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Novartis Research and Development

Clinical Trial Protocol Title:

A randomized, parallel-group, 24 week, double-blind, placebo-controlled, multicenter Phase 3 study to assess the efficacy and safety of secukinumab compared to placebo in adult patients with active rotator cuff tendinopathy

Clinical Trial Protocol Number: CAIN457O12301

Version Number: v01 (Clean, Amended Protocol)

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Brief Title: Study of efficacy and safety of secukinumab in participants with moderate-severe rotator cuff tendinopathy

Study Phase: III

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): NCT05722522 (NCT Number);

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Amendment 1 (17-Feb-2023)

Amendment rationale

The key reasons for this amendment are editorial changes.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 1.1: the word 'active' has been added in the protocol title in order to be aligned with the protocol title of the cover page.
- Table 1-2: although WORC PSD, [redacted] will be taken [redacted] visit, the "X" for these assessments in the Run-in column of Table 1-2 "Assessment Schedule" do not apply as these assessments are accounted for by the "X" under the baseline visit and therefore have been removed.
- Table 1-2: vital signs had been introduced in error at Week 1 and Week 3 in the Table 1-2 "Assessment Schedule" and consequently have been removed.
- Table 1-2: as the test will be performed by central labs and skin test is no longer an option, footnote 6 and "S" removed from Tuberculosis test, and "X" entered at Screening to indicate the test result will be received electronically from the central labs instead of documented in the source documents.
- Table 6-2: the footnote #1 "topical NSAIDs at stable dose (e.g., bid) as well as low- to mid-potency topical and inhaled corticosteroids are permitted" in Table 6-2 has been revised as "low- to mid-potency topical and inhaled corticosteroids are permitted" since topical NSAIDs are prohibited as described in Table 6-2 "Prohibited medication". As a result, the reference to this footnote has been removed from "Unstable dose (greater than stable dose taken during run-in period) of NSAIDs (including selective cyclooxygenase-2 (COX-2) inhibitors) or use of NSAID injection (such as ketorolac)" in Table 6-2 "Prohibited medication".
- Table 8-1: Documentation changed from "Source only" to "Database" for Tuberculosis test, as skin test is not an option for testing. Test to be performed by central labs.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

A randomized, parallel-group, 24 week, double-blind, placebo-controlled, multicenter Phase 3 study to assess the efficacy and safety of secukinumab compared to placebo in adult participants with active rotator cuff tendinopathy.

Brief Title:

Study of efficacy and safety of secukinumab in participants with moderate-severe rotator cuff tendinopathy.

Purpose

The purpose of the present study is to assess the efficacy of secukinumab 300 mg s.c. (subcutaneous) compared to placebo, each in combination with standard of care, in improving signs, symptoms and physical function in participants with moderate to severe rotator cuff tendinopathy (RCT), using a randomized, double-blind, placebo controlled, parallel group design to minimize bias.

Study Indication /Medical Condition:

Moderate to severe rotator cuff tendinopathy

Treatment type

Biologic

Study type

Interventional

Objectives and Endpoints:

Table 1-1 Primary and secondary objectives and related endpoints

Objectives	Endpoints
Primary	
Demonstrate that the efficacy of secukinumab 300 mg s.c., is superior to placebo, in improving physical shoulder symptoms in participants with moderate to severe RCT at Week 16	Change from Baseline (BSL) in the Western Ontario Rotator Cuff Index (WORC) Physical Symptom Domain (PSD) score at Week 16
Secondary	
● Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in achieving a clinically meaningful response in improving physical shoulder symptoms in participants with moderate to severe RCT at Week 16	● Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in WORC PSD at Week 16

Objectives	Endpoints
● Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in improving symptoms caused by RCT and the associated impact on day-to-day functioning in participants with moderate to severe RCT at Week 16	● Proportion of participants who achieve an improvement (increase) of at least 50 points from BSL in the WORC total score at Week 16
● Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in improving physical function in participants with moderate to severe RCT at Week 16	● Change from BSL in Patient-Reported Outcomes Measurement Information System (PROMIS) - Short Form (SF) Upper Extremity score at Week 16
● Evaluate the ability of secukinumab 300 mg s.c. compared to placebo, to improve physical symptoms at Week 24	● Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in WORC PSD at Week 24
	● Change from BSL in WORC PSD at Week 24
● Evaluate the pharmacokinetics (PK) of secukinumab 300 mg s.c., in the population of participants with moderate to severe RCT	● Secukinumab serum concentrations on Day 1 and Weeks 4 and 16
● Evaluate safety, immunogenicity and tolerability of 300 mg s.c. secukinumab, in participants with moderate to severe RCT	● Safety and tolerability demonstrated by assessing: AEs and SAEs (incidence, severity, and relationship with study drug) Incidence of clinically significant changes in laboratory parameters and vital signs Incidence of binding and neutralizing anti-drug antibodies (ADAs) at Day 1 and Week 16

Trial Design:

The trial is designed as a randomized, double-blind, placebo-controlled Phase III study over 24 weeks in approximately 234 participants with moderate to severe RCT, refractory to standard of care (SoC) (NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) course as per local standard practice (if not intolerant or contraindicated) and a course of physiotherapy over a period of 8 weeks). Secukinumab 300 mg s.c. will be compared to placebo.

234 participants will be enrolled in a 1:1 ratio (117 per group) who have a diagnosis of unilateral, moderate to severe symptomatic RCT with no/partial tear, who have inadequate response to SoC, and who have been experiencing active disease from at least 6 weeks to 6 months at BSL.

The study will be double-blinded up to the Primary Endpoint readout at Week 16 including all data collected up to the last patient assessment at Week 24, after which Novartis clinical trial and submission teams will be unblinded.

Brief Summary:

The purpose of this study is to measure the efficacy and safety of AIN457 [secukinumab] compared to placebo in participants with moderate to severe RCT, who are refractory to standard therapies. The primary outcome is to measure the improvement in physical shoulder symptoms based on WORC Physical Symptoms domain.

- The study duration will be up to 32 weeks, consisting of a 8-week screening period (inclusive of 2-week run-in period), 16-week treatment period and 8-week safety follow-up period.

- The treatment period will consist of an initial loading regimen where the participant has weekly doses for the first 4 weeks, followed by dosing once every 4 weeks, with final dose at Week 12.

The visit frequency will be weekly until Week 4 and then once every 4 weeks thereafter until Week 24. This may vary until Week 4, as home administration is an option at Week 1 and 3 to allow participants to not attend on–site

Treatment of interest

The randomized treatment, which consists of either the investigational treatment AIN457/secukinumab or the control treatment/placebo.

Number of Participants:

Approximately 234 participants will be randomized.

Key Inclusion criteria

1.Unilateral rotator cuff tendinopathy with ≥ 6 weeks to ≤ 6 months symptom duration at BSL.

2.Nocturnal pain in shoulder on at least 3 out of 7 nights in the week prior to Baseline or "positive painful arc test" on examination.

3.Total WORC percentage score ≤ 40 at the Screening and Baseline visits.

4.Average weekly (i.e., the average of the 7 scores taken once a day) numerical rating scale (NRS) pain score of ≥5 during the past 7 days prior to the Baseline visit.

5.Refractory to standard of care: NSAIDs course as per local standard practice (if not intolerant or contraindicated) and a course of physiotherapy over a period of 8 weeks.

6.Participant must agree to remain on stable NSAID dosage regimen (if not intolerant or having contraindications; NSAID dose is permitted to be reduced, but not increased above dose established at run-in) and physiotherapy regimen from run-in period until EOS (see Section 4.1 for details).

7.Presence of tendinopathy in the affected shoulder on a centrally read MRI (Magnetic Resonance Imaging), with the following conditions: with no tear or partial tear (maximum 50% tendon thickness; AP length maximum 10 mm) (see Section 8.2.2).

Key Exclusion criteria

1. Rheumatological and non-rheumatological inflammatory diseases, including but not limited to polymyalgia rheumatica (PMR), psoriatic arthritis (PsA), axial spondyloarthritis (AS: Ankylosing Spondylitis, nr-axSpA: non-radiographic Axial Spondyloarthritis), psoriasis (PsO), and rheumatoid arthritis (RA); fibromyalgia or severe pain disorder unrelated to the target shoulder; gout; and systemic lupus erythematosus.
2. Rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibodies positive at Screening.

3. Oral, intramuscular or i.v. corticosteroid treatment within the last 12 weeks prior to randomization, or presence of any condition that might require intermittent corticosteroid use.
4. Lack of compliance with adhering to NSAID (unless intolerant or contraindicated) and physiotherapy regimen during run-in period.
5. Positive painful arc test result in contralateral shoulder
6. Inability or unwillingness to undergo MRI of the shoulder (e.g., participants with pacemakers, or metal fragments/foreign objects in the body that are not compatible with performing an MRI) to fulfill eligibility criteria (unless centrally read MRI images acquired within 3 months of Baseline can be provided and the quality of images is deemed sufficient).

Treatment Groups:

Investigational and control drug

- Arm 1: secukinumab 300 mg s.c. at Baseline, Week 1, 2, 3, 4, 8, and 12
- Arm 2: placebo at Baseline, Week 1, 2, 3, 4, 8, and 12

NSAIDs

During the 2-week run-in period, participants should take NSAIDs at a stable dose and still have inadequate control of symptoms at randomization in order to participate in the study. Alternatively, NSAID use should have been stopped in participants who are intolerant or having contraindications. Participants who tolerate NSAIDs will continue taking their stable NSAID regimen from the run-in period until Week 24. Reduction in dose is permitted, but participants may not increase above the dose established during run-in.

Data Monitoring/Other Committee:

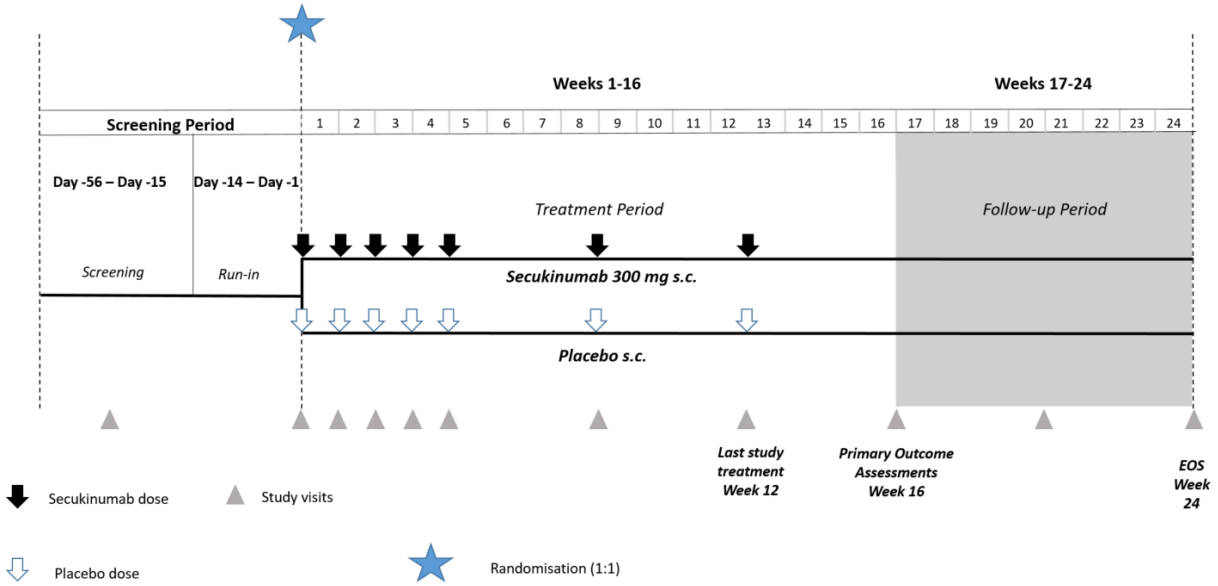
Steering Committee

Key words

Moderate to Severe Rotator Cuff Tendinopathy, Adult, Unilateral, Refractory to standard of care

1.2 Schema

Figure 1-1 Study Design



1.3 Schedule of activities (SoA)

The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

If the Investigator deems it feasible and subject to adequate training, the participants may be able to administer study drug at home (self-administered or administered by caregiver) at Week 1 and Week 3. Participant or caregiver must demonstrate their ability to administer study drug at the BSL visit at the site before home administration is permitted. Tele-visits, i.e., secure videoconferencing, between the Participant and Investigator may also be utilized as additional support for administration of study drug at home.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment should still attend all visits until End of Study (EOS) as indicated in the SoA.

Participants who discontinue from study should be scheduled for a final evaluation visit (EOT assessments should be performed as final evaluation, or EOS if participant has already completed EOT at Week 16) if they agree, as soon as possible, at which time all of the assessments listed for the EOT visit will be performed. At this final visit, the AEs and concomitant medications not previously reported must be recorded on the Case Report Form (CRF).

Pharmacokinetic samples should be taken prior to study drug administration.

Patient Reported Outcomes (PRO) questionnaires must be completed before any assessments are performed at any given visit.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, or unscheduled safety assessments may be performed at the discretion of the Investigator if there is a concern or need follow up for an AE.

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele-consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	Screening[2]		Treatment									Treatment Completion Follow-Up	
Visit Name	Screening	Run-in[3]	Baseline	Week 1[4]	Week 2	Week 3[4]	Week 4	Week 8	Week 12	Week 16 EOT	Unscheduled[5]	Week 20	Week 24 EOS
Visit Numbers[1]	1	20	30	40	50	60	70	80	90	100	110	120	1999
Days	-56 to -15	-14 to -1	1 to 1	8	15	22	29	57	85	113	Unscheduled	141	169
Informed consent	X												
[redacted]													
Additional Research Informed Consent (Optional)	X												
IRT contact	S		S	S	S	S	S	S	S				
Inclusion / Exclusion criteria	X		X										
Medical history/current medical conditions	X												
Medical History: Rotator Cuff Tendinopathy	X												
Demography	X												
Prior medication for tendinopathy	X												
Hepatitis B, C or HIV screening[6,7]	S												
Pregnancy Test (serum)[8]	X												
Tuberculosis test[9]	X												
Pregnancy test (urine)[8,10]			S				S	S	S	S		S	S
Randomization			X										
Study drug administration			X	X	X	X	X	X	X				
Physical Examination	S		S							S	S		S
Body Height	X												
Body Weight[11]	X		X										X
Vital Signs[11]	X		X		X		X	X	X	X	X		X

Period	**Screening**[2]		**Treatment**									**Treatment Completion Follow-Up**	
Visit Name	**Screening**	**Run-in**[3]	**Baseline**	**Week 1**[4]	**Week 2**	**Week 3**[4]	**Week 4**	**Week 8**	**Week 12**	**Week 16 EOT**	**Unscheduled**[5]	**Week 20**	**Week 24 EOS**
Visit Numbers[1]	**1**	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**1999**
Days	**-56 to -15**	**-14 to -1**	**1 to 1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**Unscheduled**	**141**	**169**
Clinical Chemistry[11]	X		X							X			X
Hematology[11]	X		X							X			X
Shoulder X-Ray[6,12,13]	S												
Shoulder MRI[13,14,15]	X												
Painful Arc test	X		X										
Physiotherapy[16,17]		Completed in paper diary											
RF/anti-CCP	X												
WORC Total[18]	[redacted]												
PROMIS-SF Upper Extremity[18]													
[redacted]													
Site contact with participant[19,20]		S	S		S		S	S	S	S		S	S
WORC PSD[21]	[redacted]												
[redacted]													
NSAIDs[17] [redacted]													
[redacted]													

Period	**Screening**[2]		**Treatment**									**Treatment Completion Follow-Up**	
Visit Name	**Screening**	**Run-in**[3]	**Baseline**	**Week 1**[4]	**Week 2**	**Week 3**[4]	**Week 4**	**Week 8**	**Week 12**	**Week 16 EOT**	**Unscheduled**[5]	**Week 20**	**Week 24 EOS**
Visit Numbers[1]	**1**	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**1999**
Days	**-56 to -15**	**-14 to -1**	**1 to 1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**Unscheduled**	**141**	**169**
[redacted]													
PK blood collection[11]			X				X			X			
Immunogenicity[11]			X							X			
Trial Feedback Questionnaire[26]			X							X			X
Concomitant medications	Update as necessary												
Adverse Events[27]	Update as necessary												
Treatment period completion form[28]										X			
Follow-up completion form[28]													X

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] The Screening period will consist of an on-site screening visit and 14 day run-in period commencing with a site telephone contact
[3] Run-in is not a site visit. It will serve to standardize physiotherapy regimen, stabilize NSAIDs and will start 14 days before Baseline
[4] Optional at-home administration available for this visit. See Section 1.3 and Section 4.1
[5] Any assessment pertaining to recording a safety measure or obtaining a repeat sample may be performed at an unscheduled visit as determined necessary by the investigator. The following information is mandatory to record at every unscheduled visit: AEs, concomitant medication, physical examination and vital signs.
[6] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF
[7] Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during screening period only if required as per local medical practice or local regulations. These assessments will be done by central laboratory if no accredited local laboratory is available and will be documented in the source only.
[8] The pregnancy test will be conducted for women of childbearing potential
[9] A QuantiFERON TB-Gold test must be performed at screening. A QuantiFERON TB-Gold test can be performed at the screening visit and the results must be known prior to randomization to determine the subject's eligibility for the trial. The sample 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
[10] Kits will be provided by the central laboratory and the test is to be performed locally
[11] Collected pre-dose
[12] Historical data may be accepted if obtained ≤3 months before

Period	Screening[2]		Treatment									Treatment Completion Follow-Up	
Visit Name	Screening	Run-in[3]	Baseline	Week 1[4]	Week 2	Week 3[4]	Week 4	Week 8	Week 12	Week 16 EOT	Unscheduled[5]	Week 20	Week 24 EOS
Visit Numbers[1]	1	20	30	40	50	60	70	80	90	100	110	120	1999
Days	-56 to -15	-14 to -1	1 to 1	8	15	22	29	57	85	113	Unscheduled	141	169

[13] All imaging results should be confirmed before start of run-in period (day -14)
[14] Shoulder MRI can be performed at any time during Screening period
[15] centrally read MRI done within 3months from baseline may be accepted
[16] Standardized physiotherapy regimen will start from run-in (day -14) to EOS and will be collected in the paper diary
[17] Information from paper diary will be transcribed to relevant eCRF
[18] Patient Reported Outcomes must be done before any other assessments
[19] The site staff must make contact with each participant two weeks (14 days) prior to their scheduled Baseline visit to remind them to charge and switch on the device and to complete the e-diary as required in order for the respective inclusion criteria to be evaluated on the day of the Baseline visit
[20] Site should make confirmed contact with participant (phone call, email, text message, etc.) to remind them to fill out the PRO assessments as required in the e-diary. This should be done on the day before they are due to commence entering data into the e-diary for each marked assessment.

[redacted]

[26] This will be collected in a separate database outside of the clinical database
[27] Including collection of anaphylaxis events if applicable
[28] Information on the participant's status (i.e., continuation, discontinuation or completion of the study) and any reason for discontinuation will be recorded on the appropriate Study Phase Completion eCRF page

2 Introduction

2.1 Study rationale

RCT is a highly prevalent musculoskeletal condition associated with gradual onset of pain, weakness, decrease in shoulder function and impairment to Range Of Motion (ROM). It has considerable impact on the daily activities and quality of life of the participants (Consigliere et al 2018). Despite the common occurrence of this condition, the therapeutic options are limited to conservative pain management, local corticosteroid injections, or surgical intervention in extreme cases. Therefore, there is a high unmet need for an approved targeted drug therapy for this condition.

Pre-clinical studies have shown that IL-17A (Interleukin 17-A) is a key mediator of tendon inflammation and inhibition of tendon matrix repair (Millar et al 2016). Based on biological rationale from pre-clinical studies and translational research models, a Phase II, proof of concept (POC) study was undertaken to determine the efficacy of secukinumab in treating participants with a diagnosis of non-systemic inflammatory unilateral RCT (referred to as RCT) and to confirm the safety and tolerability profile of secukinumab, in comparison to placebo. A loading regimen of 300 mg was given weekly for 5 weeks, followed by a dose every 4 weeks up to 12 weeks. The efficacy of secukinumab was evaluated at Week 14, based on PROs including changes in signs and symptoms, physical function and quality of life, as well as range-of-movement. While there was improvement noted in terms of functional and pain-related endpoints, there was no statistical difference between secukinumab and placebo groups.

Although the Phase II study population was initially foreseen to include only a population displaying more severe, non-acute disease (based on discussion with external experts), the final inclusion criteria were relaxed based on recruitment considerations to include mildly symptomatic participants who still experience the burden of disease and could benefit from anti-IL-17 treatment. These milder participants would have had less severe manifestations of disease, as indicated by physical functioning, pain and impact on quality of life. However, post-hoc analyses suggest a potential treatment effect in a subpopulation of participants with more severe, non-acute disease with symptoms lasting longer than 6 weeks, but no longer than 6 months. This selected post-hoc subgroup was restricted to more severe participants as defined by measures of disease severity (the Western Ontario Rotator Cuff Index, WORC), disease duration, or more severe findings by Magnetic Resonance Imaging (MRI) (Sein score $\geq$2 or Bauer Tear score $\geq$1). Participants with acute tendinopathy (symptoms present for < 6 weeks) were excluded from the post-hoc analyses. Participants with non-acute, but not yet chronic disease, defined using a cut-off of $\leq$ 6 months symptom duration, were included in the subgroup. This decision is supported by research demonstrating an increase in IL-17A in early stages of tendinopathy in human tendinopathy samples (Millar et al 2016). Inhibition of IL-17A was also shown to improve tendon structure and function in rat models of early supraspinatus tendinopathy indicating that early intervention is beneficial. This post-hoc analysis provides evidence of a potential treatment difference in this subpopulation (comprising 42% of the overall study population) with moderate to severe, non-acute disease, which demonstrated a significant, clinically relevant improvement in function and pain at Week 14 (Day 99).

This Phase III study aims to confirm the efficacy and safety of secukinumab compared to placebo in an adult population with moderate-severe RCT, based on the outcome observed in the post-hoc analysis of the Phase II study, but in a larger sample size. The Phase III study population is based on selection criteria that aim to represent those experiencing more moderate-severe symptoms for a period of 6 weeks to 6 months at BSL, who are refractory to standard of care. This involves setting a WORC Total threshold of ≤40, and weekly average pain NRS score of ≥ 5 during the 7 days prior to BSL in order to be included into the study, so as to enroll the intended target population. Participants will also be required to either not have a tendon tear, or if there is a tear, it must be ≤50% of the rotator cuff where the tendinopathy has occurred with a maximum AP length of 10mm. Those with tears greater than 50% would be seen as too severe and would be more aligned with a population that could be considered for surgical intervention. Participants must also show imaging evidence of tendinopathy by MRI. The treatment regimen will be administered as 7 injections of secukinumab 300 mg or placebo s.c. over a 12-week period to replicate the regimen administered in the POC study.

Frequent visits during this period are planned in order to administer study drug but also to allow for data collection with the intention to demonstrate early onset of therapeutic effect of secukinumab. The primary analysis will occur at Week 16, with endpoints to examine effect on physical shoulder symptoms, including shoulder pain, and shoulder function. These variables are known from the literature to be some of the most prevalent symptoms of RCT. [redacted] A follow up period of 8 weeks will examine the durability of the effect of secukinumab in this cohort of participants and the same outcomes will be measured at this later timepoint at Week 24.

Safety and tolerability will also be assessed throughout the study.

During the course of the study, concomitant medications with potential to have confounding effects will be prohibited in order not to produce any false positive effects. The participants will be advised to adhere to a stable NSAID regimen (unless intolerant or having contraindications) where the dose can be lowered but not increased above initial stable dose, and physiotherapy regimen throughout in order to minimize any background effects from pain medications. This is in line with standard of care.

2.2 Background

Rotator cuff tendinopathy

RCT is a highly prevalent condition and accounts for more than 4.5 million physician visits per year in the US (Weber and Chahal 2020). The condition is characterized by gradual onset of activity-related shoulder pain and weakness, with impairments in function and range of motion. It can also be associated with impaired sleep due to nocturnal pain, and negatively impacts the ability to perform basic activities of daily living such as recreational activities, work and mobility. Current standard of care is limited to relief of pain using analgesics and NSAIDs along with physiotherapy.

A significant proportion of patients fail to respond to non-surgical, SoC treatment with conventional modalities of rest, hot and cold packs, physiotherapy including therapeutic ultrasound, laser therapy, hyperthermia and/or extracorporeal shockwave therapy, but do not qualify for surgery. NSAIDs are the first-line option for pain relief but are associated with known safety risks that include upper gastrointestinal tract bleeding and cardiovascular events (Wolfe et al 1999). Local corticosteroid injections can provide short-term pain relief and restoration of function in RCT. The effect is generally short lasting of a few months duration, and there is no evidence of benefit beyond 6 months (Lin et al 2019). Furthermore, it has been shown that repeated corticosteroid injections have the potential to increase the risk of tendon rupture (Lipman et al 2018). Non-surgical treatments have been shown to be effective in the short term with NSAIDs shown to be effective for 2 weeks and corticosteroids effective for 6 weeks. However, it has been shown that patients who present with a longer duration and greater severity of symptoms are more likely to have a poor response to both corticosteroid injections and/or oral NSAIDs (Andres, Murrell 2008). In addition, SoC treatments for RCT only address symptom relief and are generally not targeted against specific pathways to treat the molecular root cause.

Role of IL-17A in tendinopathy

Interleukin (IL)-17A plays a central role in mediating multiple autoimmune and inflammatory processes (McGeachy et al 2019). Studies have shown that IL-17A mediates tendon inflammation, inhibits tendon matrix repair, and induces cell death in tenocytes. Immune cells expressing IL-17A have been found to be resident in tendinopathic tissue, with increased IL-17A messenger ribonucleic acid (mRNA) and protein expression levels in early human tendinopathic tissues samples (Millar et al 2016). In human tenocytes, IL-17A can regulate pro-inflammatory cytokines and key apoptotic mediators, causing the induction of apoptosis *in vitro*. As a consequence of this apoptosis, the tendon matrix adopts a mechanically inferior type III collagen phenotype (Millar et al 2016). Thus, evidence suggests that IL-17A is a key player in the pathogenesis of tendinopathy (Millar et al 2017).

Recent attention in musculoskeletal research has been given to the immunobiology of the enthesis, the specialized connective tissue matrix joining tendon or ligament to bone. This fibrous tendon-to-bone interface is a structurally continuous gradient leading from uncalcified tendon to calcified bone, with multiple zones differentiated by resident cell types, vascularity, and extracellular matrix protein composition. Pathological processes in this area can be considered analogous to tendinopathy, as both the enthesis and tendon are sites of high mechanical stress (Gracey et al 2020). Enthesitis is often a primary pathological process underlying skeletal inflammation in the spectrum of diseases defined as spondyloarthropathies (SpA) (Benjamin, McGonagle 2009, Watad et al 2018), for which secukinumab has demonstrated efficacy.

Secukinumab

Secukinumab, a recombinant high-affinity fully human monoclonal anti-IL-17A antibody, is approved for the treatment of immune mediated disorders including moderate to severe plaque psoriasis in patients 6 years and older, psoriatic arthritis (PsA) in patients 2 years of age and older (US) or 6 years and older (EU), adults with axial spondyloarthritis [axSpA] (which

includes ankylosing spondylitis [AS], and non-radiographic axial spondyloarthritis [nr-axSpA]), and active enthesitis-related arthritis (ERA) in patients 4 years of age and older (US) or 6 years and older (EU). Of note, these latter rheumatic indications involve connective tissue inflammation in the joints and entheses as a central component of their pathogenesis. Secukinumab is currently being evaluated in other inflammatory conditions such as hidradenitis suppurativa, giant cell arteritis, lupus nephritis, and thyroid eye disease (Graves' orbitopathy).

Secukinumab has demonstrated a consistently favorable benefit-risk profile in multiple indications. As of 25-Jun-2022, over 29,393 participants and healthy volunteers have received secukinumab in Novartis-sponsored investigational clinical trials (either completed studies or ongoing studies with interim analyses) at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg intravenous (i.v.) and 25 mg to 300 mg s.c. The cumulative patient exposure from is available in the Investigator's Brochure (IB).

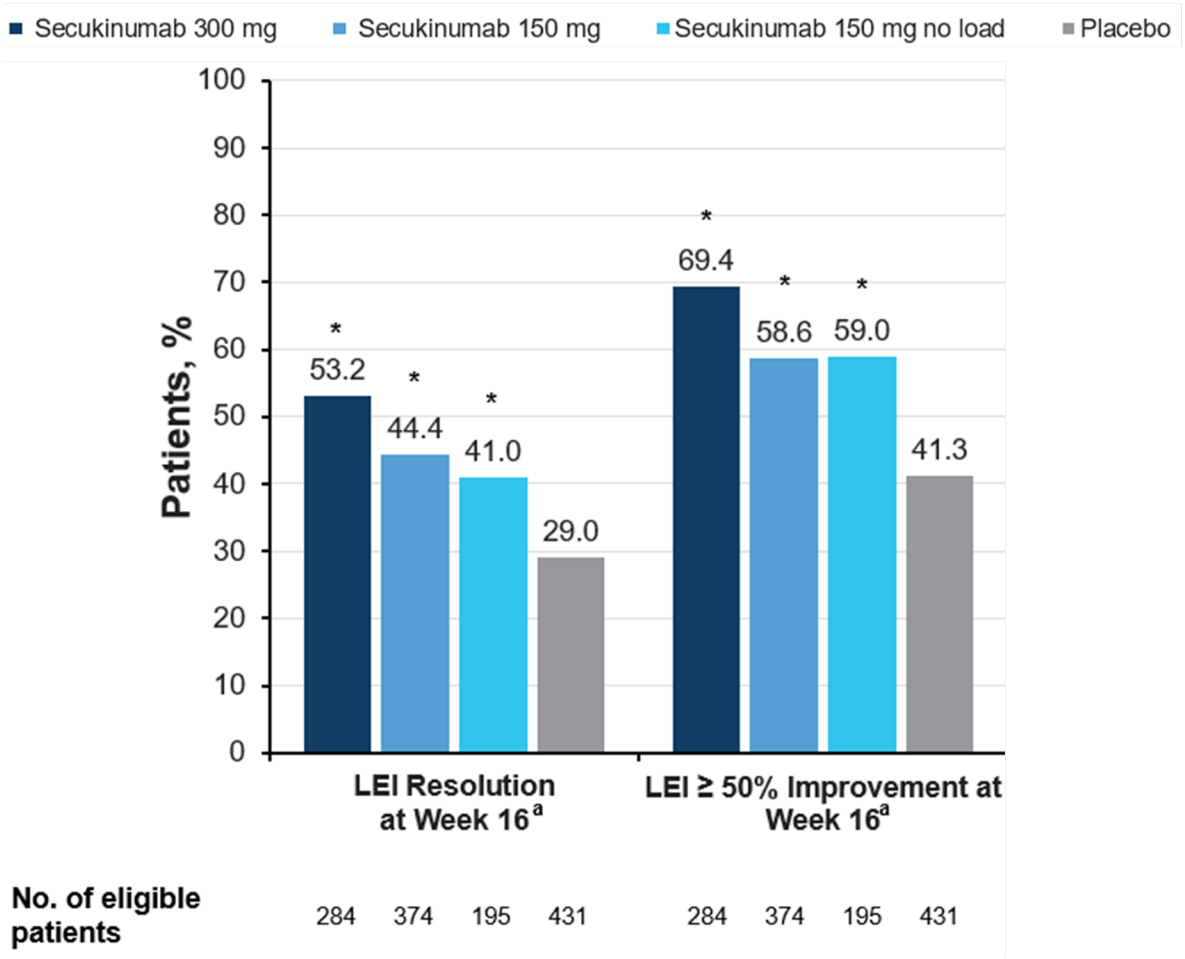
The safety profile of secukinumab, which has been consistent across all indications, supports its long-term use in chronic inflammatory conditions. Please refer to the IB for more information on secukinumab.

Efficacy of secukinumab in the resolution of enthesitis

Enthesitis, a pathophysiologically related condition to tendinopathy, has been widely investigated with secukinumab in the context of the large SpA program specifically in PsA and axSpA. Analyses of the effect of secukinumab on enthesitis have been conducted using the Leeds enthesitis index (LEI) and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index in PsA studies, and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) in AS studies.

In a pooled analysis (Orbai et al 2020) of the FUTURE 2-5 studies in PsA (CAIN457F2312, CAIN457F2318, CAIN457F2336, and CAIN457F2342, in ascending order), the robust efficacy of secukinumab on enthesitis was demonstrated (Figure 2-1). The LEI assesses 6 sites: bilateral Achilles tendon insertions, medial femoral condyles, and lateral epicondyles of the humerus. Among participants who received secukinumab 300 mg, 53% achieved complete resolution of enthesitis at Week 16. This is compared to 41% to 44% for the 150 mg without loading (no load) and 150 mg with loading regimens and 29% for placebo, as seen in Figure 2-1.

Figure 2-1 Percentage of participants with improvement in enthesitis in studies FUTURE 2-5



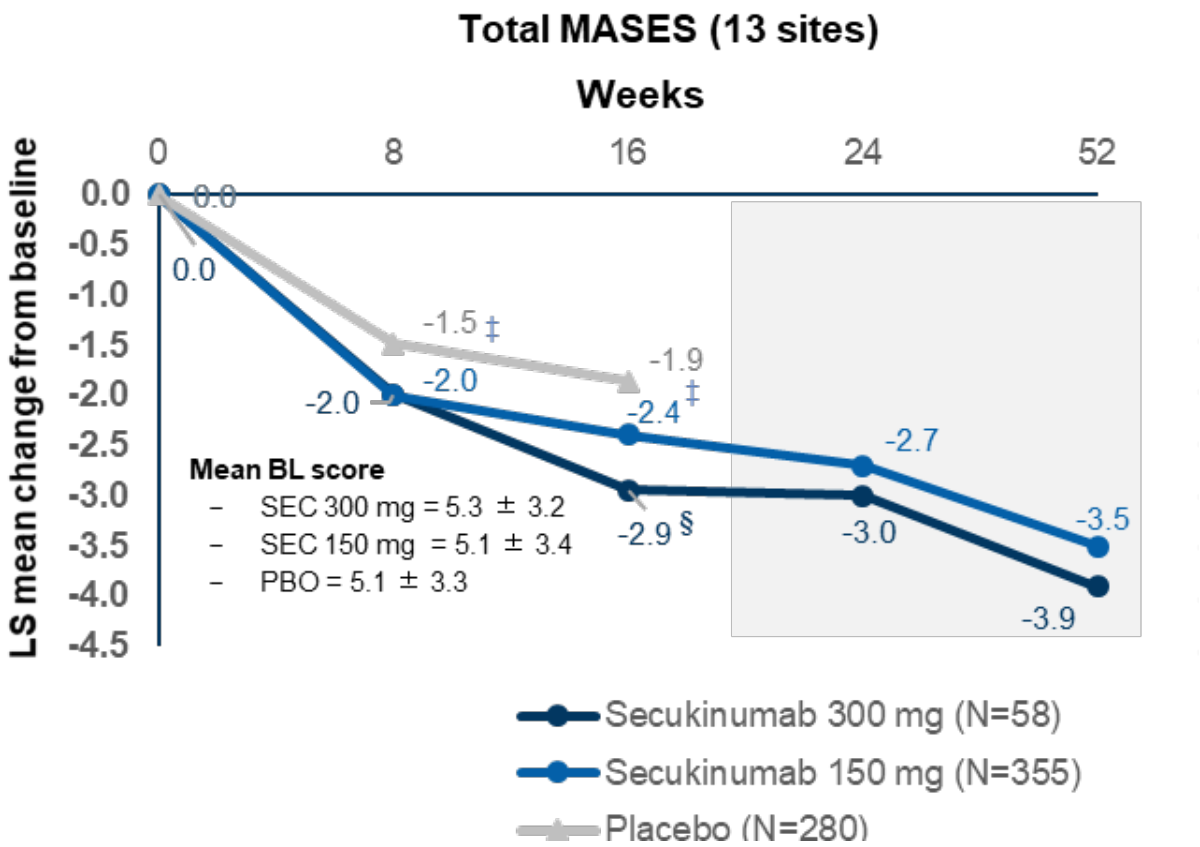
[a]Percentage of participants with improvement in enthesitis. LEI: Leeds Enthesitis Index. * P < 0.05 vs placebo.

Resolution of enthesitis was assessed by the SPARCC index (evaluating 16 entheseal sites) in CAIN457F2366, a head-to-head study of secukinumab (300 mg) versus adalimumab (40 mg) in participants with active PsA (McInnes et al 2020); 39% of subjects treated with secukinumab demonstrated resolution of enthesitis at Week 16, which increased to 53% after 52 weeks. Of the subjects treated with adalimumab, 50% achieved resolution of enthesitis at 52 weeks. As assessed by the LEI, 61% of subjects treated with secukinumab showed resolution of enthesitis at Week 52, compared with 54% of subjects on adalimumab.

In a pooled analysis (Schett et al 2021) of studies MEASURE 1-4 in AS (CAIN457F2305, CAIN457F2310, CAIN457F2314, and CAIN457F2320, in ascending order) in a total of 693 participants, enthesitis was evaluated using the MASES score. This included data for the 150 mg dose vs. placebo, with one study (CAIN457F2314) including the 300 mg dose, and a variety of administration routes but all utilizing s.c. regimens for maintenance dosing. Secukinumab groups showed greater changes in total MASES score at Week 16, maintenance of effect up to Week 52, and higher rates of complete resolution. The 300 mg group had an improved rate of

resolution compared with the 150 mg group when observed over a 52-week period, as seen in Figure 2-2.

Figure 2-2 Mean change from baseline in MASES score in studies MEASURE 1-4[a]



§*P* <0.01; ‡*P* <0.05 versus placebo. LS Mean, and *P*-value are from MMRM (Mixed-effects Model Repeated Measures) until Week 16. Observed data thereafter through Week 52. BL, baseline; LS, least squares; MMRM, mixed-effects model repeated measures.
[a] MEASURE 1 (CAIN457F2305) and MEASURE 3 (CAIN457F2314) utilized an i.v. loading regimen; 300 mg dose was only studied in MEASURE 3 (CAIN457F2314).

Overall, these pooled analyses of the FUTURE 2-5 and MEASURE 1-4 studies show a robust effect of secukinumab on enthesitis at peripheral sites and suggest dose-dependent activity, with a numerically higher response in most analyses for the 300 mg s.c. dose (with an i.v. loading regimen) in MEASURE 3. Thus, there is potential for secukinumab 300 mg s.c. to be an effective treatment for the related connective tissue condition of RCT.

Proof-of-concept study CAIN457X2201

Based on the biological rationale from preclinical and translational research models, Novartis conducted a randomized, double-blind, placebo-controlled, multi-center, Phase II, proof-of-concept study to determine the efficacy of secukinumab in participants with RCT. The population consisted of male and female participants (N=98), 18 years to 65 years of age at randomization with a diagnosis of non-systemic inflammatory unilateral RCT, with no more than than a 50% tear, and with clinical symptoms present for at least 6 weeks but not more than

12 months. They were also refractory to NSAIDs/paracetamol (acetaminophen), physiotherapy or local corticosteroids. A dose of secukinumab 300 mg s.c. was administered at Day 1 and weekly up to and including Week 4, with two additional doses at Weeks 8 and 12. The efficacy of secukinumab was evaluated at the end of Week 14, with follow-up for safety and efficacy parameters up to Week 24. The primary objective of this study was to evaluate the treatment effect on the change from BSL in the total WORC (Kirkley et al 2003) index scores at Week 14. The WORC index is a disease-specific quality of life questionnaire evaluating symptoms and functional ability. Clinically relevant improvements were observed in both the secukinumab and placebo groups, with no statistically significant difference between the treatment groups (+37.0 in the secukinumab 300 mg group and +37.77 in the placebo group; higher scores denote improvement; treatment difference −0.77; 90% CI: −8.84, 7.30; p=0.87).

Post-hoc analysis in non-acute, moderate to severe participants.

Post-hoc analyses of study CAIN457X2201 suggest a treatment effect in a subpopulation of participants with more severe, non-acute disease. The selected subgroup was restricted to participants with non-acute but not yet chronic disease (disease duration of 6 weeks to 6 months) and with more severe disease defined by WORC ≤ 40 or more severe findings by MRI (Sein score ≥2 or Bauer Tear score ≥1).This post-hoc analysis, based on the "per protocol" data set, provides evidence of a treatment difference in this subpopulation (comprising 42% of the overall study population) with moderate to severe, non-acute disease, which demonstrated a significant, clinically relevant improvement in the WORC index (treatment difference in total WORC score of 16.43 points, p=0.048) and pain (treatment difference on visual analog scale (VAS) of -16.11 points, p = 0.045) at Week 14 (Day 99) (Millar et al 2021). In sum, IL-17A inhibition with secukinumab shows potential as a novel target in the treatment of RCT.

Figure 2-3 Average WORC score (subgroup analysis)

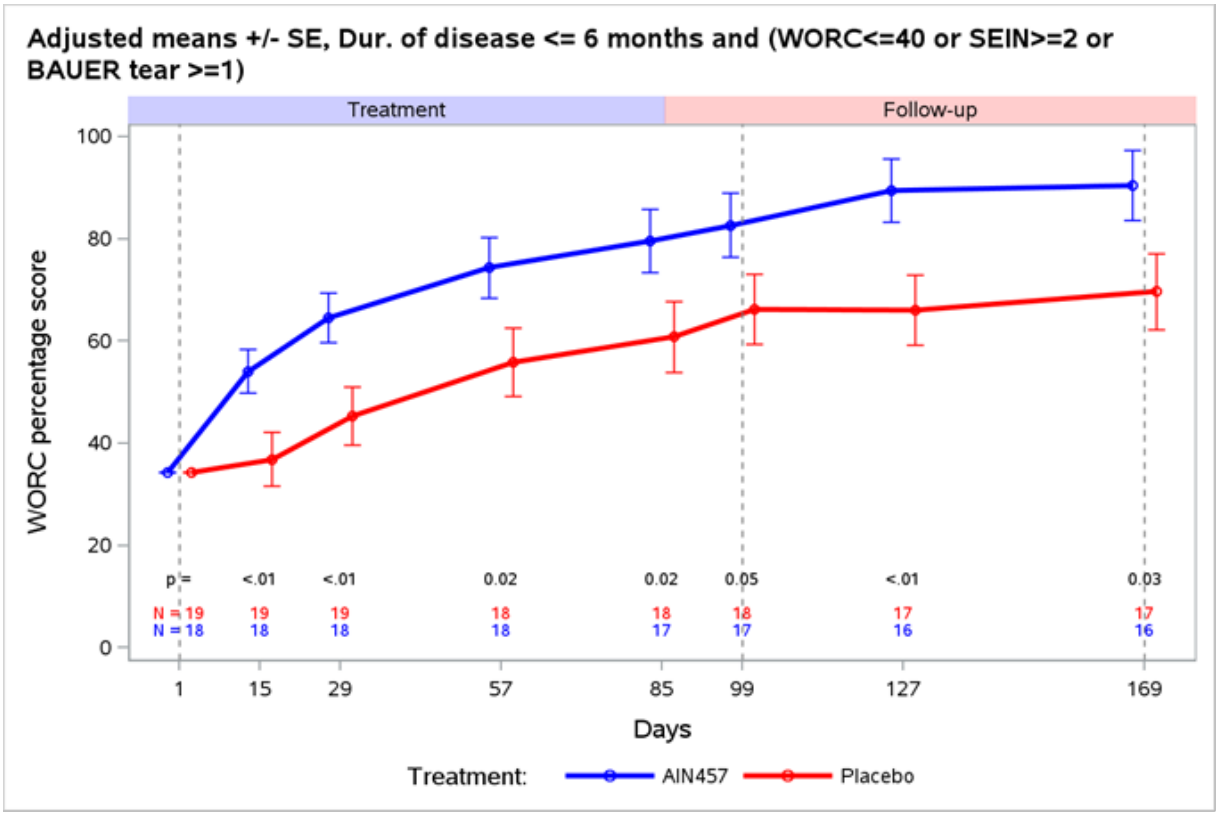
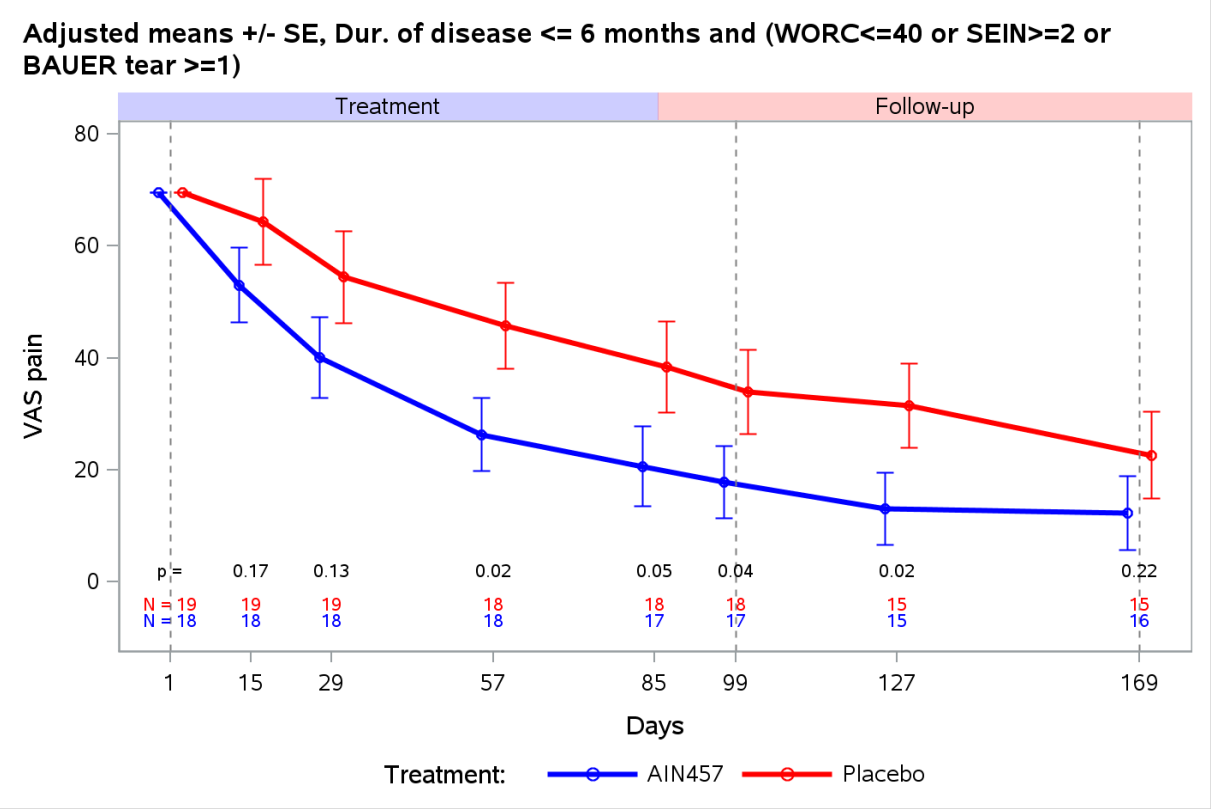


Figure 2-4 Average VAS Pain score (subgroup analysis)



2.3 Benefit/Risk assessment

Secukinumab has demonstrated a consistently favorable benefit-risk profile in the extensive Novartis clinical program across multiple indications comprising more than 25 Phase III studies, with data collection over a period of up to 5 years in the approved indications of moderate to severe plaque psoriasis in patients 6 years and older, psoriatic arthritis (PsA) in patients 2 years of age and older (US) or 6 years and older (EU), adults with axSpA, which includes AS, and nr-axSpA, and active enthesitis-related (ERA) in patients 4 years of age and older (US) or 6 years and older (EU).

A consistent safety profile is demonstrated by the safety data collected from the completed and ongoing studies across various indications. This includes AE and SAE data, laboratory parameters and immunogenicity data. For more details, please refer to the current IB.

In the PoC study CAIN457X2201, the treatment regimen with secukinumab of 300 mg s.c. as planned in the present study (5 weekly loading doses followed by a dose at Week 8 and Week 12) was generally well tolerated, and the safety profile in the population of participants with a diagnosis of RCT was consistent with previous secukinumab studies. Overall, 70/96 (72.9%) patients experienced at least one AE of any grade. Among all grades, those occurring in ≥10% of secukinumab-treated participants by preferred term were nasopharyngitis, headache and nausea. All of the AEs were of mild (196 AEs in 64/96 patients) or moderate (32 AEs in 20/96 patients) severity with no noticeable differences between the secukinumab group and placebo group. There were no noticeable differences between the secukinumab group and the

placebo group in the number of patients with AEs related to injection site, and no treatment-emergent anti-drug antibodies were observed in any of the patients

Current non-operative SoC for management of RCT is very limited to analgesics, NSAIDs and physiotherapy. While corticosteroids are often administered there is also the risk of acceleration of degeneration of the tendon. With this added risk, there is little benefit as corticosteroid treatment offers only minimal transient pain relief that does not modify the natural course of the disease (Mohamadi et al 2017). Considering the high unmet medical need for an approved therapy for RCT, there is the potential for participants to receive treatment that may have beneficial effects on their quality of life in terms of improved physical function and reduction in pain. As noted previously in Section 2.2, secukinumab has been shown to be efficacious in the resolution of enthesitis, which occurs in the same connective tissue system as tendinopathy.

The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring by the Investigator, with extensive guidance provided in the current version of the secukinumab IB.

Secukinumab has been noted to potentially increase the incidence of infection, most commonly in the upper respiratory tract, and caution should be exercised when used in participants with a chronic infection or history of recurrent infection. Although there was no demonstrated increase in susceptibility to tuberculosis (TB) in clinical trials, secukinumab should not be given to participants with active TB. COVID-19 has similar impact on risk-benefit as other infections, and no additional risk is anticipated due to COVID-19 infection. Active infection should be excluded in order to comply with eligibility criteria (see Section 5.2).

In clinical studies there was an increase in non-systemic mucosal or cutaneous candidiasis cases following treatment with secukinumab when compared to placebo. These events were responsive to standard treatments and were mostly mild or moderate in severity.

Exacerbation in inflammatory bowel disease (IBD) has been noted in clinical studies in both secukinumab and placebo groups, and new-onset IBD has also been reported. As a result, caution should be exercised and those with active IBD should be excluded from the study.

Urticaria and rare cases of anaphylactic reactions have been observed in clinical studies in patients receiving secukinumab. Administration of secukinumab should be discontinued if anaphylactic or serious allergic reaction occurs (see Section 8.6.1).

Live vaccines should not be given with secukinumab concurrently; however, inactivated or non-live vaccines are permitted. Clinical data suggest that secukinumab at a dose of 150 mg does not suppress the humoral immune response to meningococcal or influenza vaccines (Chioato et al 2012).

Information published by the American College of Rheumatology (ACR) and National Psoriasis Foundation (NPF) recommends that participants with autoimmune and inflammatory rheumatic disease on therapy with biologics should be prioritized for SARS-CoV-2 vaccination. A recent study by (Furer et al 2021) investigated the immunogenicity, efficacy and safety of two-dose regimens of BNT162b2 mRNA vaccine (Pfizer) in adult patients with a range of autoimmune inflammatory rheumatic diseases (AIIRD). The results demonstrated an adequate immunogenic response with an acceptable safety profile and high seropositive rates in the majority of AIIRD patients following vaccination, as 100% of patients who were receiving anti-

IL-17A therapies became seropositive. These data suggest that the protective effects of BNT162b2 mRNA vaccine will not be impacted negatively by secukinumab therapy.

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. In order to participate in the study, they must agree to adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study. Although there is no evidence to indicate if secukinumab is excreted in human milk, immunoglobulins are known to be present in human milk. As caution is required, nursing/lactating women will be excluded from study inclusion.

Shoulder X-rays may be performed as part of the assessment of participant eligibility for inclusion into the study. The amount of radiation exposure would be considered as low, incurring minimal risk. Shoulder MRI is also performed as part of the eligibility assessment. There is no risk of radiation exposure with shoulder MRI.

Overall, taking into consideration the known safety profile from the extensive data accrued from the secukinumab clinical program across all indications and the positive benefit-risk assessment in its approved indications, the anticipated benefit-risk profile for secukinumab in RCT is considered favourable.

2.3.1 Risks and benefits for planned off-site procedures

It is not anticipated that participants will be exposed to greater risks with administration of study drug at home (self-administered or administered by caregiver). Safety management in an off-site setting will adhere to the same quality standards as for the traditional onsite model and remains under the responsibility of the Investigator.

3 Objectives, endpoints, and estimands

The primary objective of this trial is to demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo in improving physical shoulder symptoms in participants with moderate to severe RCT, based on change from BSL in the WORC Physical Symptoms domain (PSD) score at Week 16. The PSD questionnaire in the e-diary will provide the data for the primary endpoint. See Section 8.5.1.1 and Section 8.5.1.2

Secondary objectives are to demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo in participants with RCT in achieving a clinically meaningful response in improving physical shoulder symptoms, improving physical function, improving symptoms caused by RCT and the associated impact on participants' day to day functioning, based on the objectives outlined in Table 3-1. Secondary endpoints at Week 24 will be tested based on the Week 24 data available at the Week 16 database lock (DBL). In order to control for the type I error rate ('false positive rate') at the level of the individual studies, the testing strategy as defined in Section 9.4.1 will be implemented. Safety and tolerability will also be monitored as part of the secondary objectives of the study.

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● Demonstrate that the efficacy of secukinumab 300 mg s.c., is superior to placebo, in improving physical shoulder symptoms in participants with moderate to severe RCT at Week 16	● Change from BSL in the WORC PSD score at Week 16
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in achieving a clinically meaningful response in improving physical shoulder symptoms in participants with moderate to severe RCT at Week 16	● Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in the WORC PSD at Week 16
● Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in improving symptoms caused by RCT and the associated impact on day-to-day functioning in participants with moderate to severe RCT at Week 16	● Proportion of participants who achieve an improvement (increase) of at least 50 points from BSL in the WORC total score at Week 16
● Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in improving physical function in participants with moderate to severe RCT at Week 16	● Change from BSL in the Patient-Reported Outcomes Measurement Information System (PROMIS) - Short Form (SF) Upper Extremity score at Week 16
● Evaluate the ability of secukinumab 300 mg s.c. compared to placebo, to improve physical symptoms at Week 24	● Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in the WORC PSD at Week 24 ● Change from BSL in the WORC PSD score at Week 24
● Evaluate the PK of secukinumab 300 mg s.c., in the population of participants with moderate to severe RCT	● Secukinumab serum concentrations on Day 1 and Weeks 4 and 16
● Evaluate safety, immunogenicity and tolerability of 300 mg s.c. secukinumab, in participants with moderate to severe RCT	● Safety and tolerability demonstrated by assessing: AEs and SAEs (incidence, severity, and relationship with study drug) Incidence of clinically significant changes in laboratory parameters and vital signs Incidence of binding and neutralizing ADAs at Day 1 and Week 16

Objective(s)	Endpoint(s)
[redacted]	

3.1 Primary estimands

The primary scientific question of interest is: what is the effect of secukinumab 300 mg s.c. compared to placebo in participants with moderate to severe RCT in change from BSL in the WORC PSD score at Week 16 regardless of discontinuation due to any reason, use of prohibited medication, or use of rescue medication?

The primary estimand will be based on the following attributes:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted moderate to severe RCT population
- Endpoint: change from BSL in the WORC PSD score at Week 16

- Treatment of interest: the randomized treatment (secukinumab or placebo)
- Handling of remaining intercurrent events is the following:
  1. Discontinuation of study treatment due to any reason (including AE and lack of efficacy): if participants discontinue study treatment due to any reason (including AE and lack of efficacy), the event will be ignored (treatment policy)
  2. Prohibited medication: if participants receive prohibited medication without study treatment discontinuation, the event will be ignored (treatment policy)
  3. Rescue medication: if participants take rescue medication without study treatment discontinuation, the event will be ignored (treatment policy)
- Summary measure: difference in means between treatments.

3.2 Secondary estimands

The secondary clinical questions of interest include:

- What is the effect of secukinumab 300 mg s.c. compared to placebo in the proportion of participants with moderate to severe RCT who achieve an improvement (increase) of at least 40 points from BSL in the WORC PSD at Week 16 regardless of discontinuation due to any reason, use of prohibited medication, or use of rescue medication?
- What is the effect of secukinumab 300 mg s.c. compared to placebo in the proportion of participants with moderate to severe RCT who achieve an improvement (increase) of at least 50 points from BSL in the WORC total score at Week 16 regardless of discontinuation due to any reason, use of prohibited medication, or use of rescue medication?
- What is the effect of secukinumab 300 mg s.c. compared to placebo in participants with moderate to severe RCT in change from BSL in the PROMIS-SF Upper Extremity score at Week 16 regardless of discontinuation due to any reason, use of prohibited medication, or use of rescue medication?
- What is the effect of secukinumab 300 mg s.c. compared to placebo in the proportion of participants with moderate to severe RCT who achieve an improvement (increase) of at least 40 points from BSL in the WORC PSD at Week 24 based on the Week 24 data available at the Week 16 DBL regardless of discontinuation due to any reason, use of prohibited medication, or use of rescue medication?
- What is the effect of secukinumab 300 mg s.c. compared to placebo in participants with moderate to severe RCT in change from BSL in the WORC PSD score at Week 24 based on the Week 24 data available at the Week 16 DBL regardless of discontinuation due to any reason, use of prohibited medication, or use of rescue medication?

The estimand definition of all secondary objectives related to change from BSL (e.g., change from BSL in PROMIS-SF Upper Extremity score) will have the same attributes as that for the primary estimand, except for the endpoint.

The estimand definition for the secondary objectives related to proportion (e.g., proportion of participants achieving certain amount of improvement from BSL in WORC PSD and WORC total score) is described by the following attributes:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted moderate to severe RCT population
- Endpoint: proportion of participants who achieve a certain amount of improvement from BSL in the variable of interest
- Treatment of interest: the randomized treatment (secukinumab or placebo)

The intercurrent events will be handled as follows:

1. Discontinuation of study treatment due to any reason (including AE and lack of efficacy): if participants discontinue study treatment due to any reason (including AE and lack of efficacy), the event will be ignored (treatment policy)
2. Prohibited medication: if participants receive prohibited medication without study treatment discontinuation, the event will be ignored (treatment policy)
3. Rescue medication: if participants take rescue medication without study treatment discontinuation, the event will be ignored (treatment policy)

Summary measure: difference in proportions between treatments

4 Study design

4.1 Overall design

The trial is designed as a randomized, double-blind, placebo-controlled Phase III study over 24 weeks in approximately 234 participants with moderate to severe RCT, refractory to SoC (NSAIDs course as per local standard practice, if not intolerant or contraindicated, and a course of physiotherapy over a period of 8 weeks).

The trial comprises the following periods:

Screening / run-in period

A screening period of up to maximum of 56 days will be used to assess participant eligibility. During this time, the participant can demonstrate that they are refractory to SoC. During the 2-week run-in period prior to the BSL visit, the participant will need to have 2 weeks of stable NSAID intake and standardized physiotherapy. This is important in order to ensure the participants are refractory to SoC and to establish compliancy with the stabilized dosing of NSAID treatment and physiotherapy regimen to be maintained throughout the study.

MRI will be performed during Screening period to exclude other shoulder pathologies and tears (if present) >50%. Evidence of tendinopathy should be established by a centrally read MRI. MRI performed within 3 months from baseline may be accepted if deemed suitable by the central reader.

Shoulder x-rays will also be performed in order to rule out other shoulder pathologies. Historic x-rays will be accepted if performed ≤ 3 months prior to BSL.

Study period 1 (BSL to Week 16)

During Study period 1, double-blinded treatment is administered over 12 weeks, reflecting 16 weeks of total drug exposure. Approximately 234 eligible participants will be randomized at BSL in a 1:1 ratio to one of the following arms:

- Arm 1 (N=117): secukinumab 300 mg s.c. at Day 1 and Weeks 1, 2, 3, 4, 8, and 12
- Arm 2 (N=117): placebo at Day 1 and Weeks 1, 2, 3, 4, 8, and 12

The last dose of study treatment will be administered at Week 12; the primary outcome assessments will be performed at Week 16.

Randomization will be stratified by tear status (no tear/partial tear). Participants should continue on stable NSAID pain medication and a standardized physiotherapy regimen. Reduction in NSAID dose is permitted after BSL, but participants must not increase above dose established during run-in. Use of corticosteroid injections is not permitted during this time.

Study period 2 (Follow-up period)

A follow-up period of 8 weeks after the end of the treatment period is planned to assess the maintenance of effect and collect follow-up safety data up to Week 24. Investigator, site personnel, persons performing the assessments and participants will remain blinded, but Novartis clinical trial and submission teams will be unblinded after Week 16 readout. Participants should continue on stable NSAID therapy and physiotherapy during this period. Reduction in NSAID dose is permitted after BSL, but participants must not increase above dose established during run-in. Corticosteroid injections are also not permitted after Week 16.

Please refer to Section 6.8.2 for more information on medication prohibited throughout the course of study (up to Week 24). Refer to Section 1.2 for study design figure.

Off-site procedures

At the Investigator's discretion, participants may avail of home administration of study drug (self-administered or by a care-giver) at Week 1 and Week 3. Participant and/or caregiver would need to be trained and approved by Investigator for these administrations. Site should have confirmed contact with participant for these home administrations. Tele-visits, i.e., secure videoconferencing, between the Participant and Investigator or designated site staff may also be utilized to support administration of study drug at home.

4.2 Scientific 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 is intended to enable the evaluation of treatment effect of the secukinumab 300 mg s.c. regimen compared to placebo.
Randomization (strata, allocation ratio)	All eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms at a 1:1 ratio. Stratification factor of partial or no tear will be included.
Blinding	Double-blinding is used in this study to minimize bias in the evaluation of safety and efficacy. Blinding is maintained beyond the primary endpoint for Investigator, site personnel, persons performing the assessments and participants, but Novartis clinical trial and submission teams will be unblinded after the Week 16 readout.

Study Design Aspect	Rationale
Use of Placebo	Treatment with placebo is justified to ensure reliable evaluation of the efficacy and safety of the active treatment in light of the nature of the condition and the outcome measures used.
Duration of study periods	A 16-week treatment duration (last dose administered at 12 weeks) was chosen as this is considered a reasonable treatment duration with a biologic for non-acute RCT. The primary endpoint of the trial is assessed at Week 16, 4 weeks following the last injection of study treatment. The follow-up period after the end of study treatment is included to generate data to assess maintenance of the treatment effect and to collect treatment safety follow-up data in this indication.

The study will enroll participants with moderate to severe symptomatic RCT with inadequate response (refractory) to physiotherapy, NSAIDs, or local subacromial corticosteroid injection, or intolerance to NSAIDs or local corticosteroid injection. The last corticosteroid therapy must have been ≥ 12 weeks prior to randomization. Participants must be naïve to IL-17 inhibition therapy.

The participant population with RCT was chosen as this is one of the most frequent tendinopathies. Tendinopathy most commonly presents during adulthood from 18 up to 65 years of age, as incidence is rare in adolescent and pediatric populations Zbojniewicz et al 2014. Moreover, the clinical evidence for a role for IL-17 in the pathogenesis of tendinopathy has so far only been shown for RCT and has not been investigated for other tendinopathies (Millar et al 2017).

Participants with a symptom duration of ≥ 6 weeks and ≤ 6 months based on medical convention will be identified, where an acute condition may be defined as up to 6 weeks in duration from onset and a chronic condition would be expected to persist beyond 6 months. Evidence of the early biological involvement of IL-17A in this disease process can be seen in preclinical models (data on file):

- Increased IL-17A mRNA and protein expression level previously noted in early human tendinopathic biopsies (Millar et al 2016)
- IL-17A high-expressing tendon-resident immune cells were most prevalent in early versus late human tendinopathy biopsies (Millar et al 2016), whileIL-17A blockade significantly improved tendon structure and function in a rodent model of supraspinatus tendinopathy that is, by definition, a model of early disease (Millar et al 2018).

In addition, the post-hoc exploratory analyses conducted on data from the Phase II PoC trial CAIN457X2201 support these assumptions, as participants with symptom duration greater than 6 months did not appear to benefit from secukinumab treatment.

The definition of participants with moderate to severe symptoms in the proposed Phase III trial is supported by the inclusion of average weekly pain NRS ≥5 (on a scale from 0 to 10) in the eligibility criteria, which corresponds to a moderate to severe pain level (Jensen et al 2017), in combination with WORC ≤ 40 (normalized to a 100-point scale where 100 points is symptom free and 0 indicates worst symptoms). It became evident from the analyses of the CAIN457X2201 study that applying more stringent selection criteria would lead to the inclusion of a participant population more likely to benefit from secukinumab treatment.

The study participant population is enrolled with a Baseline WORC Total of ≤ 40 points, representing a disease severity ranging from moderate to severe. This cut-off is intended to match the same severity range defined by physicians using the PhGA tool. According to clinicians with experience using the PhGA scale, as well as references in the literature (Harrington 2009), PhGA values below 40 are representative of milder symptoms, whereas values above 50 are clearly indicative of moderate disease, with higher values representing severe disease. Therefore, a cut-point of 50 points on PhGA VAS was used to classify Phase II POC study participants into two distinct groups: PhGA VAS < 50 to define participants with mild disease and PhGA VAS ≥ 50 to define participants with moderate to severe disease. Using receiver operator characteristic curve analysis (Phase II POC study), a WORC Total score of 40 was identified as the optimal cut-off to discriminate mild participants from those with moderate to severe disease based on the PhGA VAS. Special attention is given to minimizing the probability of enrolling participants with mild tendinopathy in the proposed study, to favor targeting those most likely to benefit from the intervention under investigation.

A pain score of ≥ 5 (on a scale from 0 to 10) on NRS to denote inadequate control of pain is justified based on a study in a broad sample of participants with rheumatological as well as mechanical musculoskeletal conditions (Falgarone et al 2005), in which the median level of pain requiring analgesic intake as judged by the participants was 48, with a mean of 51.56 on a 100 mm VAS, which would equate to a score of 5 on NRS.

An upper age limit of 65 years at randomization is set based on the expectation that treatment with an IL-17A inhibitor will not target aging-related root causes of RCT in an elderly population. Tendons have been shown to undergo structural changes with age, such as glycosaminoglycan infiltration, fibrocartilaginous change, calcification, blood vessel wall thickening, and tenocyte loss (Chard et al 1994). Moreover, the healing response has been shown to be impaired due to a slower metabolic rate in aged tenocyte-like cells (Klatte-Schulz et al 2012). Hence, treatment with secukinumab may have a lower likelihood of providing efficacy in patients of advanced age.

4.3 Justification for dose

Both doses of secukinumab 150 mg and 300 mg have been approved for use across several indications. A loading dose of 150 mg every week for the first 4 weeks followed by maintenance dosing once every 4 weeks thereafter is recommended for treating nr-axSpA. A starting dose of 150 mg every 4 weeks (which may include a weekly loading regimen over the initial 4 weeks) has been recommended for PsA and AS, but can be increased to 300 mg if disease remains active. The recommended dose for plaque psoriasis in adults is a weekly loading regimen of secukinumab 300 mg for the initial 4 weeks and maintenance dosing every 4 weeks thereafter at the same dose. Thus, despite the approval of both the 150 mg and 300 mg dose options for PsA and AS, the 300 mg regimen provided greater efficacy across multiple domains in PsA (study CAIN457F2312) and in AS (study CAIN457F2314).

The enthesis can be considered analogous to tendon tissue in terms of biomechanical load and in the pathological processes in inflammatory disease (Benjamin, McGonagle 2009). In PsA study CAIN457F2312, the LEI showed numerically better improvements in the 300 mg group compared to the 150 mg group. Furthermore, in AS study CAIN457F2314, the MASES score

also showed numerically better outcomes at longer-term timepoints in the 300 mg group compared to 150 mg.

The safety profile of secukinumab showed no overall dose dependency across multiple indications including PsA, AS, nr-axSpA, and psoriasis; an exception is *Candida* infections (mainly non-serious, localized mucosal or cutaneous candidiasis), which have been more frequent in the 300 mg regimen compared to 150 mg regimen (PSUR 2020). Moreover, the safety results from the Phase II study CAIN457X2201 were consistent with previous secukinumab studies. Thus, the cumulative safety data collected from clinical studies and post-marketing data support a consistent safety profile for secukinumab and the use of the proposed 300 mg s.c. dose, with 5x weekly initial loading up to Week 4, and two additional doses at Weeks 8 and 12.

4.3.1 Rationale for choice of background therapy

NSAIDs (AxMP: Auxiliary Medicinal Product**):** Current drug therapy SoC for management of RCT symptoms, alongside physiotherapy, is limited to NSAIDs. During the 2-week run-in period, participants should take NSAIDs at a stable dose and still have inadequate control of symptoms at randomization in order to participate in the study. Alternatively, NSAID use should have been stopped in participants who are intolerant or who have contraindications. Participants who tolerate NSAIDs will continue taking their stable NSAID regimen from the run-in period until Week 24. A stable NSAID dosing regimen during the treatment period and up to the primary outcome assessment at Week 16 is intended to avoid confounding the treatment effect of secukinumab on the tendinopathy. Participants may decrease their dose after BSL and are permitted to subsequently return to the dose that was established during run-in period. However, the dose of NSAID should not increase above that established during the run-in. It is also maintained throughout the 8-week follow-up period in order to establish the maintenance of effect is not affected by a change of NSAID dosing regimen. Any changes to NSAID type and/or increase in dose will be recorded as a deviation to the protocol, but would not result in study treatment discontinuation or withdrawal of the participant.

Corticosteroid use: If participants received previous corticosteroid injections in the affected shoulder, these must have been given ≥ 12 weeks prior to randomization (no more than 2 injections). During the 16-week treatment period, local corticosteroid injection is not allowed. The avoidance of corticosteroid injections up to the primary outcome assessment at Week 16 is intended to avoid confounding the treatment effect of secukinumab on the tendinopathy. Participants are not permitted to receive a corticosteroid injection after Week 16 in order not to confound the evaluation of maintenance of effect 8 weeks after the end of the treatment period.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The placebo effect in interventional trials in the treatment of RCT is considerable (as also observed in the Phase II study CAIN457X2201); hence, a placebo control is warranted. All participants (both study treatment arms) will in addition receive SoC (NSAIDs, physiotherapy). Blinding of Investigator, site personnel, persons performing the assessments, participants and sponsor up to the primary outcome assessment at Week 16 allows for an unbiased assessment of subjective readouts such as efficacy parameters (especially the PROs) and also for AEs

evaluation. The blinding is maintained for Investigator, site personnel, persons performing the assessments and participants beyond the primary endpoint until the end of the 24-week study to ensure reliable efficacy and safety assessments. Novartis clinical trial and submission teams will be unblinded after Week 16 readout.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

The primary endpoint analysis will be performed after all participants have completed the visit at Week 16 or discontinued earlier in order to support regulatory filings.

Novartis clinical trial and submission teams will be unblinded following the primary endpoint analysis database lock, but Investigator, site personnel, persons performing the assessments and participants will remain blinded.
At the end of the study, the final CSR analysis of all data collected will be performed when all participants have completed their last study visit. The Investigators, site personnel and participants will remain blinded until final database lock.

4.7 End of study definition

Study completion is defined as when the last participant finishes their last study visit (at Week 24), and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator (e.g., each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them in the scope of the trial).

All randomized and/or treated participants who a) discontinue study treatment and do not return for remaining scheduled visits or EOS, or b) discontinue study and do not come in for final evaluation (EOT) should have a safety follow-up call conducted 60 days after last administration of study treatment. A safety follow-up call is only necessary for all participants who discontinued the trial. The information is kept as a source documentation. SAE reporting continues during this time period as described in Section 8.6.3.

5 Study population

The target population is to consist of male and non-pregnant non-nursing female participants at least 18 years of age, but less than or equal to 65 years of age at the time of randomization, with a diagnosis of unilateral RCT, with symptoms present for at least 6 weeks but not more than 6 months at BSL. 234 participants to be enrolled.

Participants must have been refractory to standard of care: NSAIDs course as per local standard practice (if not intolerant or contraindicated) and a course of physiotherapy over a period of 8 weeks, as defined in the inclusion criteria. This can be incorporated into the 8 week screening period. Participants should also have had at least 2 weeks of a standardized physiotherapy treatment prior to BSL, as well treatment with a stable NSAID regimen (unless intolerant or contraindicated). Participants should avoid performing activities that could induce further pain or injury. Participants must have no tendon tear or if there is a tear, it must be a partial thickness tear with ≤50% thickness tear and maximum AP diameter of 10mm. The study sample should have a maximum of 50% of participants with a partial tear as established by MRI during screening. Evidence of tendinopathy on a centrally read MRI should also be established. MRI performed within 3 months from baseline may be accepted if deemed suitable by the central reader. Bilateral shoulder x-rays will also be required in order to rule out other shoulder pathologies as listed in exclusion criteria. Historic image may be accepted if performed ≤3 months prior to BSL.

Participants must have an average weekly pain score on NRS ≥ 5 (corresponding to moderate to severe pain on a 0-10 point scale where 10 indicates worst pain) during the past 7 days in the week prior to BSL, nocturnal pain in shoulder on at least 3 out of 7 nights in the week prior to BSL or a positive painful arc test on examination, in combination with WORC score ≤ 40 (where 100 points is symptom-free and 0 is worst symptoms) at Screening and BSL.

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. Participant must be able to understand and communicate with the Investigator, comply with the requirements of the study, and must provide written, signed and dated informed consent before any study assessment is performed.
2. Males and non-pregnant, non-nursing females between 18 and 65 years of age at the time of randomization.
3. Unilateral rotator cuff tendinopathy with ≥ 6 weeks to ≤ 6 months symptom duration at BSL.
4. Nocturnal pain in shoulder on at least 3 out of 7 nights in the week prior to Baseline OR "positive painful arc test" on examination.
5. Total WORC score ≤ 40 (where 100 points is symptom-free and 0 is worst symptoms) at the Screening and Baseline visits.
6. Average weekly (i.e., the average of the 7 scores taken once a day) NRS pain score of ≥5 during the 7 days prior to the Baseline visit.
7. Refractory to SoC: NSAIDs course as per local standard practice (if not intolerant or contraindicated) and a course of physiotherapy over a period of 8 weeks.
8. Participant must agree to remain on stable NSAID dosage regimen (if not intolerant or contraindicated; NSAID dose is permitted to be reduced, but not increased above dose established at run-in) and physiotherapy regimen from run-in period until EOS (see Section 4.1 for details).

9. Presence of tendinopathy in the affected shoulder on a centrally read MRI, with the following conditions: with no tear or partial tear (maximum 50% tendon thickness; AP length maximum 10 mm) (see Section 8.2.2).

5.2 Exclusion criteria

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

1. Positive painful arc test result in contralateral shoulder
2. Rheumatological and non-rheumatological inflammatory diseases, including but not limited to PMR, PsA, axial spondyloarthritis (AS, nr-axSpA), PsO, and RA; fibromyalgia or severe pain disorder unrelated to the target shoulder; gout; and systemic lupus erythematosus.
3. RF or anti-CCP antibodies positive at Screening.
4. History of adhesive capsulitis/frozen shoulder (in affected or contralateral shoulder), calcific tendonitis or any other pathological condition of the shoulder joints that can confound the assessment of pain and function confirmed clinically or by medical imaging (microcalcifications are acceptable).
5. Moderate to severe osteoarthritis of the shoulder (gleno-humeral, acromioclavicular) in affected or contralateral shoulder confirmed by medical imaging during screening period (or acceptable imaging performed within 3 months of BSL)
6. Neck conditions, including but not limited to cervical spine syndrome, or history or current diagnosis of cervical radiculopathy confirmed through clinical assessment, which in the opinion of the investigator, may explain the participant's symptoms.
7. Any intra-articular/subacromial corticosteroid treatment in affected shoulder, alone or in conjunction with lidocaine, within 12 weeks prior to randomization or more than 2 injections for the current tendinopathy at any time.
8. Oral, intramuscular or i.v. corticosteroid treatment within the last 12 weeks prior to randomization, or presence of any condition that might require intermittent corticosteroid use.
9. Previous platelet rich plasma (PRP) in target shoulder within the last 12 months prior to randomization.
10. Previous fluroquinolone/quinolone antibiotics within the last 6 months prior to randomization.
11. Neuromuscular or primary/secondary muscular deficiency which limits the ability to perform functional measurement.
12. Previous surgery, or plans for surgery on the affected shoulder, during the study period.
13. Participants with traumatic rupture of the rotator cuff who would be considered eligible for surgical repair of cuff tear.
14. Use or planned use of prohibited concomitant medication (see Table 6-2).
15. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor.
16. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer.

17. Any other biologics within 4 weeks or within 5 half-lives of the drug (whichever is longer) prior to randomization.
18. Participants taking moderate to high potency opioid analgesics (e.g., methadone, hydromorphone, morphine) within 12 weeks of BSL.
19. History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as SGOT (AST: Aspartate Aminotransferase), SGPT (ALT: Alanine Aminotransferase), alkaline phosphatase, and serum bilirubin. The investigator should be guided by the following criteria:
    - AST / ALT may not exceed 2 x the upper limit of normal (ULN).
    - Total bilirubin concentration may not exceed 1.5 x ULN.

    Any one of these parameters, if elevated above ULN, should be re-checked once more as soon as possible, and in all cases, at least prior to randomization, to rule-out laboratory error.
20. Total white blood cell (WBC) count < 3,000/µL, neutrophils < 1,500/µL, hemoglobin < 8.5 g/dL (85 g/L) or platelet count < 100,000/µL.
21. 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, or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
22. Known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) (if not treated and cured).
23. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar classes.
24. Active systemic infections during the last two weeks prior to randomization (exception: common cold).
25. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test as indicated in the assessment schedule.

    Participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated.
26. Any surgical, medical, psychiatric (including ongoing alcohol or drug abuse within the past 6 months prior to randomization) or additional physical condition that the Investigator feels may potentially jeopardize the participant during participation in this study or could interfere with the study objectives, conduct or evaluation.
27. 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 human chorionic gonadotropin (hCG) laboratory test.
28. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the

entire study or longer if required by locally approved prescribing information (e.g., 20 weeks in EU). Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. Male sterilization (vasectomy) of the male partner(s) at least 6 months prior to screening of female participants
- Barrier methods of contraception: Condom or Occlusive cap (e.g., diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. 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.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

29. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
30. Inability or unwillingness to receive injections with pre-filled syringes (PFS).
31. Donation or loss of 400 mL or more of blood within 8 weeks before dosing.
32. Anticipate administration of live vaccines during the study period (during study treatment and for 12 weeks after last study treatment dose) or 6 weeks prior to randomization.
33. Previous hyaluronic acid (HA) in target shoulder within the last 12 weeks prior to randomization.
34. Participants with active IBD.
35. Participants who require upper body limbs for mobility, e.g., wheelchair users.

36. Significant medical problems or disease, including but not limited to the following: uncontrolled hypertension, congestive heart failure, uncontrolled diabetes, or very poor functional status precluding ability to perform self-care.
37. Active ongoing disease which in the opinion of the investigator immunocompromises the participant and/or places the participant at unacceptable risk for treatment with immunomodulatory therapy.
38. Lack of compliance with adhering to NSAID (unless intolerant or contraindicated) and physiotherapy regimen during run-in period.
39. Participant missed 3 or more answers to the WORC PSD questionnaire [redacted].
40. Participant missed 3 or more entries to the sleep and/or pain questionnaire on the 7 days prior to BSL.
41. Inability or unwillingness to undergo MRI of the shoulder (e.g., participants with pacemakers, or metal fragments/foreign objects in the body that are not compatible with performing an MRI) to fulfill eligibility criteria (unless centrally read MRI images acquired within 3 months of Baseline can be provided and the quality of images is deemed sufficient).
42. Participants who are expected to require glucocorticoid treatment throughout the trial duration at BSL (e.g., systemic, intramuscular, local injections in shoulder)
43. Participants who are occupationally involved in repetitive overhead action e.g., manual laborer
44. Participants who are seeking worker's compensation

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, eligibility criteria, and any SAE occurring during the screening period.

Participants who sign a consent form and are 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 SAE during the screening phase (see SAE section for reporting details). 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.

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.

If consent was withdrawn during the Screening period before the participant was randomized, the appropriate eCRF should be completed.

Re-screening

It is permissible to re-screen a participant once if s/he fails the initial screening. Participants can be re-screened only once.

If a participant is re-screened for the study, the participant must sign a new ICF and be issued a new participant number prior to any Screening assessments being conducted under the new participant number. For all re-screened participants, the Investigator/qualified site staff will record if the participant was re-screened on the re-screening eCRF, as well as recording the original Screening number the participant was issued prior to the current Screening number. The date of the new informed consent signature must be entered in the Informed Consent eCRF corresponding to the new participant number. No re-screening study related procedures should be performed prior to written re-consent by the participant.

For re-screening, all Screening assessments must be performed per protocol, except the TB work up (if applicable). If the date of the TB work up is less than 12 weeks from the projected Baseline date, then it is not required that the TB work up be repeated; however, the re-screened participant must repeat the QuantiFERON TB-Gold performed by the central laboratory.

5.3.1 Replacement policy

Not applicable

5.3.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

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 Study treatment(s) and concomitant therapy

Participants will be randomized in a 1:1 ratio to one of the following double-blinded intervention arms:

- Arm 1: Secukinumab 300 mg s.c. at Baseline, Week 1, 2, 3, 4, 8, and 12
- Arm 2: placebo at Baseline, Week 1, 2, 3, 4, 8, and 12

6.1 Study treatment(s)

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)
2 X Secukinumab 150 mg / 1 mL	Solution for s.c. injection	Subcutaneous use	Double blinded supply; PFS	Sponsor (global)
2 X Placebo for secukinumab 1 mL	Solution for s.c. injection	Subcutaneous use	Double blinded supply; PFS	Sponsor (global)

Placebo PFS contain a mixture of inactive excipients, matching the composition and the appearance of the secukinumab 150 mg dose.

Secukinumab and the matching placebo will be labeled as "AIN457 150 mg / Placebo" (1 mL) to maintain the blinding.

6.1.1 Additional study treatments

Participants should adhere to a stable NSAID (AxMP) dose (if tolerated) as established during the run-in period. Participants continuing NSAIDs should adhere to a stable NSAID dose and should not exceed the dose used during run-in period. Dose may be decreased and if needed increased to the initial dose they were on during run-in period.

6.1.2 Treatment arms/group

Participants will be assigned at Baseline visit to one of the following 2 treatment arms/groups in a ratio of 1:1.

Group 1: Secukinumab 300 mg s.c.

Group 2: Placebo s.c.

6.1.3 Treatment duration

The planned duration of treatment administration is 12 weeks (16-week treatment period, with last dose administered at 12 weeks). Participants will receive investigational treatment at Baseline, Week 1, 2 and 3, followed by administration every 4 weeks starting at Week 4, until Week 12. Participants may be discontinued from the treatment earlier at the discretion of the Investigator or the participant.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section.

A unique medication number is printed on the study medication label.

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.

Where transport of Investigational Medicinal Product (IMP) directly to a participant's secure off-site location (e.g., home) is permitted by national and local governing regulations, dispatch of IMP from the site to the participant will be performed under the accountability of the Investigator. The provisioning of supply will be for a maximum of 1-weeks supply. In this case, regular contacts (every week 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 participant's next visit to the study site.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees, as appropriate) 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. 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 week or 4 weeks or more frequently if needed, as per the administration schedule) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.2.1 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 Country Organization Quality Assurance.

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

The Investigator or designated site staff (blinded or unblinded, as applicable) 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 field monitors during site or remote monitoring visits, and at the completion of the trial. The Investigator must provide accountability also for locally sourced materials used for administration (e.g. i.v. bags).

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, 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.

The treatment for optional off-site administrations at Week 1 and Week 3 will be handled and dispatched in line with the pharmacy manual and required procedures for transport.

6.2.2 Handling of other treatment

The handling of other treatments such as NSAIDs is within the responsibility of the site.

6.2.3 Instruction for prescribing and taking study treatment

Participants will receive secukinumab (300 mg s.c.) or placebo at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12. Participants will receive secukinumab or placebo doses at the investigational site. However, at Baseline if the participants feel comfortable with self-administration they will be instructed by the site staff on how to self-administer via the pre-filled syringe. Instructions for Use (IFU) containing detailed information about self-administration of study treatment should be provided to each participant at the Baseline visit. After providing detailed explanations and instructions, participants will be invited to raise any questions. Thereafter, they may proceed with self-administration. If the Investigator deems it feasible based on the capability of self-administration or administration by a caregiver, the participant may also be able to administer study drug at home at Week 1 and Week 3 (self-administered or administered by caregiver).

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

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

At baseline all eligible participants will be randomized via IRT to one of the 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 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 Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.3.2 Treatment blinding

Investigator, site personnel, persons performing the assessments and participants will remain blinded through the Week 24 final database lock. The Novartis clinical trial and submission teams will remain blinded to the identity of the treatment from the time of randomization until the Week 16 database lock (for the primary endpoint analysis). The following methods are utilized for blinding: (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: bioanalyst; (2) the identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration, and appearance.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential (not released to clinical trial team) until the Week 16 database lock.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

6.3.3 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.

Most often, discontinuation from study treatment 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.

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.

6.4 Study treatment compliance

The Investigator should promote compliance by instructing the participant to attend the study visits as scheduled and by stating that compliance is necessary for the participant's safety and

the validity of the study. The participant should be instructed to contact the Investigator if he/she is unable for any reason to attend a study visit as scheduled.

Off-site treatment administration compliance will be assessed by the Investigator in consultation with the participant as per standard process and regulations. Compliance is expected to be 100%, unless temporary treatment interruption is needed for safety reasons. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

All dates and times of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with secukinumab, as detailed in pharmacokinetics section.

Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

6.4.1 Recommended treatment of adverse events

Treatment for AEs should follow general guidelines for standard-of-care and is at the discretion of the Investigator or treating physician. There are no specific treatment recommendations for AEs that may possibly occur in this trial. Refer to the IB for AEs related to secukinumab.

Medication used to treat AEs must be recorded on the appropriate CRF.

6.5 Dose modification

Investigational or other study treatment dose adjustments are not permitted.

Study treatment interruption is also not permitted, 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 within a period of 6 weeks prior to randomization to 12 weeks following study treatment. during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be discontinued.

Any study treatment interruption must be recorded on the Dosage Administration Record eCRF.

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

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable

6.5.2 Follow-up for toxicities

Not applicable

6.6 Continued access to study treatment after the end of the study

There is no planned post-trial access to secukinumab after the study ends. The treatment is planned as a once-off therapy to treat episodes of RCT and maintenance therapy using secukinumab is not planned.

6.6.1 Post-trial access

Not applicable

6.7 Treatment of overdose

Doses up to 30 mg/kg (i.e., approximately 2,000 to 3,000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event of overdose, it is recommended that the participant be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Any events of over-dose should be reported to the Global Team.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the participant (GVP – Annex 1, Rev 4 2017).

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 misuse or abuse will be recorded irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, including misuse and abuse, will be reported on AE page and reported using SAE form when events meet seriousness criteria.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

The Investigator must instruct the participant to notify the study site about any new medications he/she takes after the participant was enrolled into the study. All medications, procedures, and significant non-drug therapies (including physiotherapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate CRF.

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 randomizing 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.

NSAIDs:

During the 2-week run-in period, participants should take NSAIDs at a stable dose (not exceeding the maximally tolerable dose, e.g., 3x 600 mg ibuprofen per day or as per local recommendations). Alternatively, NSAID use should have been stopped in participants who are intolerant or having contraindications. Participants who tolerate NSAIDs will continue taking the stable NSAID regimen from the run-in period through to Week 24. Reduction in NSAID dose is permitted after BSL, but participants must not increase above dose established during run-in.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Use of NSAIDs should be monitored on an on-going basis by the Investigator due to potential side effects caused by long-term use.

NSAIDs have been seen to increase the risk of heart attack and stroke. Participants should contact site or seek medical attention if they experience symptoms such as chest pain, shortness of breath or trouble breathing, weakness in one part or side of their body, or slurred speech.

NSAID use has also been shown to increase incidence of gastrointestinal-related events such as bleeding, gastric ulceration, diarrhea and nausea or vomiting. Participants should notify the Investigator if these symptoms emerge or if pre-existing symptoms worsen.

6.8.2 Prohibited medication

Use of the treatments listed in the table below are not allowed within the time periods displayed for each treatment.

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

Corticosteroid use:

If participants received previous corticosteroid injections in the affected shoulder, these must have been ≥ 12 weeks prior to randomization and no more than 2 injections may have been received. During the 16-week treatment period and 8-week follow-up period, corticosteroid injections are not allowed.

Table 6-2 Prohibited medication

Medication	Prohibition period (before randomization)	Action taken (post randomization)
Unstable dose (greater than stable dose taken during run-in period) of NSAIDs (including selective cyclooxygenase-2 (COX-2) inhibitors) or use of NSAID injection (such as ketorolac)	2 weeks[2]	If dose is increased, reduce dose as soon as possible back to Baseline dose. Dose decreases after randomization are allowed.
Nerve block agents	4 weeks	Discontinue study medication
Local corticosteroid injections in the affected shoulder (until Week 24), alone or in conjunction with lidocaine	12 weeks and not more than 2 injections	Discontinue study medication[3]

Medication	Prohibition period (before randomization)	Action taken (post randomization)
Any immunomodulating biologic drugs, including but not limited to Tumor Necrosis Factor Alpha (TNFα) inhibitors or other biologic drugs targeting IL-17 or IL-17 receptor	Never[3]	Discontinue study medication
Any investigational treatment other than study medication or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	Discontinue study medication
Any other biologics	Any other biologics within 4 weeks or within 5 half-lives of the drug (whichever is longer)	Discontinue study medication
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents	Never	Discontinue study medication
Conventional Disease-modifying antirheumatic drugs (DMARD) (e.g., MTX) including apremilast, tofacitinib	Never	Discontinue study medication
Analgesics other than NSAIDs, paracetamol/paracetamol (acetaminophen) and low strength opioids PRN	2 weeks	Discontinue the prohibited medication. All medications must be recorded.
Topical NSAIDs or analgesics, such as Voltaren	2 weeks	Discontinue the prohibited medication. All medications must be recorded.
Medium to high potency opioids	12 weeks	Discontinue the prohibited medication. All medications must be recorded.
Systemic corticosteroids (including oral, intramuscular or i.v.)[1]	12 weeks	Discontinue study medication
Fluoroquinolone	6 months	Discontinue study medication
Shock wave therapy	12 weeks	Discontinue study medication
Live vaccinations[4]	6 weeks	Discontinue study medication
Platelet rich plasma injections in the affected shoulder	12 months	Discontinue study medication
Medication with ill-defined mechanism, e.g., traditional Chinese medicine, acupuncture, aryuvedic medicine, homeopathic medicines, herbal medicines, etc.	4 weeks	Discontinue study medication
Hyaluronic acid injections in the affected shoulder	12 weeks	Discontinue study medication
Oral or topical retinoids	12 weeks	Discontinue study medication

[1] Low- to mid-potency topical and inhaled corticosteroids are permitted.
[2] Period in weeks refers to prohibited period of medications during screening counted from BSL visit.
[3] Never = no prior exposure is allowed and medication is prohibited from study start and up to and including the follow-up visit
[4] The effect of secukinumab on live vaccines is unknown; therefore, live vaccines should not be administered from 6 weeks prior to baseline and until 12 weeks after the last study drug administration. Subjects receiving secukinumab may receive concurrent inactivated or non-live vaccinations, including those against COVID-19 (vaccines should be administered at least 48 h prior to any efficacy assessments in order to avoid confounding efficacy assessments due to, e.g., injection site pain).

6.8.3 Rescue medicine

Any changes to type of NSAID taken by the participant or any increase in NSAID dosages from stable dose established during run-in period are considered prohibited throughout the duration of the study.

If pain or discomfort is intolerable, participants may use non-NSAID medication including, for example, acetaminophen/paracetamol, low-dose opioids and tramadol (AxMPs) PRN. If the participant continues to experience intolerable pain or discomfort, then any increase to the dose of NSAID taken should be kept to an absolute minimum in terms of dosage and duration. Any changes to NSAID type and/or increase in dose will be recorded as a deviation to the protocol but would not result in withdrawal of the participant.

Decisions regarding medications for pain or increase in NSAID use as rescue medication should be made by the Investigator, based on local practice and individual participant needs. The maximum dose should not exceed the approved dose in each country.

[redacted]

6.8.4 Physiotherapy

Participants will be provided with a standard home-based physiotherapy exercise regimen from start of run-in period and until Week 24. An Exercise Manual for participants will be provided separately. Each participant will perform the same set of exercises. This will be recorded in a paper diary provided to the participant.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the End of Treatment, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of specified prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding

- AEs, abnormal laboratory values or abnormal test result that indicate a safety risk to the participant.
- Unsatisfactory therapeutic effect
- Participant's condition no longer requires study treatment
- Emergence of the following AEs:
  1. Any AE that in the judgement of the Investigator, taking into account the participant's overall status, prevents the participant from continuing study treatment.
  2. Any severe or serious AE that requires treatment with a prohibited medication
  3. Severe hypersensitivity reaction or anaphylactic shock (see Section 8.6.1)
- Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant's overall status prevents the participant from continuing participation in the study

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in Section 1.3 Schedule of Activities.

Participants who **agree to continue attending study** visits following treatment discontinuation should continue attending all subsequent scheduled site visits for clinical and safety study assessments until Week 24 End of Study visit. Participants initially continuing to attend site visits after premature study treatment discontinuation may subsequently decide to discontinue the study at any time.

Participants who **disagree to continue attending all remaining study** visits after prematurely discontinuing the study treatment (including those who initially continued to attend site visits but subsequently decided to discontinue the study) should perform an end of treatment visit, 4 weeks after their last study treatment administration (or as soon as possible upon the decision of study discontinuation if more than 4 weeks elapsed since last dose of study treatment). A corresponding end of study post-treatment safety follow up visit should be performed 12 weeks after the last administration of the study treatment (or as soon as possible, if more than 12 weeks elapsed since last dose of study treatment).

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

- New / concomitant treatments
- AEs / Serious Adverse Events

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

Participants who are prematurely withdrawn from the study will not be replaced.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

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 their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), 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.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to)

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment: If applicable, an End of Treatment visit and the safety follow-up period must be completed. 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 Novartis depending on local regulation will be responsible for informing Institutional Review Board (IRB)s/Independent Ethics Committee (IEC)s of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, or unscheduled safety assessments may be performed at the discretion of the investigator if there is a concern or need follow up for an AE.

8.1 Screening

Screening / run-in period

Following informed consent, a screening period of up to maximum of 56 days will be used to assess participant´s eligibility and to commence wash out period for prohibited medication(s). Participants must adhere to the requirements outlined in Section 6.8.2, which will otherwise result in screen failure. A run-in period is incorporated into the maximum of 56-day screening period from day -14 to day -1.

All screening assessments should be performed during the period preceding the start of the run-in, i.e., from Day -56 to -15.

If participants do not have bilateral shoulder X-rays available within 3 months of BSL, the X-rays (X-ray outside of the 3 month window) should be performed after it is certain the participant meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation.

A centrally read MRI within 3-months from baseline may be accepted if already performed.

During the 14-day run-in period prior to the BSL visit, the participant will need to have 14 days of stable NSAID intake (wherein they must adhere to the same dose of prescribed NSAID) and standardized physiotherapy.

In the case where a safety laboratory assessment at screening and/or 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 once if s/he fails the initial screening. Rescreened participants will receive a new participant number after they have re-consented. Shoulder X-rays and MRI would not need to be repeated, however if X-ray was historic they would need to be performed within 3 months of the new baseline visit.

Participants who are mis-randomized cannot be rescreened.

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

8.2 Participant demographics/other baseline characteristics

Participant demographic and BSL characteristics data to be collected on all participants and to be recorded in the eCRF include:

- Year of birth, sex, race, predominant ethnicity (if permitted); Participant's race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.
- Relevant medical history/current medical conditions (until date of signature of informed consent) will also be recorded in the CRF. Where possible, diagnoses, not symptoms, should be recorded.

- All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented in the Concomitant medications/ Significant non-drug therapies section of the CRF as outlined in Section 6.8.1.

Country-specific regulations should be considered for the collection of demographic and BSL characteristics in alignment with CRF.

Table 8-1 Eligibility assessments

Assessment	Description	Documentation
Shoulder X-Ray	To be performed in both shoulders (affected and contralateral) to exclude shoulder pathologies as per exclusion criteria (Section 5.2); historical shoulder X-rays are acceptable if obtained ≤3 months before BSL.	Source only
Shoulder MRI	Image analysis to be performed centrally to confirm evidence of tendinopathy and exclude other shoulder pathologies and tears (if present) >50% thickness and AP diameter >10mm; a centrally read MRI within 3 months from baseline may be accepted if already performed.	Database
Patient Reported Outcomes	To be performed to include participants experiencing moderate-severe symptoms based on WORC PRO and meeting specific pain criteria, as outlined in inclusion criteria (Section 5.1)	Database
Physical examination	See Section 8.4.1	Source only
Hematology, Clinical chemistry	via central laboratory	Database
RF/anti-CCP	via central laboratory; only performed at screening	Database
Tuberculosis test	QuantiFeron Gold	Database
Pregnancy and assessments of fertility	See Section 8.4.6	Database
Hepatitis B, C or HIV screening	Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed locally during screening period only if required as per local medical practice or local regulations prior to initiation of therapy. These assessments will be done by central laboratory if no accredited local laboratory is available, and will be documented in the source only.	Source only
Painful Arc test	Painful arc test will be performed at screening and BSL in order to assess eligibility for inclusion criteria 4 (nocturnal pain in shoulder on 3 out of 7 nights prior to BSL also accepted to fulfill this criterion if Painful Arc test is negative).	Database

8.2.1 Shoulder X-ray

An X-ray of the shoulder will be taken during Screening in order to rule-out other shoulder conditions, as outlined in Section 5.2. If a historic X-ray is available from within 3 months of BSL, then this will be accepted. It is recommended that the x-ray is performed in anterior-posterior and lateral planes in order to evaluate the shoulder.

8.2.2 Shoulder MRI

MRI images will be acquired at 1.5 T or greater in multiple planes by using an imaging sequence optimized for tendon/surrounding tissue separation and adapted to the MRI system capabilities. The MRI read should be performed centrally during the screening period. However, centrally read shoulder MRIs performed within 3 months of BSL may also be accepted (provided that

the quality of the images is deemed sufficient). Detailed information on the MRI procedure can be found in the imaging manual. The coded MRI medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.2.3 Tuberculosis screening

The QuantiFERON TB-Gold 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. The results must be known prior to randomization to determine the participant's eligibility for the study.

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
- if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated prior to enrollment.

Participants with indeterminate test result should repeat test once more as soon as possible. If subsequent test result is positive, further work up is required, as outlined above.

Any significant findings should be recorded in the eCRF.

8.2.4 Painful Arc test

The Painful Arc test will be performed at screening and BSL in order to assess eligibility as outlined in Section 5.1. The result will be reported as a negative or positive result, with a positive result indicated by participant expressing pain between 60-120°. The test should be performed in both shoulders, actively and passively.

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities. The following key [redacted] assessments are PROs and therefore described in Section 8.5.1:

- WORC Index
- [redacted]
- PROMIS-SF Upper Extremity
- [redacted]
- [redacted]
- [redacted]
- [redacted]

These will be collected on an electronic device that will be used at the participants' home and on site.

[redacted]

8.3.4 Appropriateness of efficacy assessments

The efficacy assessments selected are commonly used in studying this and similar indications.

8.4 Safety assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to the Section 8.6.

Evaluation of all AEs and SAEs including injection site reactions, physical examination, vital signs and laboratory assessments will occur. Anti-secukinumab antibody development (immunogenicity) will also be evaluated.

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.

- Physical examination
- Height and weight
- Vital signs
- Laboratory evaluations (Hematology, Clinical Chemistry)
- Evaluation of AE/SAEs
- Pregnancy
- Tolerability of secukinumab
- Immunogenicity

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (according to visit schedule or more frequently if needed) for

safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

The physical examination will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF that meet the definition of an AE must be recorded in the AE eCRF and if SAE criteria are met, also reported as a SAE.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

ROM assessments will be performed throughout the study to physically assess shoulder (see Section 8.3.1). Painful arc test will also be performed in order to assess eligibility (see Section 8.2.4)

8.4.2 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing) (both 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.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2

8.4.3 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the participant has been sitting for five minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, e.g., OMRON, with an appropriately sized cuff. 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.

If possible, vital sign assessments should be performed by the same study site staff member using the same validated device throughout the study.

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.

8.4.4 Electrocardiograms

Not applicable

8.4.5 Clinical safety laboratory tests

A central laboratory will be used for analysis of all blood specimens detailed in this section, unless otherwise specified. Samples will be collected according to the assessment schedule.

Details on the collections, shipment of samples, and reporting of results by the central laboratory will be provided to Investigators in the central laboratory manual.

Clinical site practice will be applied for point-of-care tests (urine pregnancy testing). Adequate documentation of these test results needs to be maintained in the participant's source documentation.

Clinically notable laboratory findings are defined in Section 10.3.

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 should be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-2 Laboratory assessments

Test Category	Test Name
Hematology	Erythrocyte Cell Morphology, Hemoglobin, Leukocytes, Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other *(absolute value and %)*)
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, Amylase, AST, Calcium, Creatinine, Direct Bilirubin, Glucose (non-fasting), Lactate dehydrogenase (LDH), Lipase, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin, Urea Nitrogen or Urea, Uric Acid,
Pregnancy Test	Serum / Urine pregnancy test (refer to 'Pregnancy testing', Section 8.4.6) Urine dipstick to be assessed locally.

8.4.6 Pregnancy testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Kits will be provided by the central laboratory. A serum β-hCG test will be performed in all women of childbearing potential at Screening. All pre-menopausal women who are not surgically sterile at Screening will have local urine pregnancy tests as indicated in Table 1-1. A positive urine pregnancy test requires immediate interruption of study treatment until an unscheduled serum β-hCG is performed and found to be negative. If positive, the participant must be discontinued from the trial. Additional pregnancy testing might be performed if requested per local requirements. Refer to Section 8.6.4 for details of reporting of pregnancy.

Effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2).

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can 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. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the Investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.7 Tolerability of investigational treatment

Tolerability will be assessed by adverse events, laboratory values, injection site reaction and immunogenicity.

The local tolerability at the site of s.c. injection of the study treatment will be assessed in case of any local reaction, until this has disappeared.

The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the appropriate CRF capturing AEs, including the severity (mild, moderate, severe) and the duration of the adverse reaction.

8.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

The following additional assessments to be performed are:

- Clinical Outcome Assessments (COAs)
  - Patient Reported Outcomes (PROs) to be performed on eDiary devices
  - Paper diary to record [redacted] physiotherapy
  - Clinician reported Outcomes (CROs)
  - Trial Feedback Questionnaires (TFQs)

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, COA data may be collected remotely (e.g., web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Patient reported outcomes (PRO)

PROs will be completed at the scheduled visits as outlined in Table 1-1 using an electronic device. Please note that all scoring calculations will be performed electronically by the device and scores required for inclusion to study will be available for review by the Investigator.

Site and participants will receive appropriate training and guidance on the use of the electronic device and will receive clear instructions on the completion of the assessments.

All questionnaires will be available in the local languages of the participating countries.

Participants should complete the PRO measures before any clinical assessments are performed at a given visit. Participants will be given sufficient instruction, space, time and privacy to complete all study PROs. The study coordinator will check the responses to the questionnaire for completeness and encourage the participant to complete any missing responses. If participants have trouble with submission after they complete the PROs, the study staff will assist them with submitting their PRO responses. Attempts should be made to collect responses to all PROs for all participants, including participants who prematurely discontinue the study prior to the end of treatment visit. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system/study source records and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Exceptionally, if there is an issue with the electronic device, there will be a web-based alternative.

The participant should be made aware that completed measure(s) are not reviewed by the Investigator/study personnel and that they should report any discomfort, unusual symptoms or medical problems directly to the Investigator/ study personnel, according to the ICF. A reminder should be implemented in ePRO with the support of External Development Operations.

The following instruments will assess the impact of RCT on various aspects of participant's physical function, pain, and health-related quality of life (QoL):

The Western Ontario Rotator Cuff Index (WORC)

The WORC is a patient reported outcome tool, uniquely developed for rotator cuff conditions by Kirkley and co-workers (Kirkley et al 2003). The WORC is self-administered and consists of 21 items divided into five domains: Physical Symptoms (6 items); Sport/Recreation (4 items); Work Function (4 items); Lifestyle Function (4 items) and Emotional Function (3 Items) [redacted]

For ease of interpretation and in accordance with recommendations from instrument authors (Kirkley et al 2003), the WORC score will be calculated for the total score as well as the five domains.

WORC Total (all domains) will be collected at scheduled visits on site where WORC is indicated in Table 1-1.

WORC Physical Symptoms Domain

Change in the Physical Symptom sub-domain of the WORC PRO is the primary endpoint for the main study objective and will be used to demonstrate the effect of study drug on improving physical symptoms caused by RCT. The WORC PSD comprises 6 questions (with a maximum score of 60 [redacted] possible) that capture the key symptoms experienced by participants with RCT relating to pain, weakness, stiffness, and mechanical symptoms. A score of 0 is the best outcome in terms of physical symptoms and a score of 60 is the worst possible score. For the Primary Endpoint there is a separate questionnaire in the e-diary which is completed by the participant at home inclusive of the questions in the PSD. [redacted]

Pain Numeric Rating Scale (NRS)

The pain NRS is a single 11-point numeric scale with 0 representing "no pain" and 10 representing "worst possible pain". Participants will be asked to report pain severity in the eDiary every day during the 7 days prior to a visit (but not including day of visit) where indicated in Table 1-1 using the pain NRS [redacted]

Patient Reported Outcomes Measurement Information System (PROMIS)-Short Form (SF) Upper Extremity

PROMIS-SF Upper Extremity measures self-reported capability of Physical Function. Participants will complete this questionnaire on site and will be asked a series of 7 questions rating their ability to perform a range of physical activities related to daily life that would be impacted by shoulder function. Each response is scored from 5 (Without any difficulty) to 1 (Unable to do). The 7 scores are added to give a total score out of 35. The lowest possible raw score is 5; the highest possible raw score is 35. Total raw score will be translated into a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. There is no recall period for this questionnaire.

If in the case where the PROMIS-SF Upper Extremity PRO is not available in any particular country's language, participants from that country may still be enrolled and participate in the study without needing to complete the questionnaire. As soon as the PRO is available in that country's language and has received the necessary local regulatory approvals for implementation, it should become available on the device and the participants should commence completing the questionnaire.

[redacted]

[redacted]

8.5.1.2 Participant diary

Participants will be asked to complete an e-diary and paper diary during the periods outlined in Table 1-1.

E-Diary

The e-diary will be given to all participants at Screening. They will complete entries at home starting during the run-in period.

[redacted]
and other indicated visits (see below for further details regarding schedule of recording data and Table 1-1 and Figure 8-1).

The device will remind the participants to complete the questions; however, the site staff must make a telephone call to each participant at the start of the run-in period (two weeks prior to their scheduled BSL visit) to remind them to charge and switch on the device, and to [redacted], in order for the respective inclusion criteria to be evaluated on the day of the BSL visit. **Therefore, it is extremely important that participants adhere to entering in the data prior to BSL.** [redacted] Site will also contact the participant on the day before they are due to start filling in information into the e-diary in order to remind them to ensure compliance.

Participants must bring their e-diaries with them to every scheduled visit. The participant e-diary will be checked by a designated study staff member at each visit; in case of an incomplete e-dairy entry, the study site staff will counsel the participant on the correct use and frequency of the participant e-diary.

Entries starting during the run-in period prior to the scheduled BSL visit and continued throughout study:

WORC Physical Symptoms Domain.

Participants will record their responses to the WORC PSD questionnaire [redacted] the scheduled BSL visit and visits indicated, and every visit capturing WORC data as indicated in Table 1-1. [redacted]. These data should be recorded ideally in the evening.

[redacted]

[redacted]

[redacted]

8.5.1.3 Clinician reported outcomes (CROs)

The impact of RCT on participants' condition will be assessed by the following measures:

[redacted]

8.5.1.4 Trial Feedback Questionnaires

By participating in the clinical trial, participants will be invited to respond in TFQs for feedback about the trial experience, as appropriate and in adherence to local regulations and guidelines. Individual trial participant responses will not be reviewed by Investigators. Responses may be used by Novartis to understand where improvements can be made in the clinical trial process. This feedback asks questions about trial experience. It does not ask questions about the trial

participant's disease, symptoms, treatment effect, or adverse events, and, therefore is not considered as trial data.

TFQs are not considered study data and will be received electronically outside the clinical database.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of AEs and SAEs can be found in Section 8.6.1 and Section 8.6.2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

The occurrence of adverse events can 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 examinations findings, laboratory test findings, or other assessments.

8.6.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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 (e.g., participant reported outcomes as described in Section 8.5.1).

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 8.6.2):

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 must be reported.
4. Whether it constitutes a SAE (see *Section 8.6.2* 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:
   - Dose not changed
   - Drug interrupted/withdrawn
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 not recovered/not resolved (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.

Additional information for potential cases of anaphylaxis should be collected, in accordance with the clinical criteria for diagnosis of potential cases of anaphylaxis as discussed in the statement paper from the Second Symposium on the Definition and Management of Anaphylaxis (Sampson et al 2006Sampson et al 2006) and is presented below.

Anaphylaxis is highly likely when one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips tongue uvula) AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (e.g., dyspnea, wheeze bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin mucosal tissue (e.g., generalized hives, itch flush, swollen lips tongue uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Information about adverse drug reactions for the investigational drug can be found in the 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 Baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying adverse events. Clinically notable laboratory values are outlined in Section 10.3.1.

8.6.2 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 conditions(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, fetal death or a congenital abnormality or birth defect

- requires inpatient 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 outpatient 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 and the malignant neoplasm is not a disease progression of the study indication.

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

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 12 weeks after last study dose must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Any SAEs experienced after the 12 week period after last study dose should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Screening and run-in failure participants

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

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 immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the participant continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and 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 national regulatory requirements in participating countries.

8.6.4 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of study participation (or longer depending on local contraceptive requirements, as outlined in Section 5.2).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is

necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant 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 pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable

8.6.6 Adverse events of special interest

Not applicable

8.7 Pharmacokinetics

PK samples will be collected at the visits defined in Section 1.3. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PK samples will be obtained and evaluated in all participants at all dose levels except the placebo group (collected and analyzed only if as needed).

The anticipated Lower Limit of Quantification (LLOQ) is 200 ng/mL.

Concentrations will be expressed in mass per volume units.

Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

For standard pharmacokinetic abbreviations and definitions see the list provided in the appendices of this protocol.

The following pharmacokinetic parameter will be determined using the actual recorded sampling times with Phoenix WinNonlin (Version 6.4 or higher): minimal concentration per dosing interval (Cmin).

[redacted]

- [redacted]

[redacted]

[redacted]

8.9 Immunogenicity assessments

Immunogenicity (IG) samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

In case of suspected allergic hypersensitivity, the participant should return to the site and a sample to assess immunogenicity will be collected.

Anti-secukinumab-antibodies will be evaluated in serum samples collected from all participants according to Section 1.3 Schedule of Activities. Additionally, serum samples should also be collected at the end of treatment visit from participants who discontinued study treatment or were withdrawn from the study.

Serum samples will be screened for anti-secukinumab-antibodies and the titer of confirmed positive samples will be reported. The neutralizing capacity of anti-secukinumab-antibodies will be evaluated in positive samples to further characterize the immunogenicity of secukinumab.

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken at the scheduled time points as indicated in SoA.

The actual sample collection date and exact time will be entered on the Immunogenicity blood collection eCRF page. All blood samples will be taken by direct venipuncture.

8.9.1 Immunogenicity blood sample collection and handling

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

8.9.2 Immunogenicity analytical method(s)

An electrochemiluminescence based method will be used for the detection of potential anti-secukinumab antibody formation. Confirmed immunogenicity positive samples may be further analyzed for presence of neutralizing antibodies using a validated method.

The detailed methods for immunogenicity assessment will be described in the Bioanalytical Data Report.

8.10 Health economics

Refer to Section 8.5.1 for details on COA assessments.

9 Statistical considerations

The primary endpoint analysis will be performed after all participants complete Week 16 as described in Section 9.3 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 categorical or binary variables, the number and percent of participants in each category will be presented.

The efficacy evaluation of secukinumab relative to placebo will generally focus on the 16-week treatment period except for two Week 24 endpoints that will be tested based on the Week 24 data available at the Week 16 DBL (see Section 9.4.1 for details).

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.

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

- Secukinumab 300 mg regimen
- Placebo regimen

9.1 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.

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.

9.2 Statistical analyses

9.2.1 General considerations

The analyses will be conducted on all participant data at the time when the primary analysis is performed and at the time the trial ends.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Summary statistics for discrete variables will be presented in the number and percent of participants in each category.

Unless otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

Data analyses will be presented by treatment regimen. Efficacy and safety data for the treatment period (or the entire treatment period as appropriate) will be presented by the following 2 treatment groups:

- Secukinumab 300 mg s.c. at BSL, Week 1, 2, 3, 4, 8, and 12
- Placebo s.c. at BSL, Week 1, 2, 3, 4, 8, and 12

9.2.2 Participant demographics and other baseline characteristics

Demographic and other BSL data including disease characteristics will be listed and summarized descriptively by treatment group for all participants in the randomized set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

The following common background and demographic variables will be summarized by treatment group:

- Sex, age, race, ethnicity, weight, height, and BMI.

BSL disease characteristics will also be summarized for the following variables:

- Time since first diagnosis of RCT (weeks), WORC total score, WORC PSD score, [redacted], PROMIS-SF Upper Extremity score, [redacted] affected arm (Dominant arm/Non-dom [redacted] ion during screening (Yes/no).

Relevant medical histories and current medical conditions at BSL will be summarized separately by system organ class and preferred term, by treatment group.

9.2.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of visits with active and placebo s.c. 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 week, ≥ 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 Medical dictionary for regulatory activities (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 RCT 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 RCT therapies previously. [redacted]

9.3 Primary endpoint(s)/estimand(s) analysis

9.3.1 Definition of primary endpoint(s)

The primary efficacy variable is the change from BSL in the WORC PSD score at Week 16 in participants with moderate to severe RCT.

The analysis of the primary variable will be based on the FAS participants.

9.3.2 Handling of intercurrent events of primary estimand (if applicable)

The primary analysis will account for the different intercurrent events as explained in the following:

- Discontinuation of study treatment due to any reason (including AE and lack of efficacy): data collected after treatment discontinuation will be used for the primary analysis
- Prohibited medication: data collected after taking prohibited medication will be used for the primary analysis
- Rescue medication: data collected after taking rescue medication will be used for the primary analysis

9.3.3 Statistical model, hypothesis, and method of analysis

The statistical hypothesis being tested is that there is no difference in the secukinumab 300 mg s.c. regimen versus placebo regimen in the mean change from BSL in the WORC PSD score at Week 16.

Let μ_0 denote mean change from BSL in the WORC PSD score at Week 16 for placebo regimen and μ_1 denote the mean change from BSL in the WORC PSD score at Week 16 for secukinumab 300 mg s.c. regimen.

In statistical terms, H_1: $\mu_1 = \mu_0$, H_{A1}: $\mu_1 \neq \mu_0$, i.e.,

H_1: secukinumab 300 mg s.c. regimen is not different to placebo regimen with respect to the mean change from BSL in the WORC PSD score at Week 16

The primary analysis will be conducted via mixed-effects model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption. Treatment group, stratification factor (tear status) and analysis visit will be included as categorical factors and BSL WORC PSD score and BSL weight as continuous covariates. Treatment by analysis visit and BSL WORC PSD score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

9.3.4 Handling of missing values not related to intercurrent event

The MMRM model implicitly imputes missing data under the MAR assumption.

9.3.5 Multiplicity adjustment (if applicable)

Details of the testing strategy including primary and secondary endpoints are provided in Section 9.4.1.

9.3.6 Sensitivity analyses

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 handling of missing data.

The same analysis of covariance (ANCOVA) model as for the primary estimation will be adopted. The impact of missing data on the analysis results of change from BSL in the WORC PSD score will be imputed by multiple imputation (MI) under the assumption of MAR.

9.3.7 Supplementary analysis

The target population, the primary variable and the summary measure of the supplementary estimand are the same as for the primary estimand. Supplementary estimands using hypothetical strategy for discontinuation of study treatment due to AEs or lack of efficacy and use of rescue treatment is included in analysis plan because treatment discontinuation due to AEs or lack of efficacy and administration of rescue medication, i.e., steroid injection locally, may confound the outcome when treatment policy is used (in primary analysis). Differently from the primary estimand, the intercurrent events will be handled as follows:

- Discontinuation of study treatment due to AEs or lack of efficacy: had participants taken the assigned treatment for the entire study duration (hypothetical strategy)
- Discontinuation of study treatment due to any reason (except for AE or lack of efficacy): if participants discontinue study treatment due to any reason (except for AE or lack of efficacy), the event will be ignored (treatment policy)
- Prohibited medication: if participants receive prohibited medication without study treatment discontinuation, the event will be ignored (treatment policy).
- Rescue medication: had rescue medication not occurred (hypothetical strategy)

The same MMRM will be used to impute the missing data.

9.4 Secondary endpoint(s)/estimand(s) analysis

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

Two studies of identical design (CAIN457O12301 and CAIN457O12302) are planned, each with multiple endpoints. The primary endpoint and secondary endpoints will be tested in each of the two studies separately. Secondary endpoints at Week 24 will be tested using participants who have reached Week 24 at the time of the Week 16 DBL. In order to control for the type I error rate ('false positive rate') at the level of the individual studies, the testing strategy illustrated in Figure 9-1 below will be implemented. The full alpha=0.05 will be spent at the Week 16 primary analysis. [redacted]

The following null hypotheses will be included in the testing strategy:

Primary objective:

H_1 : secukinumab 300 mg + SoC is not different to placebo + SoC with respect to change from BSL in the WORC PSD score at Week 16

Secondary objectives:

H_2 : secukinumab 300 mg + SoC is not different to placebo + SoC with respect to proportion of participants achieving an increase of at least 40 points from BSL in the WORC PSD score at Week 16

H_3 : secukinumab 300 mg + SoC is not different to placebo + SoC with respect to proportion of participants achieving an increase of at least 50 points from BSL in the WORC total score at Week 16

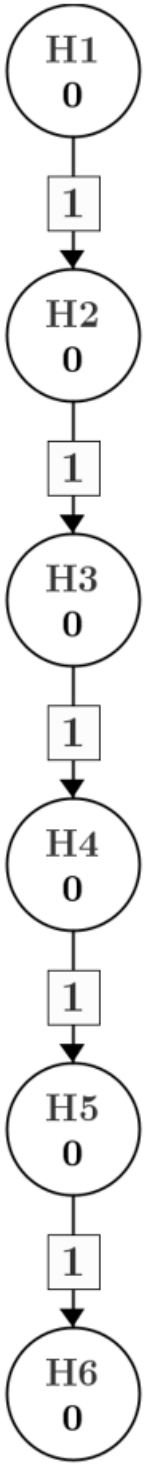
H_4 : secukinumab 300 mg + SoC is not different to placebo + SoC with respect to change from BSL in the PROMIS-SF Upper Extremity score at Week 16

H_5: secukinumab 300 mg + SoC is not different to placebo + SoC with respect to proportion of participants achieving an increase of at least 40 points from BSL in the WORC PSD score at Week 24

H_6: secukinumab 300 mg + SoC is not different to placebo + SoC with respect to change from BSL in the WORC PSD score at Week 24

The family-wise Type I error will be set to α=5% for each study (CAIN457O12301 and CAIN457O12302) separately and it will be controlled with the proposed sequential testing strategy as described in Figure 9-1. The primary hypothesis (H_1) for the primary objective for secukinumab regimen versus placebo will be tested at α-level. If the hypothesis H_1 is rejected then the whole α will be passed to the next hypothesis (H_2) which will be tested at α-level. This procedure will continue (pending rejection of the null hypotheses) until H_6 is rejected. Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however, the level of a rejected hypothesis is only passed on according to the sequence for the test of another hypothesis if the treatment effect is in favor of secukinumab.

Figure 9-1 Testing strategy



Response in WORC PSD at Week 16

Proportion of participants achieving an increase of at least 40 points from BSL in the WORC PSD score at Week 16 will be evaluated using a logistic regression model with treatment group and stratification factor (tear status) as factors and BSL score and BSL weight as covariates.

Response in WORC Total at Week 16

Proportion of participants achieving an increase of at least 50 points from BSL in the WORC total score at Week 16 will be evaluated using a logistic regression model with treatment group and stratification factor (tear status) as factors and BSL score and BSL weight as covariates.

Change from Baseline in PROMIS-SF Upper Extremity score at Week 16

Between-treatment differences in the change from BSL in the PROMIS-SF Upper Extremity score will be evaluated using MMRM with treatment group, stratification factor (tear status) and analysis visit as factors and BSL PROMIS-SF Upper Extremity score and BSL weight as continuous covariates. Treatment by analysis visit and BSL PROMIS-SF Upper Extremity score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

Response in WORC PSD at Week 24

Proportion of participants achieving an increase of at least 40 points from BSL in the WORC PSD score at Week 24 based on the Week 24 data available at the Week 16 DBL will be evaluated using a logistic regression model with treatment group and stratification factor (tear status) as factors and BSL score and BSL weight as covariates.

Change from Baseline in WORC PSD score at Week 24

Between-treatment differences in the change from BSL in the WORC PSD score at Week 24 based on the Week 24 data available at the Week 16 DBL will be evaluated using MMRM with treatment group, stratification factor (tear status) and analysis visit as factors and BSL WORC Physical Symptoms score and BSL weight as continuous covariates. Treatment by analysis visit and BSL WORC PSD score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

9.4.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of BSL data which will also be summarized where appropriate (e.g., change from BSL summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 84 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on AEs will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment-emergent AEs (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 in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related AEs, death, serious AEs, other significant AEs leading to discontinuation, and AEs leading to dose adjustment.

The number (and proportion) of participants with AEs of special interest/related to identified and potential risks will be summarized by treatment.

If a participant reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a participant reported more than one AE 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 AEs will also be summarized.

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

Separate summaries will be provided for death, serious AE, other significant AEs leading to discontinuation and AEs 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.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

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.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group, and visit/time. 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.

Immunogenicity

All immunogenicity results will be listed by treatment group, participant, and visit/time.

9.4.3 Pharmacokinetics

Secukinumab serum concentration data will be listed by treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the Lower Limit of Quantification (LLOQ) and reported as zero.
Summary statistics will include mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters. No pharmacokinetic parameters will be calculated in this study as sparse sampling does not allow valid estimation by non-compartmental analysis.
Modeling of the data may be performed as appropriate. During modeling of the pharmacokinetics of the study drugs, the broad principles outlined in the 'Food and Drug Administration (FDA) Guidance for Industry: Population Pharmacokinetics' will be followed. As the PK data from the current study may be pooled with data from previous studies, the PK modeling will be described and reported separately.

9.4.4 Patient reported outcomes

WORC Total

The average of the non-missing items will be used to calculate the raw domain score where there are two or fewer missing items for the physical symptoms domain and one or fewer missing items for each of the sports/recreation, work, lifestyle, and emotions domains. Each domain raw score will be computed by summing the non-missing item scores, dividing by the number of non-missing items and multiplying by the total number of items in the scale. For the WORC score to be derived, scores for all five domains need to be present. Specifically, for each the raw aggregate score, the total is subtracted from the maximum score and divided by the number of items, resulting in a scale of 0 to 100, where 0 represents the most symptomatic score and 100 represents no symptoms:

[redacted]

See Section 9.4.1 Efficacy and/or Pharmacodynamic endpoint(s) for details.

WORC Physical Symptom domain

In line with WORC Total analysis, the data are converted to a percent score by inverting the raw score and then converting to a score out of 100 (Kirkley et al 2003). [redacted]

The following variables will be evaluated:

- WORC PSD score: see Section 9.3 Primary endpoint(s)/estimand(s) analysis for details.
- Response in WORC PSD: see Section 9.4.1Efficacy and/or Pharmacodynamic endpoint(s) for details.

PROMIS-SF Upper Extremity score

See Section 9.4.1Efficacy and/or Pharmacodynamic endpoint(s) for details.

[redacted]

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

[redacted]

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

[redacted]

9.6 (Other) Safety analyses

Not applicable

9.7 Other analyses

Not applicable

9.8 Interim analysis

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 Investigator, site personnel, persons performing the assessments and participants will continue to remain blinded to the original treatment assignment that each participant received at randomization until after the DBL for Week 24 analysis. At the time of the Week 16 DBL, the Week 24 secondary endpoints will be evaluated in participants who have already reached Week 24. The full alpha=0.05 will be spent at the Week 16 DBL. [redacted]

Subsequent to the primary endpoint analysis, the final CSR analysis is planned after participants have completed the Week 24 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.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

An overall type I error (2-sided) of 5% will be used to control type I error. Secukinumab 300 mg s.c. will be tested versus placebo with respect to the primary endpoint (change from BSL in the WORC PSD score at Week 16). A sample size of 117 participants per group is deemed appropriate to achieve adequate power for the primary and secondary endpoints for this study.

The mean changes from BSL in the WORC PSD score at Week 12 for secukinumab 300 mg s.c. and placebo are 45.3 (SD = 25.64) and 28.5 (SD = 28.81), respectively; while the mean changes from BSL in the WORC PSD score at Week 14 for secukinumab 300 mg s.c. and placebo are 47.9 (SD = 24.47) and 35.1 (SD = 27.78), respectively, in participants with moderate to severe RCT based on data from the POC study (safety set). With 117 participants per treatment group, there would be approximately 95% power to detect a treatment difference of 14 with a SD of 30 in the mean change from BSL in the WORC PSD score between secukinumab and placebo in the evaluation of the primary efficacy hypothesis at Week 16 (two sample z-test, nQuery 8.4). The overall sample size will be 234 participants for a randomization ratio of 1:1.

9.9.2 Secondary endpoint(s)

The estimated power with the chosen sample size based on data from the POC study are summarized in Table 9-1 and Table 9-2.

Table 9-1 Summary of power for continuous secondary endpoints

Endpoint	Mean difference	SD	Power
PROMIS-SF Upper Extremity[1] at Week 16	1.2	3	84%
WORC PSD at Week 24[2]	14	30	85%

[1] Considering the missing data due to potential PROMIS-SF Upper Extremity translation issues in China , N = 110 per treatment group was used for the power calculation.

[2] Assuming 70% participants will complete Week 24 or discontinue early at the Week 16 DBL, the sample size will be 164 (N = 82 per treatment group).

Table 9-2 Summary of power for binary secondary endpoints

	Response Rate		
Endpoint	Secukinumab (N=117)	Placebo (N=117)	Power
WORC-PSD40[1] at Week 16	60%	35%	97%
WORC-TOT50[2] at Week 16	50%	25%	97%
WORC-PSD40[1] at Week 24[3]	60%	35%	87%

[1] WORC-PSD40: Proportion of participants achieving an increase of at least 40 points from BSL in WORC PSD score

[2] WORC-TOT50: Proportion of participants achieving an increase of at least 50 points from BSL in WORC total score

[3] Assuming 70% participants will complete Week 24 or discontinue early at Week 16 DBL, the sample size will be 164 (N = 82 per treatment group).

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing 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

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

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 or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center. 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. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant. Participants who are re-screened are required to sign a new ICF. Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. If applicable, in cases where the participant'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 level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document. Information about common side effects already known about the investigational treatment can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also 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. The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

[redacted]

[redacted]

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

The study includes the option for the participant to perform self-administration of study drug at Week 1 and Week 3, if the Investigator agrees, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

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.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Steering Committee

The Steering Committee (SC) will be established comprising Investigators in the trial and Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in the SC charter.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Data not requiring a separate written record will be defined in the protocol and Section 1.3 Schedule of Activities and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source

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

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC (Electronic Data Capture) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (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.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) 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 treatments 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 and adverse events will be coded using the MedDRA terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as 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 (or a designated CRO) 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 and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in the Source Data Agreement Form.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in European Clinical Trials Database (EudraCT) or Clinical Trials Information System (CTIS) public website. In addition, after study completion (defined as last patient last visit) 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, EudraCT, CTIS public website etc.).

For details on the Novartis publication policy including authorship criteria, refer to the Novartis publication policy training materials that were provided at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

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.

10.1.8.1 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 authorities 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.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse Event
AIIRD	autoimmune inflammatory rheumatic diseases
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
Anti-CCP	Anti-cyclic citrullinated peptide
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AxMP	Auxiliary Medicinal Product
BMI	Body Mass Index
BP	Blood Pressure
BSL	Baseline
CIOMS	Council for International Organizations of Medical Sciences
cm	centimeters
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
COX-2	cyclooxygenase-2
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CROs	Clinician Reported Outcomes
CSR	Clinical study report
CTIS	Clinical Trials Information System
CV	coefficient of variation
DBL	Database Lock
dL	decilitre
DMARD	Disease-modifying antirheumatic drugs
[redacted]	[redacted]
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
EOT	End Of Treatment
[redacted]	[redacted]
ERA	Enthesitis-related Arthritis
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full analysis set

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GVP	Good Pharmacovigilance Practices
h	Hour
HA	Health Authorities
HBV	Hepatitis B Virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
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
IG	Immunogenicity
IL	Interleukin
IMP	Investigational Medicinal Product
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
kg	kilogram
LDH	lactate dehydrogenase
LEI	Leeds Enthesitis Index
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPLV	Last Patient Last Visit
MAR	missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Multiple Imputation
mL	milliliter(s)
MMRM	Mixed-effects Model Repeated Measures
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
MTX	Methotrexate
NPF	National Psoriasis Foundation
nr-AxSpA	non-radiographic Axial Spondyloarthritis
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	Pharmacodynamic(s)

PEF	Peak Expiratory Flow
PFS	pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PMR	Polymyalgia Rheumatica
PoC	Proof of Concept
PRN	Pro Re Nata (as needed)
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
PRP	Platelet Rich Plasma
PsA	Psoriatic Arthritis
PSD	Physical Symptoms domain
PTY	Patient-Treatment Years
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Rotator Cuff Tendinopathy
RF	Rheumatoid factor
ROM	Range of Motion
s.c.	subcutaneous
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
SC	Steering Committee
SD	standard deviation
SF	Short Form
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standardized MedDRA Query
SoA	Schedule of Activities
SoC	Standard of Care
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TFQ	Trial Feedback Questionnaire
TNF-α	Tumor Necrosis Factor Alpha
ULN	upper limit of normal
US	United States
VAS	Visual Analog Scale
WBC	white blood cell(s)
WHO	World Health Organization
WORC	Western Ontario Rotator Cuff Index
[redacted]	[redacted]

10.2.2 Definitions

Additional study 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
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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
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
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
Remote	Describes any trial activities performed at a location that is not the investigative site.
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
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
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
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	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values

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

Clinically notable values will be forwarded to Novartis at the same time that they are sent to Investigators.

Any action based on these laboratory values should be discussed with Novartis personnel.

No specific action is pre-defined within this protocol in response to specific abnormal laboratory values; any action taken will be at the discretion of the Investigator or treating physician, taking into account the overall status and medical history of the participant.

Liver Function

ALT: > 3 x ULN

AST: > 3 x ULN

Alkaline phosphatase (ALP): > 2.5 x ULN

Total bilirubin: > 2 x ULN

Renal Function

Creatinine: > 2 x ULN

Hematology

Hemoglobin: ≥ 2 g/dl decrease from baseline

Platelet count: <100x10E9/L

White blood cell count: < 0.8 x LLN

Neutrophils: < 0.9 x LLN

10.4 Appendix 4: Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Trial Feedback Questionnaires - end of trial
- Patient expert engagement (indication agnostic)

10.5 Appendix 5: Liver safety monitoring

To date, there has been no safety signal for liver toxicity with secukinumab in over 29,000 subjects who received at least one dose of secukinumab in a clinical trial (IB Ed 22). From a mechanism of action standpoint there is no known effect of blocking IL-17A on the liver.

Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned.

All participants with laboratory tests resulting in clinically significant abnormal values (see Section 10.3 for notable laboratory values) are to be followed as per Investigator's discretion until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

10.6 Appendix 6: Renal safety monitoring

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 29,000 subjects who received at least one dose of secukinumab in a clinical trial (IB Ed 22). From a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney.

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.

All participants with laboratory tests resulting in clinically significant abnormal values (see Section 10.3 for notable laboratory values) are to be followed as per Investigator's discretion until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

11 References

References are available upon request

Andres BM, Murrell GAC (2008) Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res;466(7):1539-54.

Benjamin M, McGonagle D (2009) The enthesis organ concept and its relevance to the spondyloarthropathies. Adv Exp Med Biol 57-70.

Chard MD, Cawston TE, Riley GP, et al (1994) Rotator cuff degeneration and lateral epicondylitis: a comparative histological study. Ann Rheum Dis; 53(1):30-4.

Chioato A, Noseda E, Stevens M, et al (2012) Treatment with the interleukin-17A-blocking antibody secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in healthy subjects: results of an open-label, parallel-group, randomized single-center study. Clin Vaccine Immunol; 19(10):1597-602.

Consigliere P, Haddo O, Levy O, et al (2018) Subacromial impingement syndrome: management challenges. Orthop Res Rev; 10:83-91.

Dougados M, Simon P, Braun J, et al (2011) ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis; 70(2):249-51.

Falgarone G, Zerkak D, Bauer C, et al (2005) How to define a Minimal Clinically Individual State (MCIS) with pain VAS in daily practice for patients suffering from musculoskeletal disorders. Clin Exp Rheumatol; 23(2):235-8.

Furer V, Eviatar T, Zisman D, et al (2021) Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis; 80(10):1330-1338.

Gracey E, Burssens A, Cambré I, et al (2020) Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. Nat Rev Rheumatol; 16:193-207.

Harrington JT (2009) The uses of disease activity scoring and the physician global assessment of disease activity for managing rheumatoid arthritis in rheumatology practice. J Rheumatol; 36(5):925-9.

Jensen MP, Tomé-Pires C, de la Vega R, et al (2017) What Determines Whether a Pain is Rated as Mild, Moderate, or Severe? The Importance of Pain Beliefs and Pain Interference. Clin J Pain; 33(5):414-21.

Kirkley A, Alvarez C, Griffin S (2003) The development and evaluation of a disease-specific quality-of-life questionnaire for disorders of the rotator cuff: The Western Ontario Rotator Cuff Index. Clin J Sport Med; 13(2):84-92.

Klatte-Schulz F, Pauly S, Scheibel M, et al (2012) Influence of age on the cell biological characteristics and the stimulation potential of male human tenocyte-like cells. Eur Cell Mater; 24:74-89.

Lin MT, Chiang CF, Wu CH, et al (2019) Comparative Effectiveness of Injection Therapies in Rotator Cuff Tendinopathy: A Systematic Review, Pairwise and Network Meta-analysis of Randomized Controlled Trials. Arch Phys Med Rehabil; 100(2):336-49.e15.

Lipman K, Wang C, Ting K, et al (2018) Tendinopathy: injury, repair, and current exploration. Drug Des Devel Ther; 591-603.

McGeachy MJ, Cua DJ, Gaffen SL (2019) The IL-17 Family of Cytokines in Health and Disease. Immunity; 50:892-906.

McInnes IB, Behrens F, Mease PJ, et al (2020) Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet; 395(10235):1496-505.

Millar NL, Akbar M, Campbell AL, et al (2016) IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy. Sci Rep; 6:27149.

Millar NL, Akbar M, Weber E, et al (2018) Interleukin 17A– a Translational Target to Treat Supraspinatus Tendinopathy. Arthritis Rheumatol; abstract 404:70 (suppl 10).

Millar NL, Mcinnes I, Mindeholm L, et al (2021) EFFICACY AND SAFETY OF SECUKINUMAB IN PATIENTS WITH ROTATOR CUFF TENDINOPATHY: A 24-WEEK, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE II PROOF-OF-CONCEPT TRIAL. Annals of the Rheumatic Diseases; abstract POS0020, 80(Suppl 1):211.2-2

Millar NL, Murrell GA, McInnes IB (2017) Inflammatory mechanisms in tendinopathy - towards translation. Nat Rev Rheumatol;13:110-122.

Mohamadi A, Chan JJ, Claessen FM, et al (2017) Corticosteroid Injections Give Small and Transient Pain Relief in Rotator Cuff Tendinosis: A Meta-analysis. Clin Orthop Relat Res; 475(1):232-43.

Orbai AM, McInnes IB, Coates LC, et al (2020) Effect of Secukinumab on the Different GRAPPA-OMERACT Core Domains in Psoriatic Arthritis: A Pooled Analysis of 2049 Patients. J Rheumatol; 47(6):854-64.

Reilly MC, Zbrozek AS, Dukes EM (1993) The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics; 4(5):353-65.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol; 117(2):391-7.

Schett G, Baraliakos X, Van den Bosch F, et al (2021) Secukinumab Efficacy on Enthesitis in Patients With Ankylosing Spondylitis: Pooled Analysis of Four Pivotal Phase III Studies. J Rheumatol; 48(8):1251-58.

Watad A, Cuthbert RJ, Amital H, et al (2018) Enthesitis: Much More Than Focal Insertion Point Inflammation. Curr Rheumatol Rep; 20:41.

Weber S, Chahal J (2020) Management of Rotator Cuff Injuries. J Am Acad Orthop Surg; 28(5):e193-e201.

Wolfe MM, Lichtenstein DR, Singh G (1999) Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med; 340(24):1888-99.

Zbojniewicz AM, Maeder ME, Emery KH, et al (2014) Rotator cuff tears in children and adolescents: experience at a large pediatric hospital. Pediatr Radiol; 44(6):729-37.