligibility should not be screen failed on the basis of a medication requiring washout, unless the participant will be unable to complete the washout in the appropriate time frame before randomization.

Participants who prematurely withdraw from the study will not be replaced.

In the case where a safety laboratory assessment at screening and/or initial BSL is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

It is permissible to re-screen a participant if she/he fails the initial screening. Participants can be rescreened only once, and no study-related re-screening procedure should be performed prior to written re-consent by the participant.

If a participant rescreens for the study, then the participant must sign a new ICF and be issued a new participant number prior to any screening assessment being conducted for the participant under the new screening participant number. For all participant s, the investigator/qualified site staff will record if the participant was rescreened on the rescreening CRF and any applicable screening numbers the participant was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the Informed consent CRF to correspond to the new screening participant number. Informed Consent for a rescreened participant must be obtained prior to performing any study-related assessment or collecting any data for the Screening Visit.

For rescreening, all screening assessments must be performed as per protocol.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE Section 10.1.3 for reporting details).

Adverse events that are not serious will be followed by the investigator and collected only in the source data.

If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized, and the reason for not being randomized will be entered on the screening phase dispostion CRF page.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF. All AEs occurring after informed consent is signed should be recorded on the Adverse Event eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2 Participant demographics/other baseline characteristics

Country-specific (China) regulations should be considered for the collection of demographic and BSL characteristics in alignment with eCRF.

Participant demographic and BSL characteristic data to be collected on all participants include: age, sex, race, ethnicity, smoking history, relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses instead of symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF if, in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

The efficacy outcome measures used in this study are the standard measures, which are used across all PsA trials and required for filing.

- ACR 20, 50 [redacted] responses

  - Swollen Joint Count (SJC)/Tender Joint Count (TJC)
  - Patient's global assessment of disease activity (VAS)
  - Physician's global assessment of disease activity (VAS)
  - Patient's assessment of PsA pain intensity (VAS)
  - HAQ-DI©
  - hsCRP) and ESR
- Disease Activity Score (DAS28) and EULAR response criteria
- PASDAS

All efficacy assessments should be performed prior to administration of study treatment.

Details relating to the administration of all PROs are provided in Section 16.8

8.3.1 American College of Rheumatology (ACR) response

The ACR response Section 16.5 will be used to determine efficacy (Felson et al 1995). A participant is defined as an ACR20 responder if, and only if, the following three conditions hold:

- they have a ≥ 20% improvement in the number of tender joints (based on 78 joints)
- they have a ≥ 20% improvement in the number of swollen joints (based on 76 joints)
- they have a ≥ 20% improvement in three of the following five domains:
  - Patient's global assessment of disease activity (PaGA) (measured on a VAS scale, 0-100)
  - Physician's global assessment of disease activity (PhGA) (measured on a VAS scale, 0-100)
  - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
  - Health Assessment Questionnaire – Disability Index (HAQ-DI©) score
  - Acute phase reactant (hsCRP or ESR)

ACR50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

The components of ACR response are to be assessed at the visits/time points shown in Table 8-1.

8.3.1.1 Tender 78 joint count and swollen 76 joint count

Joint counts will be performed by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits. Refer Section 16.5

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the feet. All of these except for the hips are assessed for swelling. Joint tenderness and swelling are to be graded present (1) or absent (0). Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. [redacted]

Data is recorded for tender and swollen joints (right or left side), i.e. a box (yes, no or not applicable) needs to be ticked for all joints.

8.3.1.2 Patients global assessment of disease activity

The patient's global assessment of disease activity will be performed using a Visual Analog Scale (VAS) of 100 mm ranging from "0 -very good" to "100= very poor", after the question 'Considering all the ways Psoriatic Arthritis affects you, *please indicate with a vertical mark (|) through the horizontal line how well you are today'.*

8.3.1.3 Physicians global assessment of disease activity

The PhGA will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question '*Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today*'. To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that participant.

8.3.1.4 Patients assessment of PsA pain

The patient's assessment of pain will be performed using 100 mm visual analog scale (VAS) ranging from 'no pain' to 'unbearable pain' after the question '*Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today*'.

8.3.1.5 Health Assessment Questionnaire Disability Index (HAQ- DI)

The HAQ-DI© was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a participant's level of functional ability and activity restriction. The disability assessment component of the HAQ, the HAQDI©, assesses a participant's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task.

Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty (1), much difficulty (2), and unable to do (3).

The purpose of the HAQ-DI© in this study is to assess the functional ability of participants with PsA.

8.3.1.6 High Sensitivity C-reactive protein (hsCRP)

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

Since the results of this test may unblind study personnel, results from the central lab will be provided for screening and BSL only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

8.3.1.7 Erythrocyte sedimentation rate (ESR)

Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits as indicated in Table 8-1.

Local ESR test will be performed.

8.3.2 DAS28 and EULAR response

The DAS28 is a measure of disease activity based on Swollen and Tender Joint Counts, ESR or CRP and the Patient Global Assessment of Disease Activity. A DAS28 score > 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission. EULAR response criteria are based on DAS28 status in combination with DAS28 improvements. Refer Section 16.6.

The components of DAS28 are to be assessed at the visits/time points shown in Table 8-1.

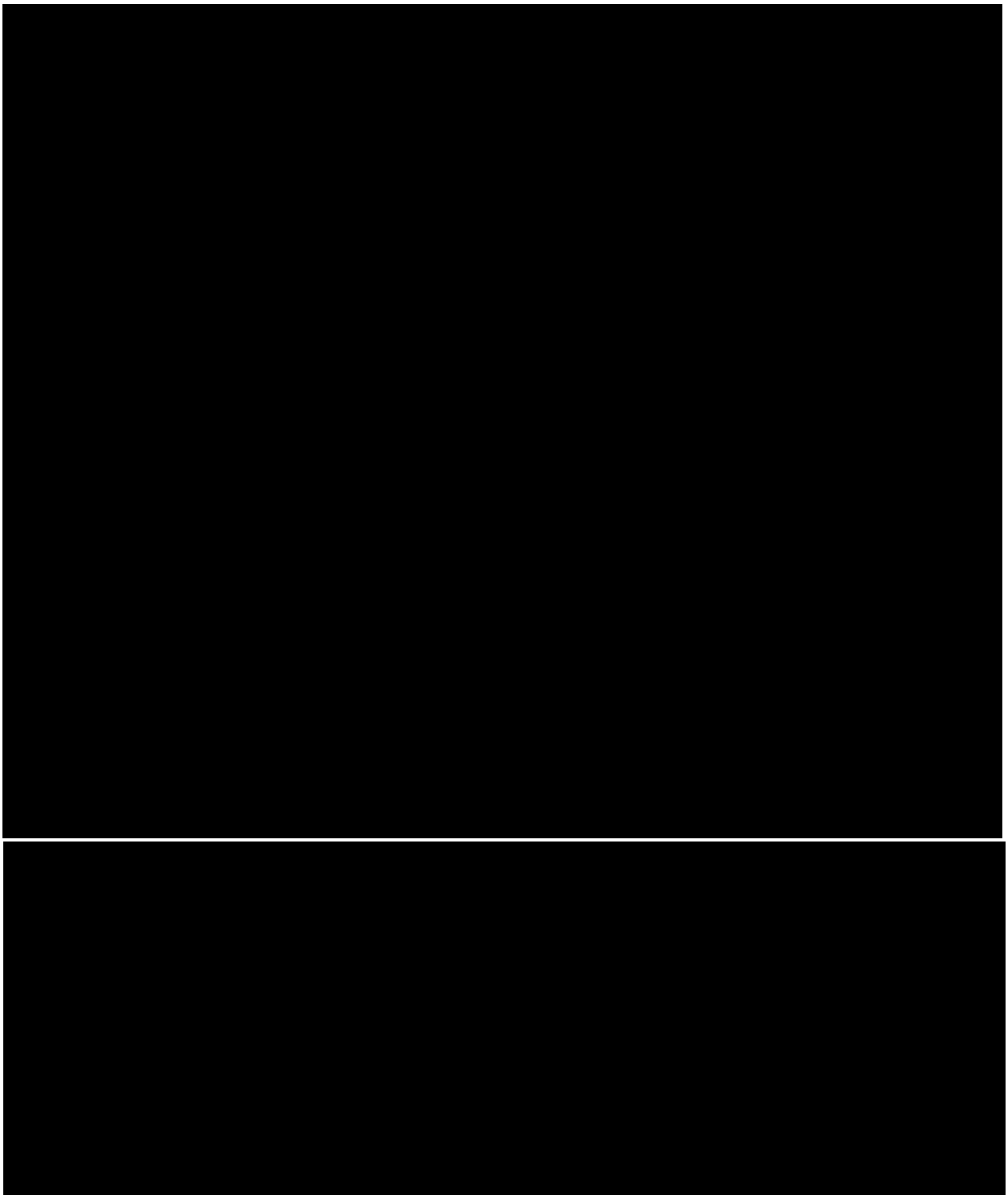
8.3.3 Psoriatic Arthritis Disease Activity Score (PASDAS)

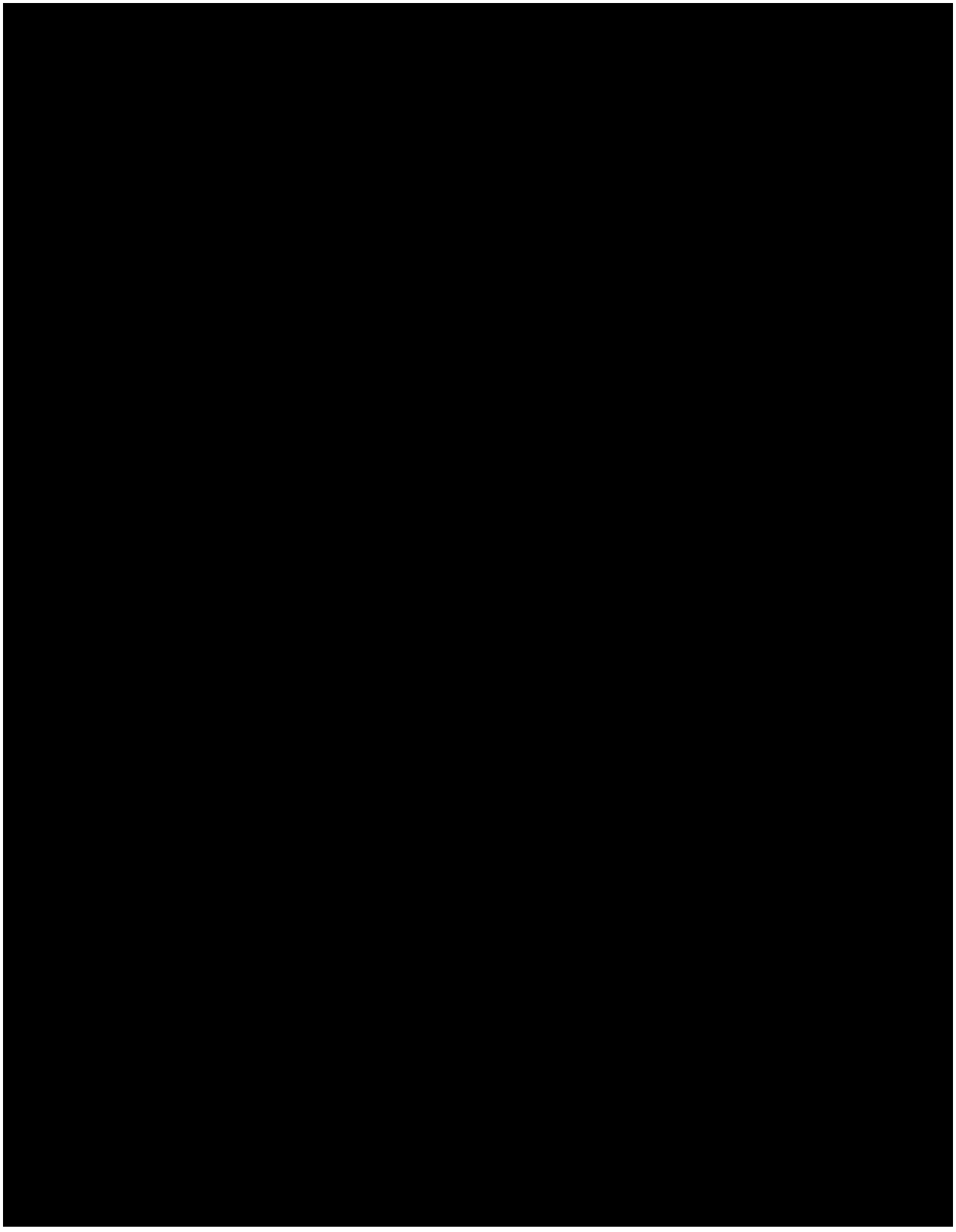
PASDAS is a new composite measure developed to access disease activity in Psoriasis (GRACE Project) Helliwell et al 2012 . It is calculated by utilizing seven measures; the seven components are: Patient reported measures [redacted] skin, peripheral joint counts (Tender and Swollen joint counts), [redacted] acute phase response (CRP) and Patient & Physician global VAS scores.

PASDAS = (0.18 x √Physician global VAS)
+ (0.159 x √Patient global VAS)
- (0.253 x √SF36-PCS)
+ (0.101 x LN (Swollen joint count + 1)
+ (0.048 x LN (Tender joint count + 1)
[redacted]
+ (0.102 x LN (CRP + 1)) +2)*1.5

8.3.3.1 VAS for PASDAS assessment

Global Disease Activity: The patient's assessment of psoriasis and arthritis will be performed using 100 mm VAS ranging from 'Excellent' to 'Poor' after the question *'Considering all the ways PSORIASIS and ARTHRITIS affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing over the past week'.*





[redacted]

[redacted]

8.3.8 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across many PsA trials and they are required for regulatory filing.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Evaluation of all AEs and SAEs including injection site reactions, electrocardiograms (ECGs), physical examination, and vital signs and laboratory assessments.

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

- Evaluation of AE/ SAE's
- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Gold test or PPD skin test
- ECG
- Local tolerability (Injection site reactions)
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab

Table 8-4 General safety assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological system.If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A physical exam will be at all visits starting from visit 2 (i.e. the screening 2 visit) until the follow-up visit at Week F60 as indicated in Table 8-1. Whenever possible, assessments for an individual participant should be performed by the same member of the study site staff throughout the study. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure and pulse measurements. Vital signs will be assessed at every scheduled visit from visit 2 (i.e. the screening 2 visit) until the follow-up visit at Week F60 as indicated in Table 8-1. Whenever possible, assessments should be performed by the same member of the study site staff using the same validated device throughout the study. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. **Three** measurements will be recorded in the source documentation and should be entered on the Vital Signs eCRF. No specific action is pre-defined within this protocol to respond to specific abnormal vital signs, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the participant.

Assessment	Specification
Height and weight	Height and body weight will be measured as indicated in Table 8-1. Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing but without shoes) will be measured. If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except for ESR, pregnancy test, Hepatitis B Virus (HBV), Hepatitis B Virus (HCV) and Human immunodeficiency virus (HIV). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. Refer to the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values.

Blood withdrawals and safety assessments should be done prior to study treatment administration and should be taken as shown in Table 8-1.

Laboratory evaluations listed below are to be measured at scheduled visit as indicated in Table 8-1.

Table 8-5 Laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, Red blood cells (RBC), Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils including Bands).
Chemistry	Albumin (Alb), Alkaline phosphatase (ALP), Alanine Aminotransferase (ALT) , Aspartate Aminotransferase (AST) , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, , Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid and Glucose.
Urinalysis	Macroscopic Panel: pH, Glucose, Protein, Blood, Bilirubin, Urobilinogen, Ketones, , Specific Gravity, White Blood Cells (WBC). A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Urine sample should be collected and sent to central lab for analysis. If the results are not in the normal ranges, the investigator will evaluate whether further testing is required or not. This testing will be done at the local lab.
Lipid panel	High-density Lipoprotein (HDL), Low-density Lipoprotein (LDL), total cholesterol and triglycerides. The lipid panel will be measured from a fasting sample.
Autoantibodies	Anti-nuclear antibodies (ANA) and anti-dsDNA will be assessed at the visits/time points indicated in Table 8-1. In addition, RF and anti-CCP must be tested negative for a participant being eligible in this study as per inclusion criteria 5.
Hepatitis markers & HIV *(locally, as applicable)*	Hepatitis and HIV testing is to be performed at the second Screening visit and the results to be known prior to randomization to determine the participant's eligibility for the trial. Hepatitis testing will include hepatitis B surface antigen (HBsAg) and anti-HCV antibodies.
Pregnancy Test (locally)	Serum / Urine pregnancy test for Women of Childbearing Potential (WoCBP). Recommended to perform urine pregnancy test at designated visits in local lab, if not feasible alternatively the serum pregnancy test should be performed.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. All participants with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

Clinically notable lab values are defined in Section 16.1.

8.4.2 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 8-1. In this study, local electrocardiogram (ECG) will be used. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable BSL. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

The original ECGs on non-heat-sensitive paper appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. Investigator should document clinical evaluation in source. For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding

Although there is no exclusion criterion based on ECG results, the BSL ECG at the Randomization Visit must be reviewed locally for major abnormalities prior to dosing.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

Secukinumab must not be given to pregnant women; therefore effective methods of birth control must be used for women of child-bearing potential for the entire study period (see exclusion criteria definitions, Section 5.2).

All pre-menopausal women who are not surgically sterile will have local urine pregnancy tests, as indicated in Table 8-1. Additional pregnancy testing might be performed if requested by local requirements. A positive urine test requires immediate interruption of study drug and needs to be confirmed with a serum β-hCG test (serum pregnancy test to be done locally). If positive, the participant must be discontinued from the study treatment.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, follicle stimulating hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening/BSL.

8.4.4 Other safety evaluations

8.4.4.1 Chest X-ray

Standard chest X-ray (PA view) will be performed except for those who have had a valid X-ray done within 3 months of screening. If participants do not have a chest X-ray obtained within 3 months preceding the Screening visit, a chest X-ray should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the participant meets all inclusion/exclusion criteria. In some sites selected by Novartis, the X-ray assessment may be replaced by MRI assessment.

8.4.4.2 QuantiFERON TB-Gold test

Either a QuantiFERON TB-Gold test **or** a PPD skin test must be performed at Screening. participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant has no evidence of active tuberculosis, or if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.

A QuantiFERON TB-Gold test is to be performed at the second screening visit and the results to be known prior to randomization to determine the participant's eligibility for the trial. The test will be used to screen the participant population for latent tuberculosis infection.

The test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

8.4.4.3 PPD skin test

A PPD skin test is to be performed at screening and read within 72 hours and before randomization to determine the participant's eligibility for the trial. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the participants must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the participant has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥5 mm (or according to local practice/guidelines) is interpreted as a positive result.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population. 12-week period following the last administration of study treatment should be reported.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Clinician Reported Outcomes (ClinRO)

The impact of study treatment on participant's disease activity will be assessed by the following measures:

- Swollen Joint Count (SJC)/Tender Joint Count (TJC) - Refer to Section 8.3.1.1 for details
- Physician's global assessment of disease activity (PhGA, VAS) – Refer to Section 8.3.1.3 for details

[redacted]

8.5.1.2 Patient reported outcomes (PRO)

Participant will be asked to complete the following PRO measures:

[redacted]

2. Medical Outcome Short Form Health Survey (SF-36 v2) version 2 (Acute form)
3. HAQ-DI©
4. Patient's Global Assessment of Disease Activity
5. Patient’s assessment of PsA Pain

The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant.

The participants should be given sufficient space and time to complete the PRO measures.

The site personnel should check PRO measures for completeness and ask the participant to complete any inadvertently missing responses. The responses stored electronically in the database will be considered the source file.

Completed questionnaires must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in section 10 of the study protocol.

HAQ-DI© , Patient’s assessment of PsA Pain and Patient's Global Assessment of Disease Activity are already described in Efficacy Section 8.3.1.5 , Section 8.3.1.4 and Section 8.3.1.2, respectively.

Trial Feedback

This trial will include an option for participants to complete an anonymized questionnaire, 'Trial Feedback Questionnaire' (TFQ) for participants to provide feedback on their experience in a Novartis clinical trial. The TFQ is a validated web-based questionnaire. The TFQ has been tested and validated by research conducted by Adelphi, PatientsLikeMe and HRM using established PRO methodology and is based on feedback from 400 adult participants across different therapeutic areas.

The optional questionnaire will be completed at the site at Week F60, end of the study period. TFQ questions relate to both protocol-specified and site-specific components, including study burden and interaction with site staff.

Feedback is anonymous. Individual participant level responses will not be reviewed by Investigators. Responses will be used by Novartis to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or adverse events and therefore the TFQ data is not trial data.

The TFQ data will be stored in the Electronic Clinical Outcome Assessment (eCOA) vendor provider database, separate from the clinical trial database.

[redacted]

8.5.1.4 Medical outcome short form health survey (SF-36), Version 2 (acute form)

The SF-36 is a widely used and extensively studied instrument to measure HRQoL among healthy participants and participants with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role- Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health Ware et al 1993. Two overall summary scores, the Physical Component Score (PCS) [redacted] also can be computed Ware et al 1994. The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual participants.

The purpose of the SF-36 in this study is to assess the Health-Related Quality of Life (HRQoL) of participants. Given the acute nature of this disease, version 2, with a one week recall period, will be used in this study.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

Participants may voluntarily discontinue from the study treatment for any reason at any time. They may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature discontinuation of study treatment occurs for any reason, the investigator must make every effort to determine the primary reason for a participant's premature discontinuation from the study treatment and record this information on the appropriate Study Phase Completion eCRF.

Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a participant.

The following circumstances **require** study treatment discontinuation:

- Participant/guardian decision
- participant's request to terminate treatment
- Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding of the treatment arm (Section 6.6.2)
- Emergence of the following AEs:
- Any severe or serious AE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable co-medication
- Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
- Life-threatening infection
- Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the participant at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Section 16.1).
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any protocol deviation that results in a significant risk to the participant's safety.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any participant whose treatment code has been broken inadvertently for any reason.

Participants who prematurely discontinued from study treatment during Treatment Period 1 had to return for assessments associated with End of TP1 visit (4 weeks after the last study treatment) and the End of study visit (12 weeks after the last study treatment). Participants who prematurely discontinued during Treatment Period 2 had to return and complete assessments associated with End of TP2 visit (4 weeks after the last study treatment) and End of study visit (12 weeks after the last study treatment), see Table 8-1

- Participants unwilling to continue attending further study visits after prematurely discontinuing the study treatment should return for the end of study (EOS) visit 12 weeks after the last administration of the study treatment.
- Participants willing to continue attending study visit should continue attending all subsequent scheduled site visits for clinical and safety study assessments, except study treatment administration.
- Participants initially continue attending site visits after premature study treatment discontinuation may decide to discontinue study at any time. For those participants, the EOS visit will be performed at time of study discontinuation. Note: the EOS visit must always be completed at least 12 weeks after the last study treatment administration.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant‘s premature discontinuation of study treatment and record this information. For participants who discontinue study treatment, a Dosage Administration Record eCRF should be completed, giving the date and primary reason for stopping study treatment.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2). **Where possible, they should return for the follow-up assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section (Section 6.6.2).

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) occurs only when a participant:

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until his/her scheduled End of Study visit would have occurred.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A participant will be considered to have completed the study if he/she received a total of 52 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Week F60.

Information on the participant's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate Study Phase Completion eCRF page.

In any case, the investigator or site staff must contact the IRT as soon as possible to record the participant's study completion (Week F60) and/or discontinuation.

The investigator must provide follow-up medical care for all participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

Continuing care should be provided by investigator and/or referring physician based on participant availability for follow-up. This care may include enrollment in a roll over study or equivalent program, as applicable, provided the participant completed end of study visit (treatment period and follow up visits) and could still deriving benefit from the study treatment based on investigator's decision.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of "not recovered/not resolved" or "recovering/resolving" must be reported based on the investigator's judgment
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- No action taken (i.e. further observation only);
- Study treatment temporarily interrupted;
- Study drug(s) permanently discontinued;
- Concomitant medication given;
- Non-drug therapy given.

6. Its outcome *(not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)*

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 12 weeks following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from BSL or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s)] which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires in participant hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency out participant basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met .

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 12 weeks following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Any SAEs experienced after the 12 week period following the last administration of study treatmen should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medial Office & Patient Safety (CMO & PS) department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator

Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per China national regulatory requirements.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported. Information will be collected at three time points after the estimated date of delivery and for a period of 12 months.

Follow up of the pregnancy (female participant) should be according to the following schedule:

Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies (including pregnancies where the participant was exposed to placebo and pregnancies due to the conduct of the study).

- EDD + 1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data.
- EDD + 2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome.
- The follow-up at EDD + 3 months is mandatory for all cases of live birth. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.
- The follow up at EDD + 12 months is mandatory for all cases of live birth. Information on the status of the baby 12 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected. If the pregnancy case is lost to follow-up (e.g., no response after 3 attempts) this information must be transferred to the Safety Desk of the Country participant Safety.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator’s awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed

The following two categories of abnormalities / AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Once a participant is exposed to study treatment, every liver event defined in Section 16.2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Section 16.2. Repeat liver chemistry tests (i.e. ALT, AST, total bilirubin (TBL), prothrombin time(PT)/international Normalized Ratio (INR), ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include

- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to participants and healthy participants exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All participants with laboratory tests containing clinically significant abnormal values (see Section 16.1) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web enabled software that conforms to 21 CFR (Code of Federal Regulation) Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trianed. Automatic validation programs check for data discrepancies in the eCRFs. The EDC system allows modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions,

concomitant and prior procedures/non-drug therapies, and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization/re-randomization codes and data about all study treatment(s) dispensed to the participant and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitoring will be performed according to relevant sections of the monitoring plan. Monitors will visit the site to check the completeness and appropriate storage of investigator site files, participant records, the accuracy of data capture / data entry, the adherence to the protocol, to the study procedures and to Good Clinical Practice. The monitor is also responsible to report any deviation from the protocol or defined procedures and to follow the progress of enrollment. Monitors are responsible to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitors during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA (Clinical Research Associate) organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent forms signed by the participant (a signed copy is given to the participant). The investigator must give the monitor access to all relevant source documents in paper or electronic format to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary endpoint analysis will be performed after all participants complete Week 16 as described in Section 12.7 and the final analysis will be conducted on all participant data at the time the study ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will generally include the number of participants (N), minimum, lower quartile, mean, standard deviation (SD), median, upper quartile, and maximum. For binary or discrete variables the absolute number of participants in each category and relative frequencies will be provided.

In case of a global health disruptive event, such as pandemic/epidemic (e.g., COVID-19), affecting the ability of the patient or the site to adhere to protocol requirements and assessments and therefore leading to a potential increase in the number of missing measurements, additional anyalysis populations may be defined as per the instructions and procedures outlined in Section 16.9.

The efficacy evaluation of secukinumab relative to placebo will generally focus on the first 16 weeks of treatment unless otherwise specified.

Data analyses will be presented by treatment group. Efficacy and safety data for the 16-week placebo-controlled period and the entire treatment period as appropriate will be presented by the following two treatment groups. participants may be included in more than one treatment group for some analyses (e.g., exposure adjusted adverse events over the entire treatment period).

These treatment groups represent the regimens to which participants will be eligible to be randomized:

- Secukinumab 150 mg regimen
- Placebo regimen

Note that the treatment groups above for a participant may differ depending on the time period of the analysis and whether one assesses the participant for efficacy or safety (see Section 12.1 for details).

Data may also be presented by a combination of the ‘original’ and ‘switch’ treatment groups. These treatment groups represent the treatment combinations the participants experience over the course of the entire trial.

12.1 Analysis sets

The following analysis sets will be used in this study:

Randomized set: The randomized set will be defined as all participants who were randomized. Unless otherwise specified, mis-randomized participants (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized participants are defined as those participants who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized participants are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all participants from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, participants will be evaluated according to the treatment assigned to at randomization. Three subsets of FAS are defined as follows:

- Psoriasis subset: The psoriasis subset will include all FAS participants who have ≥ 3% of theBSA affected by psoriatic skin involvement at BSL.

Safety set: The safety set includes all participants who took at least one dose of study treatment during the treatment period. participants will be evaluated according to treatment received.

12.2 Participant demographics and other baseline characteristics

Demographics and BSL characteristics

Summary statistics will be presented for continuous demographic and BSL characteristic variables for each treatment group and for all participants in the randomized set. The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants.

The following demographic variables and BSL disease characteristics will be summarized by treatment groups:

- Gender, age, race, ethnicity, weight, height, and Body Mass Index (BMI)
- Anti-TNF treatment history (naïve or inadequate responder), ACR components and other disease-related measures (e.g., DAS28, presense of dactylitis, presense of enthesitis, time since first diagnosis of PsA, participant with psoriasis ≥ 3%), etc., number of prior biologic PsA therapies, dose of MTX or other DMARD at randomization.

Medical history

A history of PsA with focus on previous extra-articular involvement and past therapies for PsA will be obtained and summarized by treatment group. Any other significant prior or active medical condition at the time of signing informed consent will be recorded and coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

To establish a BSL level of cardiovascular risk, the number and percentage of participants with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each participant has will also be summarized by treatment group. If it is unknown whether or not a participant currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that participant.

12.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of visits with active and placebo injections received will be presented by treatment group.

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of participants with cumulative exposure levels (e.g., any exposure, ≥ 1 weeks, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-BSL and continued into the period where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of participants receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

Prior surgeries and procedures are defined as surgeries and procedures done prior to first dose of study treatment. Any surgeries and procedures done between the day of first dose of study treatment and within the date of the last study visit will be a concomitant surgeries and procedures, including those which were started pre-BSL and continued into the period where study treatment is administered.

The number and percentage of participants receiving prior and concomitant PsA therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to PsA therapies previously. NSAID, glucocorticoid and DMARD (MTX, Leflunomide, Sulfasalazine) use will be summarized.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary objective of this study is to assess the efficacy of secukinumab relative to placebo at week 16 based on the proportion of participants achieving an ACR20 response. The consistency of the treatment difference between this bridging study and the global study will be evaluated.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary efficacy variable will be ACR20 response at Week 16. The analysis of the primary efficacy variable will be based on the FAS . Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis of ACR20 at Week 16 in the FAS will be evaluated using a logistic regression with treatment as a factor and weight as a covariate. Difference in response proportions between secukinumab regimen and placebo regimen and the corresponding 95% confidence interval (CI) will be computed utilizing the logistic regression model fitted.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for ACR20 response and other binary efficacy variables (e.g., ACR50, etc.) for data up to Week 16 will be handled as follows:

1. participants who discontinue from treatment or study for any reason will be considered as non-responders from the time of discontinuation through Week 16
2. participants who do not have the required data to compute ACR responses (i.e., tender and swollen joint counts and at least three of the five ACR core set variables) at BSL and at the specific timepoint will be classified as non-responders at the specific timepoint.

participants who are unblinded prior to the scheduled time point will be considered non-responders from the time of unblinding up to Week 16. The primary analysis will use the non-responder imputation.

Continuous variables (e.g., ACR components, etc.) will be analyzed using a mixed-effects model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption. As such, single-point imputation of missing data will not be performed (e.g., LOCF). For analyses of these parameters, if all post-BSL values are missing then these missing values will not be imputed and this participant will be removed from the analysis of the corresponding variable, i.e., it might be that the number of participants providing data to an analysis is smaller than the number of participants in the FAS.

12.4.4 Sensitivity analyses for primary endpoint/estimand

Sensitivity analysis will be conducted in order to provide evidence that the results seen from the primary analysis are robust. These analyses will center on the deviations in model assumptions and the handlingof missing data.

In order to determine the robustness of the logistic regression model used for the primary analysis, ACR20 response in active PsA participants at Week 16 will also be evaluated using a non-parametric regression (Koch et al (1998) model with the same independent variables as the logistic regression model. [redacted]

The impact of missing data on the analysis results of ACR20 in active PsA participants will be assessed as well by repeating the logistic regression model using different ways to handle missing data. This may include, but are not limited to:

- Multiple imputation
- Observed data analysis

12.4.5 Supplementary analysis

Supplementary analysis will be conducted in order to fully investigate and understand the treatment effects as well as demonstrate the consistency between the bridging study and the global study.

The analyses may include, but are not limited to:

- Meta-analysis: it combines the estimates of the treatment effect from the historical studies and delivers an overall treatment effect as well as the corresponding confidence interval. The consistency can be claimed if the treatment effect estimated from the bridging study is located within the confidence interval.
- Bayesian Meta-Analytic-Predictive (MAP) approach: it is similar as the meta-analysis, but priors should be specified carefully.
- Logistic regression: same logistic regression model will be used as the primary analysis.The odds ratio bewteen the secukinumab regime and the placebo regimen and the corresponding 95% confidence interval will be presented.

Subgroup analysis of the primary endpoint will be conducted by selected subgroup groups. The subgroups to be considered will be defined in the SAP.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy variables are described below. Secondary efficacy variables will be analyzed using the FAS population. Handling of missing data for secondary variables will be the same as for the primary variable.

ACR50 at Week 16

Response at Week 16 to ACR50 in the FAS will be evaluated using a logistic regression model with treatment group as a factor and weight as a covariate.

DAS28-CRP at Week 16

Between-treatment differences in the change from BSL in DAS28-CRP will be evaluated using MMRM with treatment group and analysis visit as factors and BSL DAS28-CRP score and weight as continuous covariates. Treatment by analysis visit and BSL DAS28-CRP score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

PASDAS at Week 16

Between-treatment differences in the change from BSL in PASDAS will be evaluated using MMRM with treatment group and analysis visit as factors and BSL PASDAS score and weight as continuous covariates. Treatment by analysis visit and BSL PASDAS score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

SF-36 PCS at Week 16

See Section 12.5.7 PROs.

Physical function (HAQ-DI©) at Week 16

Between-treatment differences in the change from BSL in HAQ-DI© will be evaluated using MMRM with treatment group and analysis visit as factors and BSL HAQ-DI© score and weight as continuous covariates. Treatment by analysis visit and BSL HAQ-DI© score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

12.5.2 Safety endpoints

Adverse events

Treatment-emergent adverse events (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of participants having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

These summaries may be presented separately by study periods.

As appropriate, the incidence of AEs will be presented per 100 patient years of exposure (exposure-adjusted incidence rates).

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

When adjudication is required of major cardiovascular events, a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from BSL to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from BSL will only be summarized for participants with both BSL and post BSL.

For each parameter, the maximum change from BSL within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a participant's BSL laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the BSL value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-BSL.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from BSL for each post-BSL visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from BSL will only be summarized for participants with both BSL and post-BSL values.

ECG

Summary statistics will be presented for ECG variables by visit and treatment group. Qualitative changes will be summarized.

12.5.3 Patient reported outcomes

SF-36

The following variables will be evaluated:

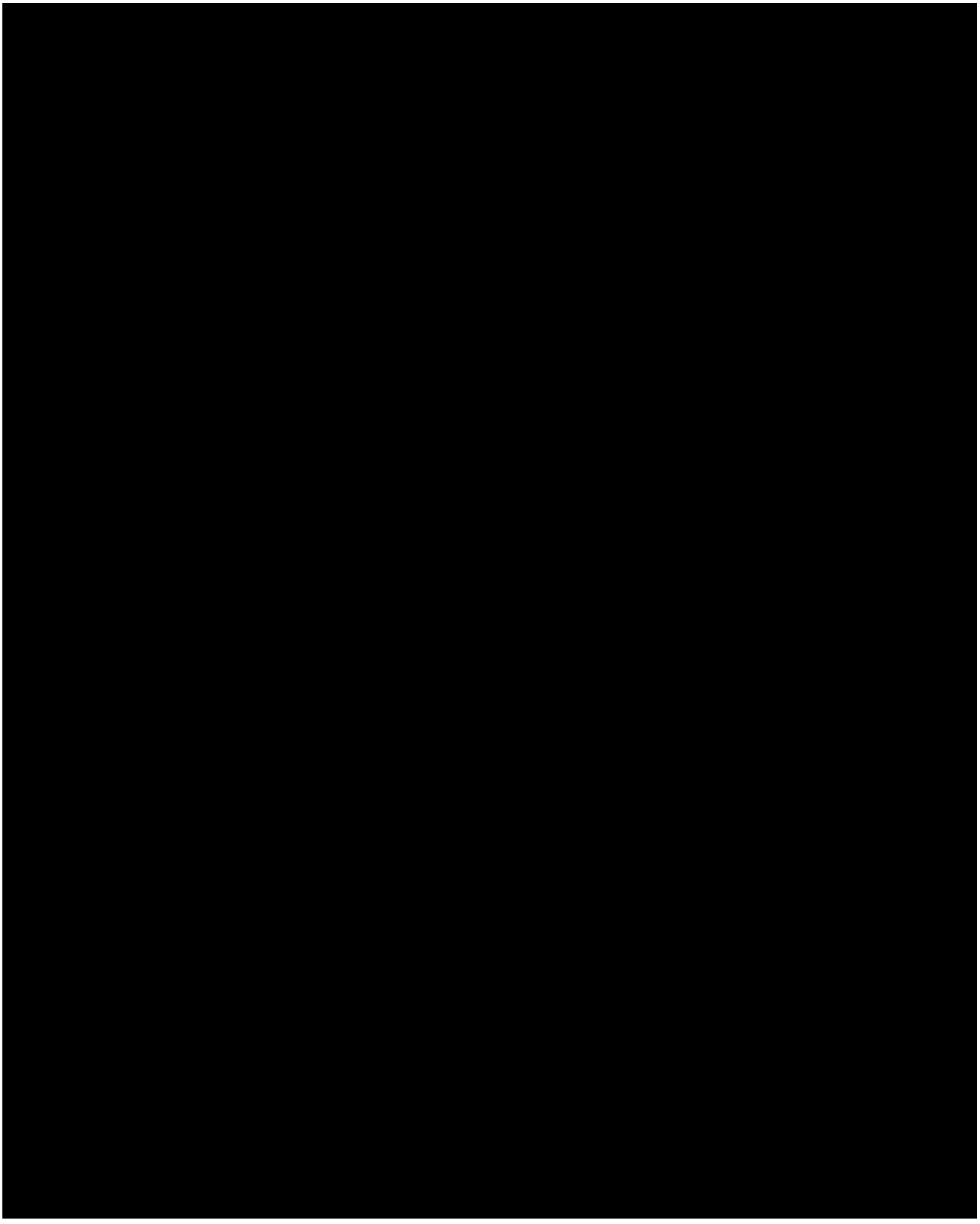
- SF-36 domain scores (based on a scale of 0-100)
- SF-36 PCS [redacted] (norm-based scores)
- [redacted]

For the change in SF-36 summary scores (PCS [redacted]), summary statistics will be provided using observed data for each treatment regimen.

[redacted]

The SF-36 domain scores will be summarized by treatment.

[redacted]



12.7 Interim analyses

Interim analysis is not applicable in this study.

The primary endpoint analysis will be performed after all participants have completed the Week 16 visit or discontinued earlier. The primary endpoint analysis will be used for regulatory submission.The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment that each participant received at randomization until after the database lock for Week F60 analysis.

Subsequent to the primary endpoint analysis, the final analysis is planned after participants have completed the Week F60 assessments and may be used for regulatory submission and/or publication purposes. Additional analyses may be performed to support interactions with health authorities, as necessary.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

As it is a bridging study for China registration, this study will pursue an estimation strategy rather than formal hypothesis testing of treatment difference.

Analysis of the pooled data of global pivotal studies (CAIN457F2312, CAIN457F2318, CAIN457F2336 and CAIN457F2342) showed an active drug response rate of about 51.4% and a placebo response rate of 23.1% after 16 weeks for ACR20. With 40 participants (1:1 ratio to two arms), there are approximately 86.0% probability to show at least 50% global treatment difference (14.15%) and approximately 96.0% probability to show positive treatment difference.

Table 12-1 shows the probability of success with different observed response rates.

Table 12-1 Probability of Success with Different Observed Response Rates

	Observed Response Rate				Criterion 1		Criterion 2	
	Secukinumab (p_1)	Placebo (p_2)	p_1-p_2	95% CI of (p_1-p_2)	Aimed Treatment Difference	PoS	Aimed Treatment Difference	PoS
Scenario 1	0.464	0.231	0.233	(-0.053, 0.519)	> 0.1415	0.772	> 0	0.922
Scenario 2	0.514	0.231	0.283	(-0.003, 0.569)	> 0.1415	0.860	> 0	0.960
Scenario 3	0.564	0.231	0.333	(0.048, 0.618)	> 0.1415	0.922	> 0	0.981
Scenario 4	0.614	0.231	0.383	(0.101, 0.665)	> 0.1415	0.961	> 0	0.992

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required by local regulation. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov).

For details on the Novartis publication policy including authorship criteria, please refer to the publication policy training materials that will be provided to you at the investigator portal.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local Good Clinical Practice (GCP) regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to

Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authority are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

Table 16-1 Clinically notable laboratory values and vital signs

Laboratory variable	Standard units	SI units
Liver function and related variables		
Serum Glutamic Oxaloacetic Transaminase (SGOT) (AST)	≥ 3 × upper limit of normal (ULN)	≥ 3 × ULN
Serum Glutamic Pyruvic Transaminase (SGPT) (ALT)	≥ 3 × ULN	≥ 3 × ULN
Bilirubin	≥ 2 × ULN	≥ 2 × ULN
Alkaline phosphatase	≥ 2 × ULN	≥ 2 × ULN
GGT	≥ 2 × ULN	≥ 2 × ULN
Renal function, metabolic and electrolyte variables		
Urea	≥ 5 × ULN	≥ 5 × ULN
Creatinine	≥ 3 mg/dL	≥ 265 µmol/L
Uric acid	M ≥ 12 mg/dL	M ≥ 714 µmol/L
	F ≥ 9 mg/dL	F ≥535 µmol/L
Glucose	< 45 mg/dL	< 2.5 mmol/L
	> 250 mg/dL	> 13.9 mmol/L
Cholesterol	≥ 350 mg/dL	≥ 9.1 mmol/L
Triglycerides	≥ 750 mg/dL	≥ 8.5 mmol/L
CK (MB)	None	None
Potassium	< or = 3.0 mEq/L	< or = 3 mmol/L
	< or = 6.0 mEq/L	> or = 6 mmol/L
Calcium	< or = 6 mg/dL	< or = 1.5 mmol/L
	> or = 13 mg/dL	> or = 3.2 mmol/L
Magnesium	< 1.0 mg/dL	< 0.4 mmol/L
	> 3.6 mg/dL	> 1.5 mmol/L
Amylase	≥ 2 x ULN	≥ 2 x ULN
Lipase	≥ 2 x ULN	≥ 2 x ULN
Hematology variables		
Hemoglobin	< 7 g/dL	< 4.39 mmol/L
Platelets (thrombocytes)	< 50 k/mm^3	< 50 × 10^9/L
	≥ 700 k/mm^3	≥ 700 × 10^9/L
Leukocytes (WBCs)	≤ 2.0 k/mm^3	≤ 2.0 × 10^9/L
	≥ 16 k/mm^3	≥ 16 × 10^9/L

Laboratory variable	**Standard units**	**SI units**
Liver function and related variables		
Hematology variables: Differential		
Granulocytes (poly, neutrophils)	≤ 1,000/mm^3	≤ 1 x 10^9/L
Eosinophils	≥ 12%	≥ 12%
Lymphocytes	≤ 1,000/mm^3	≤ 1 × 10^9/L
Vital sign variables	**Notable criteria**	
Systolic Blood Pressure (BP) (mm/Hg)	Either an increase of ≥ 30 that results in ≥ 180 or > 200 (mm/Hg) OR a decrease of ≥30 that results in ≤ 90 or < 75 (mm/Hg)	
Diastolic BP (mm/Hg)	Either an increase of ≥ 20 that results in ≥ 105 or > 115(mm/Hg) OR a decrease of ≥20 that results in ≤ 50 or < 40 (mm/Hg)	

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

LIVER LABORATORY TRIGGERS LIVER EVENTS	**Definition/ threshold** · 3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN · ALT or AST > 5 × ULN · ALP > 2 × ULN (in the absence of known bone pathology) · TBL > 2 × ULN (in the absence of known Gilbert syndrome) · ALT or AST > 3 × ULN and INR > 1.5 · Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) · Any clinical event of jaundice (or equivalent term) · ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia · Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 16-3 Follow up requirements for liver events and laboratory triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	· Discontinue the study treatment immediately Hospitalize, if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST > 8 × ULN	· Discontinue the study treatment immediately · Hospitalize if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	**Actions required**	**Follow-up monitoring**
> 3 × ULN and INR > 1.5	· Discontinue the study · treatment immediately · Hospitalize, if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	· Repeat LFT within 48 hours · If elevation persists, continue follow-up monitoring · If elevation persists for more than 2 weeks, discontinue the study drug · Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	· Discontinue the study treatment immediately · Hospitalize if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (participant is asymptomatic)	· Repeat LFT within the next week · If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated) > 2 × ULN (in the absence of known bone pathology)	· Repeat LFT within 48 hours · If elevation persists, establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated) > 2 × ULN (in the absence of known Gilbert syndrome)	· Repeat LFT within 48 hours · If elevation persists, discontinue the study drug immediately · Hospitalize if clinically appropriate	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	· Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (participant is asymptomatic)	· Repeat LFT within the next week · If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	· Discontinue the study treatment immediately · Hospitalize the participant · Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	· Consider study treatment interruption or discontinuation · Hospitalization if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal. [a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to BSL values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.*Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.*

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions and Event Follow -up

Serum Event	
Serum creatinine increase 25 – 49% compared to BSL	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to BSL	Follow up within 24-48h if possible Consider study treatment interruption Consider participant hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥3+ OR Protein-creatinine ratio > or =150 mg/g or > or =15 mg/mmol	Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New dipstick hematuria ≥3+ on urine dipstick	Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder
For all renal events: Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor participant regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of BSL or protein-creatinine ratio within 50% of BSL, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

16.4 Appendix 4: The classification criteria for psoriatic arthritis (CASPAR)

To meet the Classification of Psoriatic Arthritis (CASPAR) criteria for diagnosis of psoriatic arthritis according to Taylor et al (2006), a participant must have inflammatory articular disease (joint, spine or entheseal) and at least 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis

- Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.* (**2 points)**

- A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. (**1 points)**
- A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report. (**1 points**)

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (**1 point**)

3. A negative test result for the presence of rheumatoid factor by any method except latex (**1 point**)

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**)

5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (**1 point**)

Total score:

(The CASPAR criteria eCRF will autopopulate the total number of points of the CASPAR criteria met by the participant. If the total score ≥ 3, the participant meets CASPAR criteria for PsA diagnosis.)

* Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

16.5 Appendix 5: American College of Rheumatology (ACR) Measures and Criteria of Response

Number of tender joints

Seventy-eight joints (78) are scored as either tender or not tender: 8 distal interphalangeal, 10 proximal interphalangeal, 10 metacarpophalangeal and 2 first carpometacarpal joints of the hands, 8 distal interphalangeal, the 10 metatarsophalangeal and 10 proximal interphalangeal joints of the feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints.

Joint tenderness is to be scored present (1) or absent (0).

Number of swollen joints

Joints are to be scored as either swollen (1) or not swollen (0). The 76 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Patient's assessment of PsA pain

On a 100 mm non-anchored visual analog scale, from no pain to unbearable pain.

Patient's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity, after the question "Considering all the ways your arthritis affects you, draw a line on the scale for how well you are doing".

Physician's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity.

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©

ACR20/50[redacted]

A patient will be considered as improved according the ACR20 criteria* if she/he has at least 20% improvement in

- the two following measures:
  - Tender joint count
  - Swollen joint count
- and at least 3 of the following 5 measures:

a) Patient's assessment of pain

b) Patient's global assessment of disease activity

c) Physician's global assessment of disease activity

d) Health Assessment Questionnaire (HAQ©) score

e) C-reactive protein (CRP)/ESR.

ACR50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

[redacted]

Reference: (Felson et al 1995)

16.6 Appendix 6 Disease Activity Score (DAS)

The DAS in the clinical trials

Comparing the DAS28 from one patient on two different time-points, it is possible to define improvement or response. The EULAR response criteria are defined as follows:

Table 16-5 EULAR response criteria

Present DAS28	DAS28 improvement		
	>1.2 0.6 - 1.2 <0.6	>1.2 0.6 - 1.2 <0.6	>1.2 0.6 - 1.2 <0.6
<3.2	Good response	Moderate response	no response
3.2 - 5.1	Moderate response	Moderate response	no response
>5.1	Moderate response	no response	no response

Both the thresholds for high and low disease activity and remission and the abovementioned improvement criteria should give you a feel how to interpret your DAS28 scores. In order to calculate the DAS28, information about the following disease variables is needed:

· The number of swollen joints and tender joints should be assessed using 28-joint count (TJC28 and SJC28).

· The ESR should be measured in mm/hour.

· The patient's general health (GH) or global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm (both are useable for this purpose) must be obtained.

Using this data, the DAS28 can be calculated using the following formula:

DAS28-ESR = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.70 * ln(ESR) + 0.014 * GH

The DAS28 provides you with a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis (RA) of your patient. A DAS28 above 5.1 means high disease activity whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (comparable to the PsA remission criteria).

Disease Activity Scores using C-reactive protein

C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28, using the formulas below. CRP is a more direct measure of inflammation than ESR, and it is more sensitive to short-term changes Kushner et all 1991. CRP production is associated with radiological progression in RA Van et al 1993, and is considered at least as valid as ESR to measure RA disease activity Mallya et al(1982)Wolfe et all (1997). Another advantage of determination of CRP is that waiting time for the laboratory result is shorter and that in case of multicenter studies a central laboratory can be used.

The following formulas to calculate the DAS28 using CRP (mg/L) give good estimations of the original DAS28 values on a group level:

DAS28-CRP = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

TJC28: 28 Tender joint count; SJC28: 28 Swollen joint count; CRP: C-reactive protein; GH:General Health on a 100mm. Visual Analogue Scale.

It is strongly advised to adhere either to ESR or to CRP determinations.

[redacted]

16.8 Appendix 8: Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a participant's response might highlight issues of potential concern.

At BSL, BSA involvement with psoriasis should be determined before completing PRO questionnaire(s) to ensure that [redacted] is completed only for participants who have BSA≥3%.

Before completion

1. participants should be provided with the correct questionnaire at the appropriate visits and in the appropriate language

2. participants should have adequate space and time to complete the forms

3. participants should be provided with a firm writing surface (such as a table or a clip board)

4. Questionnaire should be administered before the clinical examination

During completion

1. Administrator may clarify the questions but should not influence the response

2. Only one response for each question

3. Also see "Addressing Problems and Concerns"

After completion

1. Check for completeness and not for content*

2. Data should be sent from the eCRF / electronic device

*However, any response which may directly impact or reflect the participant's medical condition (e.g. noting of depression) should be communicated by the study coordinator to the investigator).

Addressing Problems and Concerns

Occasionally a participant may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

The participant does not want to complete the questionnaire(s)

Tell the participant that the goal is to better understand the physical, mental and social health problems of participants. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the participant still declines, record the reason for the decline and thank the participant.

The participant is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain participant responses by reading out loud each question, followed by the corresponding response categories, and entering the participant's response. No help should be provided to the participant by any person other than the designated study coordinator. The coordinator should not influence participant responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

The participant wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the participant provide responses to the questions. Unless specified in the study protocol, proxy data are *not* an acceptable substitute for participant self-report. participants should be discouraged from asking a family member or friend for help in completing a questionnaire.

The participant does not want to finish completing the questionnaire(s)

If non-completion is a result of the participant having trouble understanding particular items, ask the participant to explain the difficulty. Re-read the question for them *verbatim* but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the participant.

The participant is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the participant that his/her answers will be pooled with other participants' answers and that they will be analyzed as a group rather than as individuals. Tell the participant that completed forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the investigator. Any response which may directly impact on or reflect their medical condition (*e.g.* noting of severe depression) will be communicated by the coordinator to the physician.

The participant asks the meaning of a question/item

While completing the questionnaire, some participants might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the participant by rereading the question for them *verbatim.* If the participant asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. participants should answer the questions based on what *they* think the questions mean.

A General Information about all questionnaire(s):

All questionnaires have to be completed by the participants in their local languages using an electronic device. The questionnaires should be completed by the participants in a quiet area free from disturbance, and before any visit assessments. participants should receive no help from family members; if questions cannot be answered alone (due to problems with reading or

understanding), then the doctor or nurse should read the questions and record the participant's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a participant has missed a question or given more than one response per question, then this should be brought to participant. Incomplete questions should not be accepted without first encouraging the participant to complete unanswered questions.

The investigator must complete the participant/visit information on the electronic device and ensure that the center number, participant's number and initials are identical to the CRF. As there are no source data for this questionnaire, the data queries will be restricted to participant/visit information.

16.9 Appendix 9: Study management during potential future pandemic/epidemic (e.g. COVID-19)

Scope

The instructions and procedures outlined in this appendix are applicable only in case of global health disruptive event, such as pandemic/epidemic [e.g. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease/COVID-19]. In order to maintain the study data integrity and ensure the safety of participants, investigators should inform and discuss with the sponsor's monitor about its applicability prior to implementing any of the following procedures,

Screening (Screening to Randomization)

In case of a global health disruptive event, such as pandemic/epidemic (e.g. COVID-19), affecting the ability of the patient or the site to adhere to protocol requirements and assessments, investigators should only randomize patients if they expect them to be able to adhere to assessments and protocol-related activities. Evaluation of the eligibility of the subject should consider the ability to attend study visits and adhere to protocol assessments. If the latter is not anticipated, screening and randomization should not proceed, and re-screening (as allowable per protocol) should be considered when conditions allow for proper trial management.

During Treatment Period (BSL to EOT)

In case of a global health disruptive event, such as pandemic/epidemic (e.g. COVID-19), affecting the ability of the patient or the site to adhere to protocol requirements and assessments and therefore leading to a potential increase in the number of missing measurements, the Sponsor may consider recruiting additional patients to restore the sample size only after consultation with local regulatory authority.Risks and Benefits

Active infection should be excluded in order to comply with eligibility criteria (Section 5.2).

The potential of secukinumab to increase the risk of infections has been identified (see IB Section 7.1). COVID-19 has similar impact on risk-benefit as other infections. No additional risks is anticipated due to COVID-19 infection.

Visits

If the COVID-19 pandemic or similar situations that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented only for the visits outlined in the Table 8-1 . Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. Any safety or efficacy assessments which could not be feasible to perform or evaluate conduct remotely or virtually, the protocol deviation need to be recorded. Such data will treated as missing data.

This **will not** apply to Screening, BSL, Week 16, Week 52 and Week 60 visit. For remaining visits per protocol, the above exceptions may be implemented, however, every effort need to be made to ensure on-site visit. If on-site visit is prevented at Screening or BSL visit, the participants should not be randomized.

Laboratory assessments

If the designated central laboratory is unable to operate, collection of samples may be modified by Novartis and if modified, will be communicated to the investigator. In such cases, it is acceptable to collect and perform laboratory tests at local laboratories that are certified for these diagnostics. Similarly, sites should inform to the Sponsor of proposed changes to sample management/collection.

IMP (administration and dispensation)

In case of a major health care event (e.g., COVID-19 pandemic, epidemic) that limits or prevents on-site study visits, delivery of IMP directly to a participant's home is generally permitted (if allowed by local regulations) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. For changes in the distribution of trial drugs, the primary goal is to provide IMP to participants based on protocol to ensure participant safety and the integrity of clinical trials. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

IMP home administration is allowed only for the scheduled dosing visits (outlined in table 8-1) if the participant or caregiver is trained on subcutaneous self-administration.

Changes in transportation and storage arrangements will not violate the blind design of treatment. The investigator should make relevant records such as the inventory and storage conditions of trial drugs.

Efficacy and Clinical Outcome Assessments (COAs)

In the event of a pandemic/epidemic that limits or prevents on-site study visits, selected efficacy assessments including PROs can alternatively be done via web-based backup portal or visits of site staff to the subject´s home, depending on local regulations and capabilities, and following any applicable training in the required process.

Exceptionally, if the electronic device is not working, the efficacy assessments and PROs may be completed using web backup portal for PROs. The data would then be transcribed in the vendor database.

For individual cases where the efficacy endpoint is not collected, the reasons for not obtaining the efficacy evaluation should be documented.

Safety

During the COVID-19 pandemic that limits or prevents on-site study visits, regular phone or virtual calls will occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

Female participants would be advised to perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment.

Informed Consent Procedures

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.). Remote informed consent should be appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial sites.

Site monitoring

In the event of a major health care disruption (e.g. pandemic, epidemic), requiring social distancing or limited travel/attendance to the clinical trial site, remote site initiation and monitoring could be considered.

Note: The details on operationalizing above-mentioned study management aspects during potential future pandemic/epidemic will be supplemented by dedicated instructions / manual to the clinical trial sites.