Novartis Research and Development

Clinical Trial Protocol Title:

A randomized, double-blind, placebo-controlled, parallel group, multicenter, 24-week study investigating the efficacy and safety of secukinumab compared to placebo in adult patients with moderate to severe rotator cuff tendinopathy and failure to conventional therapy "UnchAIN"

Clinical Trial Protocol Number: CAIN457FDE05 / NCT05569174

Version Number: 02 (Amended Protocol)

Compound: AIN457 / Secukinumab

Brief Title: Study of efficacy and safety of AIN457/secukinumab in patients with rotator cuff tendinopathy

Study Phase: IIIb

Acronym: UnchAIN

Sponsor Name: Novartis Pharma GmbH

Regulatory Agency Identifier Number(s): 2022-001516-26 EudraCT

Release Date: 10-Jul-2024

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 8.6.3 of the Clinical Trial Protocol for SAE criteria and additional requirements. Complete SAE report

- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO & PS) without undue delay, but under no circumstances later than within 24 hours
- Notify the Novartis Medical Lead

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Amendment 2 (10-JUL-2024)

Amendment rationale

Protocol amendment 2 is implemented as screening for the CAIN457FDE05 study has been discontinued on 17-MAY-2024 due to the early termination of Secukinumab Phase 3 trials in RCT (Rotator Cuff Tendinopathy).

The study is currently ongoing and 63 participants have been randomized. Under the previous assumptions for the sample size the power will be 24%. Therefore, only a descriptive analysis will be performed.

Changes to protocol:

Section	Changes made
Section 5.1 Inclusion criteria	Clarification that painful arc test needs to be “positive”
Section 6.1.1 Additional study treatment and therapies	Clarification regarding non-NSAID medication
Section 7.1 Discontinuation of study treatment	Removal that discontinuation is required in case of 2 missed doses
Section 8.5.1 Clinical Outcome Assessments (COAs)	Clarification that Paper-based PROs can be used as backup
Section 8.6.1 Adverse Events	Clarification that adverse events are monitored depending on last dose of study treatment
Section 8.6.3 SAE Reporting	Inclusion of Hy’s law language
Section 8.10 Reporting of study treatment errors, study treatment misuse/abuse and overdose	Section added
9.2 Statistical analyses	Updated to reflect that analysis will only be descriptive due to early termination of screening.

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 require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 1 (12-JUN-2023)

Amendment rationale

The main purpose of this protocol amendment is to align with other Secukinumab studies in the same indication in order to create comparable study populations and outcomes. This amendment contains:

- Update of inclusion criteria describing the severity of the symptoms
- Omission of ECG assessments
- Inclusion of high sensitivity CRP as laboratory parameter in clinical chemistry
- Addition of optional WORC PRO at screening
- Clarification on X-Ray assessment
- Update on study length justification
- Clarification of Run-in phase definition

As of 10-Mar-2023, 9 participants were enrolled. The participants who were already screened continue to be enrolled if eligible. The changes and clarifications proposed by this amendment are not expected to influence the study population. Impact on study results is not expected.

Changes to protocol and rationale:

Below is a delineation of the key changes to the protocol. This protocol amendment also includes minor changes not noted below but are seen in the track changes version of the protocol. In the track changes version, strike through red font is used for deletions and red font with underlining is used for insertions.

Section	Changes made
Section 1 Protocol summary	Updated
Section 1.3. SoA	ECG omitted from SoA in consistency with Secukinumab protocols in this indication. Shoulder X-Ray is no longer a study required assessment. It is still mentioned as a recommended diagnostic assessment to follow the current local guideline (Liem, et.al., 2017). An additional assessment of WORC can now be optionally performed at Screening to support the severity assessment of the disease. Further assessments of WORC remain unchanged.
Section 4.3 Justification for dose	Clarifications as requested by the local EC
Section 5 Study Population	Adjustment of inclusion criteria to match study population with intended population of patients with moderate to severe RCT
Section 5.2 Exclusion criteria	Clarification of wording

Section 6.1 Study treatment	Changes in the physiotherapy regimen were made in order to reflect treatment reality. Continuation of in-person physiotherapy is generally allowed if it was prescribed prior to the study. Clarification that participants with contraindications for NSAIDs can be included.
Section 8.2.2 X-ray of the shoulder	Update
Section 8.3.1 The PRO efficacy measures collected for primary, secondary [redacted] objectives:	Addition, that Pain NRS is collected during Run-in phase as well
Section 8.4 Safety assessments	Updated in accordance with the current aligned wording
Section 8.4.3 Vital signs	Assessment of body temperature is not required.
Former Section 8.4.4 Electrocardiograms	Omitted as it is no longer required
Section 8.4.4 Clinical safety laboratory tests	High sensitivity CRP is added to laboratory marker to provide an additional parameter to exclude systematic inflammatory conditions
Section 8.6.1 Adverse events	Alignment among study protocols investigating secukinumab
Section 10.2.1 List of abbreviations	Updated
Section 10.3.1 Clinically notable laboratory values and vital signs	Thresholds and calculation of eGFR added

Changes to the protocol

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 require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. A revised Informed Consent that considers the changes described in this protocol amendment has to be submitted for approval.

1 Protocol summary

1.1 Summary

Protocol Title:

A randomized, double-blind, placebo-controlled, parallel group, multicenter, 24-week study investigating the efficacy and safety of secukinumab compared to placebo in adult patients with moderate to severe rotator cuff tendinopathy and failure to conventional therapy "UnchAIN"

Brief Title:

Study of efficacy and safety and of AIN457/secukinumab in patients with rotator cuff tendinopathy

Purpose

The purpose of this study is to demonstrate the efficacy and safety of AIN457/secukinumab 300 mg subcutaneous (s.c.) vs. placebo in improving signs and symptoms in participants with rotator cuff tendinopathy. Both study arms will be accompanied by patient individualized conventional therapy. The study is tailored to support health technology assessments (HTAs) of secukinumab in Germany in this indication.

The study will enroll adult participants with a diagnosis of moderate to severe rotator cuff tendinopathy with no tear or partial tear ,who are experiencing active disease for at least 6 weeks and no more than 6 months at Baseline and who have failed to respond to conventional therapy.

Secukinumab will be administered as 7 injections of 300 mg s.c. or placebo s.c. over a 12-week period. Participants in both study arms will receive patient individualized conventional therapy consisting of home-based standardized physiotherapy and flexible dosing of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and/or paracetamol as needed (dose decrease and dose increase of NSAIDs/paracetamol relative to the optimized starting dose).

Study Indication /Medical Condition:

Moderate to severe rotator cuff tendinopathy.

Treatment type

Biologic.

Study type

Interventional / Phase IIIb

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To demonstrate the superiority of 12 weeks of treatment with secukinumab 300 mg s.c. compared to placebo (both arms in combination with patient individualized conventional therapy), in participants with moderate to severe rotator cuff tendinopathy, based on change in Western Ontario Rotator Cuff index (WORC) score from Baseline to week 24.	• Mean change in WORC patient reported outcome (PRO) score from Baseline to week 24
Secondary	
• To demonstrate the superiority of secukinumab 300 mg s.c. compared to placebo (both arms in combination with patient individualized conventional therapy), in participants with moderate to severe rotator cuff tendinopathy on signs and symptoms as well as activities of daily living and quality of life.	• Mean change in WORC score in each subdomain from Baseline to week 24 • Mean change in Patient global assessment (PaGA) score using a VAS (considering the last 24 hours) from Baseline to week 24 • Mean change in SF-36 survey (including all subscales and component summary scores) from Baseline to week 24 • QuickDASH score from Baseline to week 24 • Mean change in Pain score using a NRS (considering the last 24 hours) from Baseline to week 24 • Mean change in EQ-5D-5L health related question (VAS) from Baseline to week 24
• To evaluate the safety and tolerability of secukinumab in participants with moderate to severe rotator cuff tendinopathy.	• Number and proportion of participants with adverse events (AEs), serious adverse events (SAEs) (incidence, severity, and relationship with study drug) as well as description of clinically laboratory parameters and vital signs
[redacted]	

Trial Design:

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIIb, 24-week study to investigate the superior efficacy of AIN457/secukinumab and safety in participants with rotator cuff tendinopathy.

Secukinumab 300 mg s.c. will be compared to placebo (both arms in combination with patient individualized conventional therapy) in relieving clinical symptoms at week 24. Approximately 430 participants (215 per treatment group) will be included with a diagnosis of moderate to severe rotator cuff tendinopathy with no tear or partial tear, who are experiencing active disease for at least 6 weeks and no more than 6 months at Baseline and who have failed to respond to conventional therapy.

The study consists of a Screening period up to 6 weeks, a 2-week Run-in period, a 12-week Treatment period and a 12-week Follow-up period. Treatment and Follow-up period will be blinded. The Screening period will assess eligibility. Participants who meet the eligibility criteria at Screening will continue to Run-in period and will be randomized. In the Run-in period participants should perform 2 weeks of home-based standardized physiotherapy. The Run-in period is defined as 14 days prior to Randomization and is commenced beforehand by a telephone visit. The study comprises a total of 13 visits.

Eligible participants will be randomized 1:1 to either receive secukinumab 300 mg s.c. or placebo s.c. at Baseline, week 1, 2, 3, 4, 8 and 12 (7 injections in total) (Figure 1-1).

Brief Summary:

The purpose of this study is to investigate the efficacy and safety of AIN457 (secukinumab s.c.) compared to placebo in adult patients with moderate to severe rotator cuff tendinopathy and failure to conventional therapy.

- The study duration will be 24 weeks.
- The treatment duration will be 12 weeks with 12 weeks follow-up.
- The visit frequency will be weekly until visit 7 and 4-weekly until end of treatment and 4 follow-up visits.

Treatment of interest

The treatment of interest is randomized (the investigational treatment AIN457/secukinumab or the control treatment/placebo) in combination with the allowed concomitant medication (patient individualized conventional therapy) for moderate to severe rotator cuff tendinopathy and home-based standardized physiotherapy. The dose of the allowed concomitant medication for moderate to severe rotator cuff tendinopathy is flexible according to participant´s individual need during the trial.

Number of Participants:

To demonstrate superiority of secukinumab compared with placebo with a 90% power on a two-sided, 5% significance level the study will recruit a total of 430 participants assuming drop-outs and other protocol deviations.

Key Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Males and non-pregnant, non-nursing females between 18 and 65 years of age
3. Rotator cuff tendinopathy (unilateral)
4. Symptoms present for at least 6 weeks but not more than 6 months at Baseline
5. Moderate to severe rotator cuff tendinopathy demonstrated by all of the following criteria:
   a. WORC score ≤ 40 at Baseline
   b. Average weekly NRS pain score of ≥ 5 during the 7 days prior to Baseline
   c. Nocturnal pain in shoulder on at least 3 out of 7 days in the week prior to Baseline or positive “Painful Arc Test” on examination
6. Failure to at least 8 weeks of conventional therapy prior to Baseline: inadequate response to NSAIDs and/or paracetamol and physiotherapy; or intolerance to NSAIDs and/or paracetamol

Key Exclusion criteria

Participants fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

1. Greater than 50% partial thickness tear as established by MRI or ultrasound during assessment in Run-in phase
2. Patients who are expected to require glucocorticoid treatment throughout the trial duration at Baseline (e.g., systemic, intramuscular, local injections in shoulder)
3. Previous surgery, or plans for surgery, during the study period, in the affected shoulder
4. Rheumatologic and chronic inflammatory diseases, including but not limited to inflammatory bowel disease, polymyalgia rheumatica (PMR), PsA, axSpA and rheumatoid arthritis (RA), fibromyalgia or severe pain disorder unrelated to the target shoulder
5. Both Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies positive at Screening
6. Either history of adhesive capsulitis/frozen shoulder, or current calcification in the tendon (in affected or contralateral shoulder) confirmed clinically or by medical imaging
7. Symptomatic osteoarthritis of the shoulder (glenohumeral, acromioclavicular) in affected or contralateral shoulder confirmed by medical imaging
8. Patients with traumatic rupture that would be considered eligible for surgery for repair of cuff tear.
9. Neurological conditions including but not limited to cervical radiculopathy, which in the opinion of the investigator may explain the patient's symptoms
10. Any intra-articular/subacromial glucocorticoid treatment within 12 weeks prior to Baseline or more than 2 intra-articular/subacromial glucocorticoid injections for the treatment of the current episode of tendinopathy so far
11. Any oral, intramuscular or i.v. glucocorticoid treatment 12 weeks prior to Baseline or during the current tendinopathy, whichever takes longer
12. Previous platelet rich plasma (PRP) injections or fluoroquinolone/quinolone antibiotics within 12 weeks prior to Baseline or during the current tendinopathy, whichever takes longer
13. Neuromuscular or primary/secondary muscular deficiency which limits the ability to perform functional measurement (e.g., shoulder strength test)
14. Previous hyaluronic injections within 12 weeks prior to Baseline or during the current tendinopathy, whichever takes longer

Treatment Groups:

a) Investigational and control drugs

Group	Investigational/ Control Drug	Pharmaceutical Dosage Form and Route of Administration
Group 1	Secukinumab	1 x 2mL 300 mg PFS injection s.c.
Group 2	Placebo	1 x 2mL PFS injection s.c.

PFS – Pre-Filled Syringe

b) Additional study treatments

Patient individualized conventional therapy will be given alongside the investigational drug and placebo. Additional study medication will NOT be provided by the Sponsor and has to be managed on site level. The patient individualized conventional therapy consists of:

2.1 Home-based standardized physiotherapy based on MOON regimen (Kuhn, 2009): Participants will be instructed on home-based standardized physiotherapy by qualified study site personnel at screening visit. Participants will receive printed instructions to perform a standardized physiotherapy independently at home once or twice daily until study completion. At each visit site personnel will inquire about status of home-based standardized physiotherapy to address any questions or hurdles and review instructions with participant as needed and will document the status in electronic Case Report Form (eCRF) accordingly. Concomitant in-person physiotherapy is not prohibited. However, new-onset of in-person physiotherapy should be avoided after randomization.

2.2 NSAIDs: Dose should be **optimized** to the individual participant to achieve the best efficacy and simultaneously the best tolerability. Dosing should not exceed the respective approved dosing and the maximum tolerable dose (e.g., max. dose of 2400 mg/day ibuprofen or max. dose of 4000 mg/day paracetamol or as directed by treating physician). Should high NSAID doses not be tolerated or contraindicated, participants may receive the maximum tolerated NSAID dose in combination with paracetamol as support if necessary. The optimized dose of NSAIDs/paracetamol, starting from Run-in period, should remain stable until Baseline. Dose adjustments (dose decrease and dose increase of NSAIDs/paracetamol relative to the optimized starting dose), discontinuation of NSAIDs/paracetamol and switch of NSAIDs are possible at any time throughout the study after Baseline. [redacted]

2.3 Glucocorticoids: Glucocorticoids may be given, if required. However, they should be avoided if possible. Participants who are **expected at Baseline to require glucocorticoid treatment** throughout the trial duration will **not be randomized**. In case glucocorticoids

will be unexpectedly required during the study period (local injections in the shoulder - including intramuscular injection or systemic), treatment with glucocorticoids is allowed at any time throughout the study. [redacted] Local glucocorticoid injections for current tendinopathy should not exceed 2 injections during the course of this study. Participants exceeding 2 injections continue the study as outlined in the SoA.

1.2 Schema

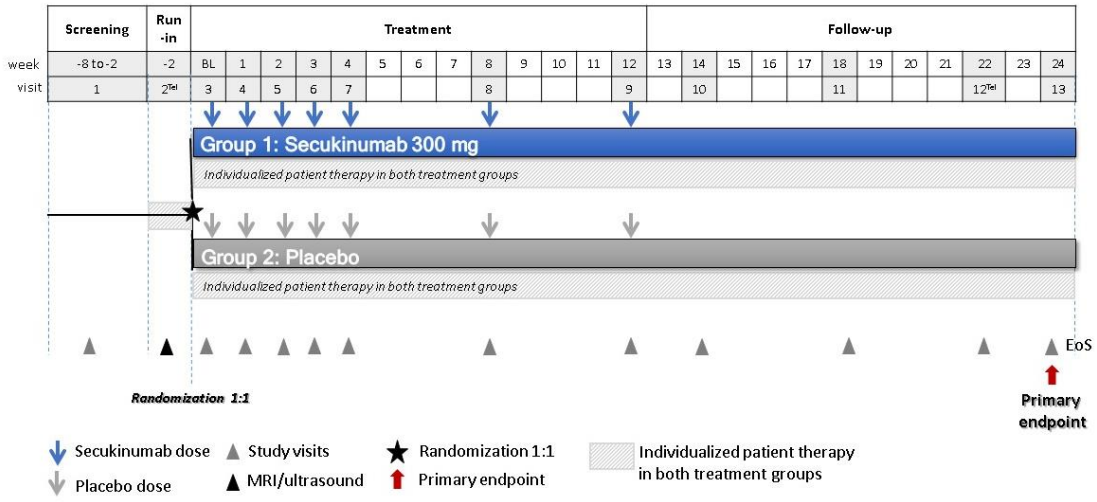

Figure 1-1 Study design

1.3 Schedule of activities (SoA)

The SoA lists all assessments and 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.

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 EoS as indicated in the SoA.

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

PRO measure(s) must be completed before any clinical assessments are performed at any given visit.

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 1-1 Schedule of Activities

Period	Screening	Run-in[1]	Treatment							Follow-Up			
Visit Name	Screening	Run-in	BL	Treatment					EOT	Follow-up			EOS
Visit Number	1	2[Tel]	3	4	5	6	7	8	9	10	11	12[Tel]	13
Day	-56 to -15	-14 to -1	1	8	15	22	29	57	85	99	127	155	169
Week	-8	-2	BL	1	2	3	4	8	12	14	18	22	24
Obtained informed consent	X												
Participant History	X												
Demography	X												
Inclusion / exclusion criteria[2]	X		X										
Relevant medical history/current medical conditions	X												
Physical Examination	S		S										S
Body Height	X												
Body Weight	X		X										X
Vital Signs (Blood pressure and pulse rate)	X		X				X	X	X	X	X		X
Hepatitis B, C or HIV serology[3]	X		X										
TB Test (QuantiFERON TB-Gold test)	S												
Physiotherapy[4]	X	X	X[§]	X	X	X	X	X	X	X	X	X	X
Hematology	X		X										X
Clinical Chemistry	X		X										X
Urinalysis			X										X
Lipid panel and glucose			X										X
RF/anti-CCP antibodies	X												
Pregnancy and assessments of fertility[5]	X		X				X	X	X		X		X
Shoulder X-Ray[6]	(X)												
Shoulder MRI[7]			X										
Shoulder US[7]			X										

Period	Screening	Run-in[1]	Treatment							Follow-Up			
Visit Name	Screening	Run-in	BL	Treatment					EOT	Follow-up			EOS
Visit Number	1	2[Tel]	3	4	5	6	7	8	9	10	11	12[Tel]	13
Day	-56 to -15	-14 to -1	1	8	15	22	29	57	85	99	127	155	169
Week	-8	-2	BL	1	2	3	4	8	12	14	18	22	24
[redacted]													
WORC (PRO)[10]	(X)		X		X		X	X	X	X	X		X
SF-36 (PRO)[10]			X		X		X	X	X	X	X		X
Patient Global assessment of disease activity - VAS (PaGA) (PRO)[10]			X		X		X	X	X	X	X		X
QuickDASH (PRO)[10]			X		X		X	X	X	X	X		X
Pain NRS (PRO)[10]			X		X		X	X	X	X	X		X
EQ-5D-5L health related question (VAS) (PRO)[10]			X		X		X	X	X	X	X		X
Shoulder/arm strength	X		X		X		X	X	X	X	X		X
Range of movement (ROM), active and passive, including - “Painful Arc Test” - Empty/full cup test - Apley scratch test	X		X		X		X	X	X	X	X		X
[redacted]													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X										
Study drug administration			X	X	X	X	X	X	X				
Study completion information													X

1 Run-in period to standardize physiotherapy and stabilize NSAIDs. The Run-in period is commenced beforehand by a visit via telephone call (Tel). An on-site visit can take place e.g. if an MRT examination of the participant is performed.

2 Eligibility assessments are conducted at Screening and Baseline visit but recorded only once in the eCRF

3 Only in case study site/lab personnel comes in contact with blood, tissue or bodily fluids of participants through contact with injection needle, cut, splash on mucous membrane or through skin damage; if HIV test is seropositive, it should be confirmed by Western blot

4 Participants will be instructed on home-based standardized physiotherapy by qualified study site personnel. Participants will receive printed instructions to perform standardized physiotherapy (based on MOON regimen, (Kuhn, 2009)) at home until study completion. Site personnel will inquire about the status of home-based standardized physiotherapy (based on MOON regimen, (Kuhn, 2009)) to address any questions or hurdles and review instructions with the participant as needed. Status of home-based standardized physiotherapy will be documented by site personnel in eCRF at each visit accordingly.

5 Non post-menopausal women require serum pregnancy tests at Screening and visit 13/EOS; for remaining visits local urine tests to be done.

6 Performance of shoulder X-Ray is strongly recommended following current national guidelines but not required. If shoulder X-Ray is performed at the discretion of the treating physician or if historic X-Ray obtained during the current episode of tendinopathy is available, imaging data should be assessed.

7 MRI has to be performed maximum 14 days before Baseline. Ultrasound may be performed in participants unable or unwilling to undergo MRI. Ultrasound is not required in participants who underwent MRI.

[redacted]

10 Patient reported outcomes must be done before clinical assessments. WORC assessment can optionally be performed at screening.

Tel: Visit can be performed via telephone call. No on-site visit required.

S: collected as source data only

§: Site personnel will document in eCRF at Baseline if 2 weeks home-based standardized physiotherapy were performed as per statement of participant.

For all participants who discontinue from the study, the investigator should ensure that the participant completes an EoT-visit 2 weeks after last study treatment, as well as an EoS-visit 12 weeks after last study treatment. Unscheduled visits are possible to ensure participant’s welfare.

2 Introduction

2.1 Study rationale

The purpose of this study is to assess the efficacy and safety of AIN457/secukinumab 300 mg s.c. vs. placebo in improving signs and symptoms in participants with rotator cuff tendinopathy. Both study arms are accompanied by patient individualized conventional therapy. The study is tailored to support HTAs of secukinumab in Germany in this indication. Study will enroll adult participants with a diagnosis of moderate to severe rotator cuff tendinopathy with no tear or partial tear, who are experiencing active disease for at least 6 weeks and no more than 6 months at Baseline and who have failed to respond to conventional therapy. Secukinumab will be administered as 7 injections of 300 mg s.c. or placebo s.c. over a 12-week period. Participants in both study arms will receive patient individualized conventional therapy consisting of home-based standardized physiotherapy and flexible dosing of NSAIDs and/or paracetamol as needed (dose decrease and dose increase of NSAIDs/paracetamol relative to the optimized starting dose). Efficacy of secukinumab will be evaluated at the end of week 24, based on validated patient reported outcomes (PROs) including improvement in signs and symptoms, physical function and quality of life. ROM will be assessed as well.

Safety will be assessed up to week 24 and participants will be followed up without drug treatment from week 12 to week 24.

2.2 Background

2.2.1 Epidemiology, clinical features, and socioeconomic impact

Rotator cuff tendinopathy is a common condition, with a complex pathogenesis. It is clinically diagnosed after gradual onset of activity-related pain, weakness, decreased function and range of motion, and sometimes localized swelling of the tendon (Riley, 2005; Riley, 2008). Rotator cuff tendinopathy is commonly associated with impaired sleep and difficulties in performing basic activities of daily life (Consigliere, et al., 2018). While the exact pathophysiology remains uncertain, it appears to develop when the pathological responses associated with tendon overuse overwhelm the protective/regenerative changes associated with tendon repair (Challoumas, et al., 2019).

Rotator cuff tendinopathy is highly prevalent. Tendinopathies are the most common reason for consultation for a musculoskeletal complaint, (Forde, et al., 2005).

The socioeconomic impact of rotator cuff tendinopathy beyond medical costs is high because the condition is associated with long-term productivity loss, sick leave and loss of employment (Chard, et al., 1988; Hopkins, et al., 2016). It has been estimated that the median recovery time for shoulder tendinopathy is 10 months (Bonde, et al., 2003).

Diagnosis and clinical evaluation of patients with Rotator cuff tendinopathy

The diagnosis of rotator cuff tendinopathy is usually made clinically; ultrasonography and MRI can enhance the diagnosis (Kaux, et al., 2011). Clinical assessment and diagnosis of rotator cuff

tendinopathy involves taking a thorough patient history and performing tests to isolate the structure causing the pain and to measure the impairment (e.g., range of movement, extension, strength and pain response, rotation resistance) (Lewis, et al., 2015). Potential differential diagnoses could be Os Acromiale, Tendinosis calcarea or of rheumatologic ethology (Liem, et al., 2017).

Treatment of rotator cuff tendinopathy

The goals of rotator cuff tendinopathy treatment are pain reduction and restoration of function. Rotator cuff tendinopathy treatment generally follows a progression from conservative, non-surgical management, through local corticosteroid injections, to surgical management, if indicated (Factor, et al., 2014). Rotator cuff disease can be associated with poor long-term outcomes (Millar, et al., 2021; Titan, et al., 2016).

First-line non-surgical treatment includes the conventional modalities of rest, hot and cold packs, and physiotherapy (including therapeutic ultrasound, laser therapy, hyperthermia and extracorporeal shockwave therapy). Evidence has shown that exercise therapy, either alone or combined with manual therapy (i.e., joint and soft tissue mobilization by a healthcare professional), can improve pain and mobility. However, some patients report no significant improvement with physiotherapy (Pedowitz, et al., 2011; Pieters, et al., 2020). In addition, most patients do not recover rapidly with these interventions.

NSAIDs are the first-line treatment option for pain relief. Evidence suggests that both oral and local NSAIDs are effective in relieving pain associated with tendinopathy in the short term (7 to 14 days) (Andres, et al., 2008). However, long-term use or overuse of NSAIDs is associated with risks that include upper gastrointestinal tract bleeding and cardiovascular events (Wolfe, et al., 1999; Food and Drug Administration (FDA), 2015). Moreover, NSAIDs have been shown to have a negative effect on tendon healing and, thus, could contribute to long-term tissue damage (Jomaa, et al., 2020).

Local corticosteroid injections can provide short-term pain relief, but there is no evidence of benefit beyond 6 months (Andres, et al., 2008; Coombes, et al., 2010; Mohamadi, et al., 2017). It has also been shown that repeated corticosteroid injections have the potential to accelerate tendon degeneration, increasing the risk of tendon rupture (Lipman, et al., 2018). In the 2020 American Academy of Orthopaedic Surgeons (AAOS) Evidence-Based Clinical Practice Guideline on Management of Rotator Cuff Pathology, it is stated that "… it is the opinion of the work group that multiple corticosteroid injections may compromise the integrity of the rotator cuff, which may affect attempts at subsequent repair." (AAOS, 2020).

Non-surgical treatments for rotator cuff tendinopathy have demonstrated efficacy in 40% to 80% of patients when treatment is prompt (Beaudreuil, et al., 2010). 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 injection and/or oral NSAIDs (Andres, et al., 2008). In addition, standard of care (SoC) treatments for rotator cuff tendinopathy only address symptom relief and are generally not targeted against specific pathways to treat the molecular root cause.

The German guideline "rotator cuff" only lists NSAID-treatment, physiotherapy, self-guided training following professional instruction and cortisone infiltration as evidence based conservative therapies (Liem, et al., 2017).

Surgical treatment can be an option in selected patients if conservative treatment fails. There is in general consensus that surgery is mainly indicated for repair of full thickness rotator cuff tears. The recently published AAOS guidelines (AAOS, 2020) provide recommendations for the treatment of full thickness rotator cuff tears but do not address partial thickness tears or rotator cuff tendonitis/rotator cuff bursitis. According to the German guideline surgical treatment follows failure of conservative treatment

Repair of partial thickness tears might be considered if conservative treatment fails or in younger patients with traumatic rupture. While factors like age, occupation, and rehabilitation time may influence the decision for surgical treatment, clinical studies showed that the percentage thickness torn has a major impact on the clinical outcome, with repair of tears > 50% thickness leading to better results (Matthewson, et al., 2015).

While surgery is considered beneficial for patients with substantial partial or full thickness tears, there is a lack of valid treatment options for patients with rotator cuff tendinopathy with no or less than 50% partial thickness tears who are not responding to conservative treatment, based on clinical recommendations, might not be eligible for surgery. Additionally, it has been reported that 54% of patients with shoulder pain experience ongoing symptoms after 3 years (Lewis, 2009).

Therefore, there is a high, unmet need to provide rotator cuff tendinopathy patients with a targeted treatment option that offers rapid onset and maintenance of pain relief and restoration of function, leading to better outcomes and improved quality of life.

Role of interleukin-17A (IL-17A) in Tendinopathy and rationale of Secukinumab (AIN457, Cosentyx®) as treatment

IL-17A is a central cytokine involved in multiple autoimmune and inflammatory processes (McGeachy, et al., 2019). It has been shown that IL-17A mediates tendon inflammation, inhibits tendon matrix repair, and induces tenocyte apoptosis (Millar, et al., 2016). IL-17A-expressing tendon-resident immune cells are present in human tendinopathy, and IL-17A mRNA (modified Ribonucleic Acid) and protein levels are increased in early human tendinopathic tissue samples (Millar, et al., 2016). In human tenocytes, IL-17A regulates pro-inflammatory cytokines and key apoptotic mediators, inducing apoptosis in vitro. As a consequence of this apoptosis, the tendon matrix adopts a mechanical 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; Millar, et al., 2017). Enthesitis is often a primary pathological process underlying skeletal inflammation in the spectrum of diseases defined as spondyloarthropathies (SpA) (Benjamin, et al., 2009; Watad, et al., 2018).

Secukinumab has been shown to provide early and sustained resolution of enthesitis in patients with PsA over 2 years (Coates, et al., 2019), and a rapid onset of action of secukinumab treatment has been shown for both synovitis and enthesitis over 12 weeks of treatment in PsA in study CAIN457F2354 (clinicaltrials.gov, NCT 02662985). Similarly, secukinumab has shown sustained benefits in the resolution of enthesitis in axial spondyloarthritis (axSpA), as demonstrated in a pooled analysis of the pivotal secukinumab AS trials MEASURE 1 and MEASURE 2, as well as the follow-on Phase 3 studies MEASURE 3 and MEASURE 4 (Deodhar, et al., 2016; Deodhar, et al., 2020).

The inflammatory conditions being targeted with anti-IL-17A treatment have significant impact on activities of daily living and quality of life. Clinically significant improvements in patient-reported measures of disease impact have been demonstrated in studies in AS (Deodhar, et al., 2016), PsA (Coates, et al., 2018), and psoriasis (Thaçi, et al., 2015; Rompoti, et al., 2019).

Based on this converging evidence, neutralization of IL-17A with secukinumab is expected to reduce tendon inflammation and halt tendon matrix degeneration, leading to improvement in the signs and symptoms of tendinopathy, quality of life, and activities of daily living. Secukinumab was therefore investigated as a disease-modifying therapy for rotator cuff tendinopathy in a Phase II / proof-of-concept study (CAIN457X2201).

[redacted]

2.3 Benefit/Risk assessment

It is anticipated that secukinumab will have a beneficial effect on the symptoms of rotator cuff tendinopathy, by inhibiting the IL-17 driven inflammation and thereby decreasing pain and improving mobility and sleep. Ultimately, this should result in few cases of tendinopathy progressing to a tear and therefore lessen the need for surgery.

The placebo participants in the study will not have this benefit, however, they will be followed closely in order to identify any progress or need for additional therapy.

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

Please refer to the IB for a detailed review of the pre-clinical and clinical information on secukinumab and risks identified from the clinical experience:

a) Infections: Secukinumab has the potential to increase the risk for infections, which are primarily upper respiratory tract infections (non-serious, mild to moderate in severity and did not lead to treatment discontinuation), oral candidiasis, and other forms of mucosal

and cutaneous candidiasis are uncommon. Caution should be exercised in patients with chronic infections or recurrent infections.

b) Inflammatory Bowel Disease (IBD): Caution should be exercised in patients with IBD and those patients need to be followed up closely for disease exacerbation.
c) Hypersensitivity reactions: Primarily non-serious, mild to moderate urticaria and rare cases of anaphylactic reactions (eczema or dermatitis) have been observed.
d) Immunizations: Live vaccines should not be given concurrently with secukinumab. Studies showed, patients in secukinumab treatment receiving inactivated and non-live vaccinations given concurrently were able to mount an adequate immune response.

Taking into account the individual risks, the expected risk profile of secukinumab from a mechanism of action perspective in tendinopathy is anticipated to be similar or less (shorter duration of treatment) to that of the approved indications.

From the standpoint of the overall risk benefit assessment, the current trial with secukinumab is justified.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the Section 5.2 (Exclusion Criteria). If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

2.3.1 Risks of imaging procedures

MRI technique will be used during Run-in period to determine the degree of tendon tear. Ultrasound may be performed in participants who are unwilling or unable to undergo MRI. MRI is a noninvasive radiology technique that has no x-ray radiation exposure. No MRI contrast agent will be administered in this study. Thus, in principle, MRI scans can be repeated in the same participant as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons. The presence of metal in the body may also be a safety hazard or affect an MRI image quality.

3 Objectives, endpoints and estimands

Table 3-1 Objectives and related endpoints

Objectives	Endpoint
Primary Objective	**Endpoint for primary objective**
• To demonstrate the superiority of efficacy of 12 weeks of treatment with secukinumab 300 mg s.c. compared to placebo (both arms in combination with patient individualized conventional therapy) in participants with moderate to severe rotator cuff tendinopathy, based on change from Baseline in WORC score at week 24.	• Mean change in WORC patient reported outcome (PRO) score from Baseline to week 24
Secondary Objectives	**Endpoints for secondary objectives**
• To demonstrate the efficacy of secukinumab 300 mg s.c. compared to placebo (both arms in combination with patient individualized conventional therapy) in participants with moderate to severe rotator cuff tendinopathy on signs and symptoms and activities of daily living, as well as quality of life, based on:	• Mean change in WORC score in each subdomain from Baseline to week 24 • Mean change in Patient global assessment (PaGA) score using a VAS (considering the last 24 hours) from Baseline to week 24 • Mean change inSF-36 survey (including all subscales and component summary scores) from Baseline to week 24 • QuickDASH score from Baseline to week 24 • Mean change in Pain score using a NRS (considering the last 24 hours) from Baseline to week 24 • Mean change in EQ-5D-5L health related question (VAS) from Baseline to week 24
• To evaluate safety and tolerability of secukinumab 300 mg s.c. in participants with moderate to severe rotator cuff tendinopathy	• Number and proportion of participants with adverse events (AEs), serious adverse events (SAEs) (incidence, severity, and relationship with study drug) as well as description of clinically laboratory parameters and vital signs

3.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest is: What is the effect of secukinumab 300 mg s.c. compared to placebo (both arms in combination with patient individualized conventional therapy) in participants with rotator cuff tendinopathy in change in WORC score from Baseline to week 24, regardless of treatment discontinuations.

The analysis of the primary endpoint will be based on the following estimand:

1. Population: Participants as defined by the inclusion/exclusion criteria to reflect the targeted rotator cuff tendinopathy population based on the FAS.
2. Variable: WORC score from Baseline to week 24
3. Treatment of interest: the randomized treatment (secukinumab 300 mg s.c. and placebo s.c.), both arms in combination with patient individualized conventional therapy
4. Intercurrent events:
    - Treatment discontinuations due to any reason:

Treatment policy strategy: interested in treatment effect regardless of these events.

- Other protocol deviations:
  Treatment policy strategy: interested in treatment effect regardless of these events.

5. Summary measure: Difference in mean change in WORC score from Baseline to week 24 between treatments.

3.2 Secondary estimands

The secondary estimands relating to continuous endpoints (mean change from baseline to Week 24 in secukinumab/placebo) are defined analogous to the primary estimand.

4 Study design

4.1 Overall design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIIb, 24-week study to investigate the superior efficacy of AIN457/secukinumab and safety in participants with rotator cuff tendinopathy. Secukinumab 300 mg s.c. will be compared to placebo s.c. (both arms in combination with patient individualized conventional therapy) in relieving clinical symptoms at week 24. Approximately 430 participants (215 per treatment group) will be included with a diagnosis of moderate to severe rotator cuff tendinopathy with no tear or partial tear who are experiencing active disease for at least 6 weeks and no more than 6 months at Baseline and who have failed to respond to conventional therapy.

The study consists of a 6-week Screening period, a 2-week Run-in period, a 12-week Treatment period and a 12-week Follow-up period. Treatment and Follow-up period will be blinded. The Screening period will assess eligibility and start participants on home-based standardized physiotherapy. The Run-in period is defined as 14 days prior to Randomization and is commenced beforehand by a telephone visit.. In the Run-in period participants should perform 2 weeks of home-based standardized physiotherapy. Participants who meet the eligibility criteria at Screening will continue to Run-in period and Baseline evaluations. The study comprises a total of 13 visits. Participants will be randomized 1:1 to either receive secukinumab 300 mg s.c. or placebo s.c. at Baseline, week 1, 2, 3, 4, 8 and 12 (7 injections in total) (Figure 1-1).

The population will consist of male and 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 moderate to severe rotator cuff tendinopathy with no tear or partial tear who are experiencing active disease for at least 6 weeks and no more than 6 months at Baseline and who have failed conventional therapy.

Participants must have failed to at least 8 weeks of conventional therapy prior to Baseline (inadequate response to NSAIDs and/or paracetamol and physiotherapy; or intolerance to NSAIDs and/or paracetamol). Furthermore, participants should have performed at least 2 weeks

of home-based standardized physiotherapy (during Run-in study period) prior to Baseline. Participants will only be included if there are no foreseeable plans for surgery in the affected shoulder during the study period.

Participants must have a WORC score ≤ 40 (where 100 points is symptom-free and 0 worst symptoms) at Baseline in combination with 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 prior to the Baseline visits.. Participants must have nocturnal pain in shoulder on at least 3 out of 7 nights in the week prior to Baseline OR a positive "painful arc test" on examination.

The screening period will be used to assess eligibility and to start/continue participants on physiotherapy. In the Run-in period the participant should have 2 weeks of NSAID/paracetamol intake and home-based standardized physiotherapy and undergo shoulder MRI (or ultrasound if participants are unable or unwilling to undergo MRI) as shown in Section 1.3 Schedule of Activities. Participants who meet the eligibility criteria after the Run-in period will go through Baseline evaluations.

Eligible participants as per inclusion/exclusion criteria will be randomized to one of the two treatment arms: 7 s.c. injections of secukinumab 300 mg or placebo in a 12-week treatment period, followed by a 12-week follow-up period. The assessments to address the primary endpoint will be performed at week 24.

Participants will come to the out-patient clinic approximately 1-3 hours prior to dosing for the evaluations. Dosing will be on-site.

Safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), pregnancy and fertility assessments, adverse event and serious adverse event monitoring.

Remote procedures

The on-site staff will perform certain procedures remotely using telephone-visits according to Section 1.3 Schedule of Activities.

4.2 Scientific rationale for study design

The study is tailored to support HTAs of secukinumab in Germany in this indication. Currently, no Health Authority guideline exists for developing drugs for the moderate to severe rotator cuff tendinopathy indication. The study uses validated Patient Reported Outcome (PRO) questionnaires including indices of signs, symptoms and physical function. The PROs used have been chosen based on their validity, reliability and specificity. The different PROs have different recall times (1 week, 24 hours).

The participant population with rotator cuff tendinopathy was chosen, as this is one of the most frequent tendinopathies. The most common age for development of tendinopathy is between 18 and 65 years; more than two-thirds of cases will develop in this age group (Hopkins, et al., 2016; Riel, et al., 2019). Moreover, the clinical evidence for an IL-17 connection has so far only

been shown for rotator cuff tendinopathy and has not been investigated for other tendinopathies (Millar, et al., 2017).

During the 2-week **Run-in period** participants should take NSAIDs/paracetamol at an optimized individual dose to achieve the best efficacy and simultaneously the best tolerability.

Glucocorticoids may be given, if required. However, they should be avoided if possible.

The rationale for key design elements in this study include:

Randomization: This decreases the chance of an imbalance in participant characteristics between groups, thereby facilitating a valid basis for the treatment comparison.

Double-blind: Blinding of participants, investigators and sponsor up to the point of week 24, the primary endpoint, allows for an unbiased assessment of subjective readouts such as the efficacy parameters measured by PROs and as well for adverse events evaluation. The blinding is maintained for participants and investigators until the end of the study to ensure reliable efficacy and safety measures. The sponsor will be unblinded after the primary endpoint analysis at week 24 after database lock.

Placebo-controlled: A placebo arm is included in this study because it is not known whether secukinumab can improve moderate to severe rotator cuff tendinopathy, and because there is no disease modifying therapy available. However, a patient individualized conventional therapy will be given alongside the investigational drug and placebo. Due to the nature of the disease and the outcome measures used, a placebo arm is necessary to obtain reliable efficacy measurements, to judge the size of the active treatment compared to change over time in the placebo group, and to reasonably attribute adverse events to secukinumab.

4.3 Justification for dose

Phase III studies in patients with active PsA (CAIN457F2306 and CAIN457F2312) demonstrated the superior efficacy of secukinumab 150 mg s.c. and 300 mg s.c. (CAIN457F2312 only) regimens over placebo. Secukinumab 150 mg s.c. and 300 mg s.c. regimens had a rapid onset of response and showed significant and clinically meaningful efficacy compared with placebo on the primary endpoint and several secondary endpoints.

Furthermore, recent musculoskeletal scientific attention has focused on the immunobiology of the enthesis, the connective tissue between tendon or ligament and bone. This area has been considered analogous to tendinopathy as both enthesis and tendon are sites of high mechanical stress (Millar, et al., 2017).

While secukinumab 150 mg and 300 mg regimens are both more efficacious than placebo, the 300 mg regimen showed higher efficacy on skin endpoints and physical function as measured by Health Assessment Questionnaire Disability Index (HAQ-DI).

Furthermore, secukinumab 300 mg was more efficacious than 150 mg in achieving clinically meaningful improvements in skin disease. There was a clear dose response favoring secukinumab 300 mg in the higher thresholds of skin clearance.

There were no clinically meaningful differences among the secukinumab doses of 300 mg and 150 mg in the exposure adjusted incidences rates of the key risks over the entire treatment period in the 2 phase III trials in PsA patients.

In study CAIN457F2312 the presence of enthesitis was assessed by using Leeds enthesitis score. Overall, the percentage of patients without resolution of enthesitis at Week 24 were 67.6%, 57.8% and 51.8% in the 75 mg, 150 mg and 300 mg s.c. groups, whereas it was 78.5% in the placebo group. At Week 24, these differences vs. placebo were greater for the 150 mg and 300 mg dose groups vs. placebo (p=0.0108 and p=0.0025, respectively), while 75 mg vs. placebo was similar (p=0.17).

Treatment duration: The 12-week treatment duration was chosen as this is considered the maximum acceptable duration for resolution or partial resolution in moderate to severe tendinopathy of the rotator cuff. According to Phase II data, the onset of a potential effect could be expected within two weeks. (Millar, et al., 2021) The 12 weeks follow-up after the EoT is included to generate follow-up data for potential relapse and to have treatment safety follow-up data in this indication. Efficacy assessments will be done at week 24 (EoS) due to requirements of HTA process in Germany. Patients requiring any additional therapy as per discretion of the investigator should be treated according to [6.6.].

4.3.1 Rationale for choice of background therapy

A patient individualized conventional therapy will be given alongside the investigational drug and placebo in both treatment groups as recommended by the German guideline and fulfilling the German HTA requirements.

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

Due to the nature of the disease and the primary and secondary outcome measures used (PROs), a placebo arm is necessary to obtain reliable efficacy measurements. Adjustment of NSAIDs is allowed, and unexpectedly required steroid injection(s) are permitted.

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 (HA) and ethics committees as appropriate.

4.6 End of study definition

Study completion is defined as when the last participant completes the last study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision (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 should have a safety follow-up call conducted 60 days after the last administration of study treatment; however, the 60 days falls within the study 12-week follow-up period, where no treatment is given. 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

Male and 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 moderate to severe rotator cuff tendinopathy with no tear or partial tear who are experiencing active disease for at least 6 weeks and no more than 6 months at Baseline and who have failed conventional therapy.

Participants must have failed to at least 8 weeks of conventional therapy prior to Baseline (inadequate response to NSAIDs and/or paracetamol and physiotherapy; or intolerance to NSAIDs and/or paracetamol). Furthermore, participants should have performed at least 2 weeks of home-based standardized physiotherapy (during Run-in study period) prior to Baseline. Participants will only be included if there are no foreseeable plans for surgery in the affected shoulder during the study period.

Participants must have a WORC score ≤ 40 (where 100 points is symptom-free and 0 worst symptoms) at Baseline in combination with 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 7 days prior to Baseline visits. Participants must have nocturnal pain in shoulder on at least 3 out of 7 nights in the week prior to Baseline OR a positive “painful arc test” on examination.

The degree of tendon tear must be assessed during the Run-in period. Ultrasound may be performed in participants who are unwilling or unable to undergo MRI. Only participants who show no tendon tear or less than 50% partial thickness tear are eligible for the study. If participants show greater than 50% partial thickness tear, they are not eligible for this study.

The investigator must ensure that all participants being considered for the study meet the eligibility criteria listed in Section 5.1 und 5.2 No additional criteria should be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

Unless specified otherwise in the inclusion/exclusion criteria, the participant selection and inclusion in the study is to be established by checking through all eligibility criteria at both Screening and Baseline, except for assessments that according to Section 1.3 Schedule of Activities are performed at only one of these visits. In this case, it is acceptable to include the participant based on only Screening or only Baseline results.

A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a participant from enrollment into the study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Males and non-pregnant, non-nursing females between 18 and 65 years of age
3. Rotator cuff tendinopathy (unilateral)
4. Symptoms present for at least 6 weeks but not more than 6 months at Baseline
5. Moderate to severe rotator cuff tendinopathy demonstrated by all of the following criteria:
    a. WORC score ≤ 40 at Baseline
    b. Average weekly NRS pain score of ≥ 5 during the 7 days prior to Baseline
    c. Nocturnal pain in shoulder on at least 3 out of 7 days in the week prior to Baseline or positive "Painful Arc Test" on examination
6. Failure to at least 8 weeks of conventional therapy prior to Baseline: inadequate response to NSAIDs and/or paracetamol and physiotherapy; or intolerance to NSAIDs and/or paracetamol

5.2 Exclusion criteria

Participants fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusion criteria may be applied by the investigator, in order to ensure that the study population will be representative of all eligible participants.

1. Greater than 50% partial thickness tear as established by MRI or ultrasound during assessment in Run-in phase
2. Patients who are expected to require glucocorticoid treatment throughout the trial duration at Baseline (e.g., systemic, intramuscular, local injections in shoulder)
3. Previous surgery, or plans for surgery, during the study period, in the affected shoulder
4. Rheumatologic and chronic inflammatory diseases, including but not limited to: inflammatory bowel disease, polymyalgia rheumatica (PMR), PsA, axSpA and RA, fibromyalgia or severe pain disorder unrelated to the target shoulder
5. Both RF and anti-CCP antibodies positive at Screening
6. Either history of adhesive capsulitis/frozen shoulder, or current calcification in the tendon (in affected or contralateral shoulder) confirmed clinically or by medical imaging
7. Symptomatic osteoarthritis of the shoulder (gleno-humeral, acromioclavicular) in affected or contralateral shoulder confirmed by medical imaging
8. Patients with traumatic rupture that would be considered eligible for surgery for repair of cuff tear.
9. Neurological conditions including but not limited to cervical radiculopathy which in the opinion of the investigator, may explain the patient's symptoms

10. Any intra-articular/subacromial glucocorticoid treatment within 12 weeks prior to Baseline or more than 2 intra-articular/subacromial glucocorticoid injections for the treatment of the current episode of tendinopathy .
11. Any oral, intramuscular or i.v. glucocorticoid treatment 12 weeks prior to Baseline or during the current tendinopathy, whatever takes longer
12. Previous platelet rich plasma (PRP) or hyaluronic injections or fluoroquinolone/quinolone antibiotics within 12 weeks prior to Baseline or during the current tendinopathy, whichever takes longer
13. Neuromuscular or primary/secondary muscular deficiency which limits the ability to perform functional measurement (e.g., shoulder strength test)

Prohibited Medications and therapies

14. Use of prohibited medications and procedures including physical therapies such as shockwave therapy and others [as listed in Table 6-3]
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. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)

Lab screening

18. History or current clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as serum glutamic oxaloacetic transaminase (SGOT) (aspartate aminotransferase, AST), serum glutamic pyruvic transaminase (SGPT) (alanine aminotransferase, ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:

    AST/ALT may not exceed 3 x the upper limit of normal (ULN). Total bilirubin concentration may not exceed 1.5 x ULN. If the total bilirubin concentration is increased above ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. 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.) Patients with severely reduced kidney function (estimated glomerular filtration rate (eGFR) <29 ml/min/1.73m2), or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L).
19. 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.

General Medical history/active medical conditions

20. History or current diagnosis of significant ECG abnormalities, including clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular block without a pacemaker
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. Active ongoing inflammatory diseases or underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immuno-comprises the participant and/or places the participant at unacceptable risk for participation in an immunomodulatory therapy.
23. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization
24. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar classes.
25. Active systemic infections during the last two weeks prior to randomization (exception: common cold)
26. History of ongoing, chronic or recurrent infectious disease or evidence of TB infection as defined by a positive QuantiFERON TB-Gold test as indicated in the SoA. Patients with a positive test may participate in the study if further work up establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to guidelines must have been initiated.
27. Any surgical, medical, psychiatric or additional physical condition that the Investigator feels may potentially jeopardize the patient during participation in this study or could interfere with the study objectives, conduct or evaluation.

<u>Pregnancy language (basic contraception level)</u>

28. Women who have a positive pregnancy result prior to initiation of study drug or are pregnant or lactating.
29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    a. 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
    b. 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

c. Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant

d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

e. Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

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

Other

30. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
31. Inability or unwillingness to receive injections with PFS
32. Donation or loss of 400 mL or more of blood within 8 weeks before dosing
33. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

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. This minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

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

All participants who have signed informed consent and are randomized into the Treatment Period of the study will have all AEs **occurring after informed consent is signed** recorded on the CRF capturing AEs, and SAEs if applicable, i.e., when SAE criteria are met.

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

5.3.1 Replacement policy

No replacement policy will be applied.

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 rescreened. 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 ICF, the participant is assigned to the next sequential Participant No. available.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing and taking study treatment are outlined in the IRT manual.

Table 6-1 Investigational and control drug

Study drug name	Formulation	Unit dose	Packaging	Provided by
Secukinumab 300 mg	1 x 2 mL PFS	2 mL (300 mg)	Double-blind supply	Novartis
Placebo	1 x 2 mL PFS		Double-blind supply	Novartis

PFS – Pre-Filled Syringe

Participants will be given the injections by the site staff on site.

The PFSs are packed in a double blinded fashion and do not need to be prepared. The study treatments will be labeled as follows:

- Double-blind secukinumab and placebo pre-filled syringe (PFS) will be labeled AIN457 300 mg/2 ml/Placebo for dosing up to and including Week 12.

The investigational treatments are to be stored at 2°C to 8°C

6.1.1 Additional study treatment and therapies

A patient individualized conventional therapy will be given to all participants alongside the investigational drug and placebo. Additional study medication will NOT be provided by the Sponsor and has to be managed on site level. The patient individualized conventional therapy consists of:

a. Home-based standardized physiotherapy based on MOON regimen (Kuhn, 2009): participants will be instructed on home-based standardized physiotherapy by qualified study site personnel at screening visit. Participants will receive printed instructions to perform standardized physiotherapy at home until study completion. The performance is recommended once or twice daily. At each visit site personnel will inquire about status of home-based standardized physiotherapy to address any questions or hurdles and review instructions with the participant as needed and will document the status in eCRF accordingly. Concomitant in-person physiotherapy is allowed. However, new-onset of in-person physiotherapy should be avoided after randomization.

b. NSAIDs: Dose should be **optimized** to the individual participant to achieve the best efficacy and simultaneously the best tolerability. Dosing should not exceed the respective approved dosing and the maximum tolerable dose (e.g., max. dose of 2400 mg/day ibuprofen or max. dose of 4000 mg/day paracetamol or as directed by treating physician). Should high NSAID doses not be tolerated or contraindicated, participants may receive the maximum tolerated NSAID dose in combination with paracetamol as support if necessary. The optimized dose of NSAIDs/paracetamol, starting from Run-in period, should remain stable until Baseline. Dose adjustments (dose decrease and dose increase of NSAIDs/paracetamol relative to the optimized starting dose), discontinuation of NSAIDs/paracetamol and switch of NSAIDs are possible after baseline. Participants should keep their regular schedule of NSAID intake 24 hours ahead of a visit. [redacted].

c. Glucocorticoids may be given, if required. However, they should be avoided if possible. Participants who are **expected at Baseline to require glucocorticoid treatment** throughout the trial duration will **not be randomized**. In case glucocorticoids will be unexpectedly required during study period (local injections in the shoulder - including intramuscular injection or systemic), treatment with glucocorticoids is allowed at any time throughout the study. [redacted] Local glucocorticoid injections for current tendinopathy should not exceed 2 injections during the course of this study. Participants exceeding 2 injections continue the study as outlined in the SoA.

6.1.2 Treatment arms/group

Participants will be assigned at visit 3 (Baseline) to one of the following 2 treatment arms in a 1:1 ratio, with approximately 215 participants per arm.

- Group 1: Secukinumab 300 mg s.c. (1 x 300 mg)
- Group 2: Placebo s.c. (1 injection)

Treatment is administered at Day 1 (Baseline visit), and Weeks 1, 2, 3, 4, 8 and 12.

6.1.3 Treatment duration

The planned duration of treatment is 12 weeks. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the participant. For participants who in the opinion of the investigator are still deriving clinical benefit from AIN457, every effort will be made to continue provision of study treatment.

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.

AIN457 will be administered to the participant via the s.c. route of administration. Participants will be given the injections by the site staff on site.

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

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 in the Investigator's Brochure.

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) 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 Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

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

6.2.3 Instructions for prescribing and taking study treatment

Study treatment (1 x 300 mg s.c. secukinumab or matching placebo) will be administered with PFSs throughout the study.

S.c. administration with pre-filled syringes

Secukinumab solution for s.c. injection (300 mg in 2.0 mL active/placebo) will be provided in PFSs.

Study treatment interruption should be avoided with the following exceptions:

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

Any study treatment interruption must be recorded on the corresponding eCRF page.

Table 6-2 Dose and treatment schedule

Investigational/ Control Drug	Dose	Frequency
Secukinumab	300 mg: 1 x 2 mL (300 mg)	Week 0, 1, 2, 3, 4, 8 and 12 (7 doses in total)
Placebo	1 x 2 mL	Week 0, 1, 2, 3, 4, 8 and 12 (7 doses in total)

All kits of study treatment assigned by the Interactive Response Technology (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 visit, all eligible participants will be randomized via Interactive Response Technology (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.

Follow the details outlined in the IRT manual regarding the process and timing of treatment assignment and randomization of participants.

6.3.2 Treatment blinding

Participants, investigator staff, persons performing the assessment and the Novartis Clinical Trial Team (CTT) will remain blind to the identity of the treatment from the time of randomization until database lock.

The following methods will be used to maintain the blinding:

(1) Randomization data will be kept strictly confidential until the time of the final database lock and will not be accessible by anyone else involved in the study.

(2) The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Unblinding 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.

All Sponsor staff (study statistician, study programmer, biomarker expert, clinical trial team, decision boards etc.) will stay blinded to treatment assignments (except in the case of a safety event necessitating unblinding) until after database lock for the analysis of the primary endpoint at Week 24. Study monitors will remain blinded throughout the study.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until database lock for the primary endpoint at Week 24.

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´s safety.

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 need to 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 unblinding can be performed at any time.

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

After study participation, the participant will continue to be treated at the Investigator's discretion according to local practice. Continuing medical care must be provided by the investigator and/or referring physician based on participant availability for follow-up or must refer them for appropriate ongoing care.

6.4.1 Post-trial access

A Post Trial Access program is not planned.

6.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting, please see the respective sections.

6.6 Concomitant therapy

6.6.1 Concomitant therapy

The investigator must instruct the participant to notify the study site about any new medications he/she takes after the participant has been enrolled into the study.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate CRFs.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

[redacted]

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication.

For physiotherapy, please refer to Section 6.1.1 Additional study treatment and details provided in the separate Exercise Manual for participants.

6.6.2 Prohibited Medication and Procedures

Use of the treatments displayed in Table 6-3 is NOT allowed after the start of the washout period unless specified otherwise below.

Live vaccines should not be given until 12 weeks after last study treatment administration. If live vaccination is necessary at week 24, it should be done after assessments at week 24 when study is completed.

Glucocorticoids should be avoided. Participants who are **expected to require glucocorticoid treatment** throughout the trial duration (e.g., systemic, intramuscular, local injections in shoulder) will **not be enrolled**. In case glucocorticoids will be unexpectedly required during study period (local injections in the shoulder - including intramuscular injection or systemic), the study medication will be nevertheless continued. Reasons for glucocorticoid use, dose and duration must be documented. Local glucocorticoid injections for current tendinopathy should not exceed 2 injections during the course of this study. Participants exceeding 2 injections continue the study as outlined in the SoA.

Other physical treatment modalities such as shockwave therapy, therapeutic ultrasound, laser therapy, iontophoresis, transcutaneous electrical nerve stimulation, therapeutic x-ray radiation, hyperbaric oxygen therapy, magnetic field therapy, hyperthermia are prohibited 12 weeks prior to Baseline and during the course of the study.

Surgery in the affected shoulder leads to the discontinuation of study medication.

Table 6-3 Prohibited medications

Medication	Prohibited period (prior to Baseline)	Action taken
Any immunomodulating biologic drugs, including but not limited to TNF or other biologic drugs targeting IL-17 or IL-17 receptor2	Never[1]	Discontinue study medication
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents[2]	Never	Discontinue study medication
DMARDs (e.g., MTX and tofacitinib) and apremilast[2]	Never	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
Analgesics other than NSAIDs/paracetamol and low strength opioids PRN	2 weeks[3]	Discontinue the prohibited medication. All medications including dose and duration must be recorded and reasons for use of other analgesics documented
High potency opioids	12 weeks	Discontinue study medication
Systemic glucocorticoids	12 weeks or during the current tendinopathy, whichever takes longer	Glucocorticoids should be avoided. Participants who are expected to require glucocorticoid treatment throughout the trial duration will not be recruited. In case glucocorticoid use will be unexpectedly required during study period, the study medication will be nevertheless continued. Reasons for glucocorticoid use, dose and duration must be documented
Local glucocorticoid injections in the shoulder (including intramuscular injection)	12 weeks	Participants who are expected at Baseline to require glucocorticoid treatment throughout the trial duration will not be recruited. In case glucocorticoid use will be unexpectedly required during study period, the study medication will be nevertheless continued. Reasons for

Medication	Prohibited period (prior to Baseline)	Action taken
		glucocorticoid use, dose and duration must be documented. Participants should not receive more than 2 injections during the course of the study. Participants exceeding 2 injections continue the study as outlined in the SoA
Fluoroquinolone	12 weeks or during the current tendinopathy, whichever takes longer	Discontinue study medication
Live vaccinations[4]	6 weeks	Discontinue study medication
Platelet rich plasma injections in the affected shoulder or any other joint tendon	12 weeks or during the current tendinopathy, whichever takes longer	Discontinue study medication
Hyaluronic acid injections in the affected shoulder or any other joint tendon	12 weeks or during the current tendinopathy, whichever takes longer	Discontinue study medication
Oral or topical retinoids	12 weeks	Discontinue study medication

1 Never = no prior exposure is allowed, and medication is prohibited from study start and up to and including follow-up visit

2 These agents fall under the category of biologic immunomodulators and are prohibited medications

3 Period in weeks refers to washout of prohibited medications during screening counted from randomization visit Administration of these agents requires study discontinuation

4 The effect of secukinumab on live vaccines is unknown; therefore, live vaccines should not be administered during participation in the study

6.6.3 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a participant is experiencing either no benefit from participation in the trial or worsening / exacerbation of their disease. Rescue medication will not be provided by the sponsor.

Glucocorticoids may be used as rescue medication. However, if possible, glucocorticoids should be avoided. Rescue medication can be used from Baseline as outlined in Section 4.

Use of rescue medication must be recorded accordingly on the corresponding eCRF.

Efficacy and safety will be assessed in detail at every study visit (except for visits at week 1 and week 3, where efficacy is not assessed). Participants who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Reasons for discontinuation must be recorded accordingly on the corresponding eCRF.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment (excluding additional study treatment) for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) other than withdrawal of informed consent should not be considered as discontinued from the study. Where possible, the participants should return for the study visits indicated in the Assessment Schedule during treatment.

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 - participant may choose to discontinue study treatment for any reason at any time.
- Pregnancy (see Section 8.4.5 (Safety) and Section 8.6.4 (Pregnancy reporting))
- The Investigator believes that continuation would negatively impact the safety of the participant or the risk/benefit ratio of trial participation.
- Use of prohibited treatment as per recommendations in the prohibited treatment section (6.6.2) including surgeries of the affected shoulder
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of the following adverse events:
  - Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable co-medication
  - Life-threatening infection
- Any protocol deviation that results in a significant risk to the participant’s safety.
- Adverse events, abnormal laboratory values or abnormal test results that indicate a safety risk to the participant.
- 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.

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

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.

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 the participant remains in the study and continues the visits as outlined in the SoA.

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

7.2 Participant discontinuation from the study

Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. This final visit should include all EOS assessments.

At this final visit, the AE and concomitant medications should be recorded in the eCRF:

For all premature discontinuations, if the patient fails to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow up section. This contact should preferably be done according to the study visit schedule.

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

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 (EoS) at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

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

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

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

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

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

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

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

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

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

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

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 the Investigator should 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 lost to follow-up until due diligence has been completed or until the EoS.

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 this indication

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 EoT 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. Novartis will be responsible for informing Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) 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.

8.1 Screening

Patient's eligibility for the study will be assessed during the Screening period (Day -42 to -1) and at the Baseline Visit. It is permissible to re-screen a participant once if she/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Patients who fail Screening for any reason may be re-screened once. Patients who are re-screened must sign a new ICF and be issued a new Patient No. before any study-related assessment is performed or any data for the Screening Period are collected for the patient under the new Patient No.

The Investigator or qualified site staff will record the re-screening on the Re-screening eCRF page and the applicable Screening number the patient was issued prior to the current Screening number. The date of the new informed consent signature must be entered on the Informed Consent eCRF page to correspond with the new Screening Patient No.

The Withdrawal of Consent eCRF page must be completed if consent was withdrawn during the Screening Period before the patient was randomized.

8.2 Participant demographics/other Baseline characteristics

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

- Year of birth, age, sex, race
- Source of participant referral (if applicable)
- Relevant medical history and current medical conditions, not including tendinopathy of rotator cuff
- Relevant tendinopathy of rotator cuff and general medical history/current medical condition data (until date of signature of informed consent), such as date of diagnosis of tendinopathy, previous tendinopathy therapies, especially pain medication and physiotherapy
- Potential glucocorticoid treatment and information on potential tear on MRI or ultrasound will be recorded to assess participants for eligibility

Whenever possible, diagnoses and not symptoms will be recorded. For screening failures record of demographic information, IC/EC and informed consent is sufficient.

All prescription medications, over-the-counter drugs and significant non-drug therapies 6 months prior to the start of the study must be documented. See the protocol Section 6.6.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

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

8.2.1 Hepatitis screen, HIV screen

Hepatitis B and/or hepatitis C and/or HIV serology testing are to be performed during screening period, only in case study site/lab personnel comes in contact with blood, tissue or bodily fluids of participants through contact with injection needle, cut, splash on mucous membrane or through skin damage. If HIV test is seropositive, it should be confirmed by Western blot.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Results for Hepatitis and HIV tests will be available as source data at the study site and will not be recorded within the CRF.

8.2.2 X-ray of the shoulder

An X-ray of the shoulder is not required but strongly recommended as per national guidelines.

8.2.3 Ultrasound of the shoulder

Ultrasound may be performed if participants are unable or unwilling to undergo MRI. The assessment is to be performed maximum 14 days before Baseline as indicated in Section 1.3 Schedule of Activities. This must be collected as source data and documented in the eCRF accordingly.

B-mode Ultrasound is utilized to rule out major structural damage to the tendon (i.e., more than 50% tear) or other shoulder pathologies.

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

8.3.1 The PRO efficacy measures collected for primary, secondary [redacted] objectives:

The impact of tendinopathy on various aspects of participant's health-related quality of life (QoL) will be assessed by the following instruments:

- The WORC index score (WORC score and WORC score in each subdomain)
- The QuickDASH score
- The EQ-5D-5L score
- SF-36

- Assessment of pain (NRS)
- Patient global assessment score (PaGA VAS)

[redacted]

All questionnaires will be available in the local language. The participants will be asked to fill in these PROs at the clinic at the visits specified in Section 1.3 Schedule of Activities.

Study participants should be given sufficient instruction, space, time and privacy to complete all study PROs. The study coordinator should check the responses to the questionnaire for completeness and encourage the participant to complete any missing responses. If participants experience any difficulties with submission after they complete the PROs, the study staff should 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 prior to the study evaluation completion visit. However, if participants refuse to complete PROs, this should be documented in study source records. Participants´ refusal to complete study PROs are not protocol deviations.

Completed questionnaires and patient diaries will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the participant. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 8.6 of the protocol. Investigators should not encourage the participants to change the responses reported in the completed questionnaires.

8.3.1.1 The Western Ontario Rotator Cuff (WORC) index

The WORC index is a patient reported outcome tool, uniquely developed for the rotator cuff diseases 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). Items are scored by a 10 cm VAS. The best possible result is 0 (asymptomatic patient) and the worst possible result is 2100 (highly symptomatic). The WORC Index has a recall period of 1 week and is filled in by the participant at the clinic at visits specified in Section 1.3 Schedule of Activities.

8.3.1.2 The Quick Disability of the Arm, Shoulder and Hand (DASH) questionnaire

The QuickDASH is an abbreviated form of the DASH. It is a patient reported outcome tool, which has been developed by the AAOS along with the Institute for Work & Health (Toronto, Ontario, Canada) (Institute for Work & Health, 2020). The QuickDASH Index is self-administered and uses 11 items to measure physical function and symptoms in participants with any or multiple musculoskeletal disorders of the upper limb. Each item of the QuickDASH has five response options. The total score is reported on a 100-point scale, with 100 indicating the

most disability. It has a recall period of 1 week. The tool is filled in by the participant at visits specified in Section 1.3 Schedule of Activities.

8.3.1.3 EuroQol 5D (EQ-5D-5L)

The EQ-5D-5L is a widely used, self-administered questionnaire designed to assess health status in adults. The purpose of the EQ-5D-5L in this study is to assess the general health status of the participants. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Participants rate each of these items from : “no problem”, “slight problems”, “moderate problems”, “severe problems”, “extreme problems/unable" A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented VAS where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires approximately 5 to 10 minutes to complete.

The EQ-5D-5L contains six items designed to assess health status in terms of a single index value or health utility score. One of the strengths of the EQ-5D-5L approach is that it allows "weighting" by the participant of particular health states and the generation of participant utilities. Published weights are available that allow for the creation of a single summary health utility score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction. The EQ-5D-5L is filled in by the participant at visits specified in Section 1.3 Schedule of Activities.

8.3.1.4 Patient’s assessment of Pain (Pain NRS)

The score for pain will be assessed by using an 11-point NRS ranging from 0 “no pain at all” to 10 “worst possible pain”, after the question *“On a numeric scale of 0-10 where would you rate your pain at this time”*. The Pain NRS is filled in by the participant at visits specified in Section 1.3 Schedule of Activities and daily in the participants diary during Run-in phase.

8.3.1.5 Participant’s global assessment of disease activity (PaGA VAS)

The participant’s global assessment of disease activity will be performed using 100 mm VAS ranging from “no activity” to “most active”, after the question " *Please indicate with a vertical mark (|) through the horizontal line the global activity of your disease in the last 24 hours*”.

The PaGA VAS is filled in by the participant at visits specified in Section 1.3 Schedule of Activities.

8.3.1.6 Short Form Health Survey (SF-36)

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and participants with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and

Mental Health (Ware, et al., 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware, et al., 1994). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different diseases, differentiating the health benefits produced by different treatments, and in screening individual participants. The purpose of the SF-36 in this study is to assess the health-related quality of life of participants.

The standard version with a 4-week recall period is filled in by the participant at visits specified in Section 1.3 Schedule of Activities.

[redacted]

8.3.2 Appropriateness of efficacy assessments

The efficacy assessments selected are appropriate for this indication/participant population and in accordance with German HTA methodology.

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 Section 8.6.

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. Assessments done as a part of the safety evaluation include:

- Evaluation of AE/ SAE's
- Physical examination
- Height and Weight
- Vital signs
- TB screening: QuantiFERON TB-Gold test
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Glucose, Urinalysis)
- Pregnancy and assessment of fertility

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 which meet the definition of an AE must be recorded in the Adverse Event eCRF.

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

8.4.2 Body 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.

8.4.3 Vital signs

This will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position.

Clinically notable vital signs are defined in Appendix 3: Clinical laboratory tests.

8.4.4 Clinical safety laboratory tests

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be recorded, as either medical history/current medical conditions or adverse events as appropriate and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should be contacted.

As per Section 4.5, changes in safety assessments can be added as one of the risk mitigation procedures during public health emergency declared by local or regional authorities.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used 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.

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

Clinically notable laboratory findings are defined in Appendix 3: Clinical laboratory tests.

Table 8-1 Laboratory tests

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelet count, Red blood cell (RBC) count, and White blood cell count (WBC) with differentials (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) (absolute value and %).
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Blood Urea Nitrogen (BUN)/Urea, Calcium, Creatine kinase (CK), Creatinine, Gamma-glutamyl-transferase (GGT), high sensitivity CRP, Phosphate, Potassium, Sodium, Total Bilirubin, Total Protein, and Uric Acid at all timepoints specified in Section 1.3 Schedule of Activities. If the Total Bilirubin concentration is increased above 1.5 times the ULN, Direct and Indirect reacting Bilirubin should be differentiated. Triiodothyronine (T3), Thyroxine (T4), Thyroid-stimulating Hormone (TSH), RF, anti-CCP Antibodies. Follicle Stimulating Hormone (FSH) is only done at screening and only in participants who are reported post-menopausal at screening.
Urinalysis	Macroscopic Panel for Blood, Protein, and WBC/Leukocytes will be performed at site and documented as source data. If dipstick measurement results are positive (abnormal), results will be captured in the CRF. Microscopic Panel must be assessed following an abnormal dipstick test with results captured in the CRF.
Hepatitis markers/ HIV serology testing	HBV Antibody, HCV Antibody, HIV 1/2 p24 Immunoassay; confirmatory tests by Western Blot for HIV, HBV and HCV to be measured only in case study site/lab

	personnel comes in contact with blood, tissue or bodily fluids of participants through contact with injection needle, cut, splash on mucous membrane or through skin damage.
Lipid panel and glucose	A lipid profile including Cholesterol, Glucose, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and Triglycerides will be measured from a fasting blood sample.
Pregnancy Test and Assessment of Fertility	Serum pregnancy test Urine pregnancy test Confirmatory serum pregnancy required in case of positive urine pregnancy test (see Section 8.4.5)

8.4.5 Pregnancy testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

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

A serum β-hCG (human Chorionic Gonadotropin) test will be performed in all women at Visit 1 (screening). All pre-menopausal women who are not surgically sterile at screening will have local urine pregnancy tests as indicated in Section 1.3 Schedule of Activities. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the participant must be discontinued from the trial. Pregnancy testing results are kept in the source data documentation.

As per Section 4.5, changes in safety assessments can be added as one of the risk mitigation procedures during public health emergency declared by local or regional authorities.

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 immediately**. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the participant must be discontinued from the trial. 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.

Assessments of Fertility

Refer to Section 5.2 point 29 for criteria to determine women that are not of child bearing potential.

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.

8.4.6 Other safety evaluations

8.4.6.1 Tuberculosis screening

A central laboratory immunological test (QuantiFERON TB-Gold) must be performed at the screening visit to screen the participant population for latent TB infection. The results must be known prior to Baseline 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 TB
- if presence of latent TB is established then treatment according to local country guidelines must have been initiated.

Central laboratory test for 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.

8.4.6.2 Assessment of anti-CCP antibodies and the rheumatoid factor

Blood (20 mL) will be obtained at the Screening Visit (Visit 1) for anti-CCP antibodies and RF assessment.

8.4.7 Appropriateness of safety measurements

The safety measures used in this study are standard measures for assessing the safety of a biological drug in participants with Rotator Cuff Tendinopathy.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

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.

Clinician reported outcomes (ClinRO)

The impact of secukinumab 300 mg s.c. on improving signs and symptoms in participants with rotator cuff tendinopathy will be assessed by the following ClinRO measures:

- Range of Movement (ROM)

  Passive and active ROM of the shoulders will be assessed by the investigator at timepoints defined in Section 1.3 Schedule of Activities. The ROM assessment will only be done once per visit. The results will be recorded in the eCRF.

  The ROM assessment will be done in both arms using a goniometer and includes abduction, forward flexion, extension, and internal/external rotation. Additionally, the "Painful Arc Test", the Apley scratch test and the full/empty cup test will be performed:

  - "Painful Arc Test": The patient expresses pain with movements between 60-120°. Test result is given as negative or positive. To be noted both for active and passive ROM.
  - Full/empty cup test: The arm is abducted to 90 degrees, 30 degrees flexion, in the plane of the scapula and full internal rotation (empty can) and full external rotation (full can), elbow extended. The patient resists downward pressure exerted by the examiner at patient´s elbow or wrist. Test result is given as negative or positive.
  - Apley scratch test: With the patient seated, the patient places the hand behind the head to touch superior angle of opposite scapula, and the patient places the hand of the affected shoulder behind back to touch the inferior angle of opposite scapula. Test result is given as negative or positive. The test is done first on the non-affected shoulder, then on the affected shoulder. To be done both for active and passive ROM.

- Shoulder/arm muscle strength

  Shoulder muscle strength will be tested with a handheld dynamometer. For all movements, the hand-held device should be applied in a direction perpendicular to the force being generated. Each test will be done once per assessment and last for 5s. The results will be recorded in the eCRF (in Newtons). The strength tests of the shoulder include adduction, abduction in the scapular plane, and internal/external rotation.

  The rotator cuff functional index will be calculated by Novartis using the muscle strength measurements as described by (Osbahr, et al., 2006).

Detailed instructions to assess ClinRO are outlined in the ClinRO manual.

Patient reported outcomes (PRO)

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

Participant questionnaires are completed in German language.

The participant should be given sufficient space and time to complete the self-administered PRO measure(s). Trained study-site personnel has to be available for assistance.

The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file. Paper-based PROs can be used as backup if electronic data capture is temporarily not available.

Completed measure(s) must be reviewed and assessed by the Investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, Investigators should not encourage the participant to change responses reported in the completed questionnaires. Investigators must follow reporting instructions outlined in Section 8.6 of the study protocol.

The impact of secukinumab 300 mg s.c. on improving signs and symptoms in participants with rotator cuff tendinopathy will be assessed by PRO measures listed in Section 8.3.1 and additionally:

[redacted]

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

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, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (see Section 7).

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.

8.6.1 Adverse events

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

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, and 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 ongoing) and the outcome 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 investigational treatment.

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

- Dose not changed
- Dose reduced/increased
- Drug interrupted/permanently discontinued

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 the 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 84 days after the participant has taken 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.

Information about common side effects already known about the investigational drug can be found in the IB. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and has then to be discussed with the participant.

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 should 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 participants with underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying adverse events. Clinically notable laboratory values and vital signs are defined in Appendix 3: Clinical laboratory tests.

The Investigator must also instruct each participant to report any new adverse event (beyond the protocol observation period) that the participant, or the participant's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the eCRF; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

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 ICH-E2D Guideline 2004 (EMA, 2004)).

- 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 ICH-E2D Guideline 2004 (EMA, 2004)).

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.

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

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 the last day of study (which is 12 weeks after last administration of study treatment) 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 in English; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Screen failures & Run-in failures

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

For participants considered Run-in Failures, SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Run-in Failure must be reported to Novartis.

Randomized participants

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last day of study (which is 12 weeks after last administration of study treatment) must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

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 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 European (EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the last day of study (which is 12 weeks after last administration of study treatment) should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Reporting of Suspected Hy's Law cases

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data. The Hy's Law criteria may be changed to increases of 2-fold above baseline values for subjects with elevated values before drug exposure.

8.6.4 Pregnancy

For all pre-menopausal women who are not surgically sterile:

- A serum β-hCG test will be performed in all women at Visit 1 (screening). All pre-menopausal women who are not surgically sterile at screening will have local urine pregnancy tests as indicated in Section 1.3 Schedule of Activities.
- A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the participant must be discontinued from the trial. 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 CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

8.6.5 Surgeries

Participants with rotator cuff tendinopathy could require surgery due to symptom worsening or progressions of tears. Unblinding should precede surgery. It is recommended to follow the DGRh guidance and schedule a surgery 4 weeks after the last secukinumab application. Emergency surgeries can take place at any time (Albrecht, et al., 2021).

8.6.6 Adverse events of special interest

There are no adverse events of special interest.

8.7 Pharmacokinetics

PK parameters are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Reporting of study treatment errors, study treatment misuse/abuse and overdose

Study treatment errors are unintentional errors in the prescribing, dispensing, and administration of study treatment.

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of study treatment, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF.

9 Statistical considerations

The analysis will be conducted on all participant data after database lock for the study. The data will be analyzed by Novartis and/or by the designated Contract Research Organization (CRO). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all participants who received at least one dose of study/reference treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

9.2 Statistical analysis

Due to early termination of Secukinumab Phase 3 trials in RCT (Rotator Cuff Tendinopathy) screening has been discontinued on 17-MAY-2024. Patients that have been screened until 17-MAY-2024 can be randomized and all randomized patients can complete the study. A number of 63 patients have been randomized, which would lead to 31/32 patients per arm. The resulting power under previous assumptions will be ca. 24%. Therefore only a descriptive analysis will be performed for all endpoints.

9.2.1 Participant demographics and other Baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively by treatment group and in total for the FAS and Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented.

Relevant medical history and current medical conditions at Baseline will be summarized by system organ class (SOC), preferred term (PT) and treatment group.

9.2.2 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented.

The duration of exposure in weeks to secukinumab 300 mg s.c. vs. placebo will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

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

The primary objective of this trial is to demonstrate that the efficacy of 12 weeks of treatment with secukinumab 300 mg s.c. is superior to placebo (both arms in combination with patient individualized conventional therapy), in participants with moderate to severe rotator cuff tendinopathy, based on change from Baseline in WORC score at week 24.

9.3.1 Definition of primary endpoint(s)

WORC (Wessel, et al., 2011)

The Western Ontario Rotator Cuff Index is a self - reported shoulder- specific QoL measure. The WORC Index consists of 21 items grouped in five domains: Physical symptoms (items 1-6), sports/recreation (items 7-10), work (items 11-14), lifestyle (items 15-18), emotions (items 19-21).

The impact of each item is rated on a visual analogue scale (0-100 mm). A score of 0 points indicates no impact on QoL, while a score of 100 points indicates the worst-case scenario. Thus, it is possible to score from 0 to 2100 points. To present the score in a more clinically meaningful format, the score is reported as a percentage of normal by subtracting the total score from 2100, dividing by 2100, and multiplying by 100. Total final WORC scores can, therefore, vary from 0%, the lowest functional status level, to 100%, the highest functional status level.

Please refer to Section 3.1.

9.3.2 Statistical model, hypothesis, and method of analysis

The alternative hypothesis is that the effect of secukinumab 300 mg s.c. is superior to placebo, in patients with moderate to severe rotator cuff tendinopathy, based on change from Baseline in WORC score at week 24. The complementary null hypothesis states that there is no difference between secukinumab 300 mg s.c. and placebo.

The primary endpoint (change from Baseline in WORC score at Week 24) will be analyzed by a mixed model for repeated measures (MMRM) including all WORC scores available. Between-treatment differences in the change from Baseline in WORC score will be evaluated using MMRM with treatment group and analysis visits (up to week 24) as factors, and Baseline WORC score as continuous covariate. Treatment group by analysis visit will be included in the model. An unstructured covariance matrix will be assumed. Least-square mean differences with corresponding confidence intervals and p-values will be calculated for each visit time point as estimates for the treatment effect.

9.3.3 Handling of intercurrent events of primary estimand

For the analysis of the primary endpoint, all patients of the FAS will be included. A patient with missing assessment will be analyzed by means of a mixed-effect model for repeated measures (MMRM), which is valid under the missing at random (MAR) assumption.

9.3.4 Handling of missing values not related to intercurrent event

The primary endpoint will be analyzed by means of a mixed-effect model for repeated measures (MMRM), which is valid under the missing at random (MAR) assumption. Missing data for continuous efficacy endpoints due to missed or skipped visits will therefore not be applicable to multiple imputation.

9.3.5 Sensitivity analyses

In case of a substantial amount of missing data, alternative analyses not relying on the MAR assumption (e.g. Retrieved Drop-Out, Jump to Reference, Copy Reference) may be considered.

9.3.6 Supplementary analysis

Supportive analyses to be conducted are primarily related to investigating possible subgroup-by treatment interaction effects for the following subgroups:

- Age (≤50 vs. >50)
- Gender (male vs. female)
- Concomitant medication (GC infiltration vs. no GC infiltration required)

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

Please refer to Section 3.1.

9.4.1 Efficacy endpoint(s)

Secondary outcomes will be analyzed analogously to the primary endpoint where appropriate, e.g. continuous endpoint variables will be evaluated like the primary endpoint using a MMRM, with treatment group and analysis visits as factors and each respective baseline score value of the endpoint variable as a covariate. Treatment group by analysis visit will be included as interaction term in the model. An unstructured covariance matrix will be assumed. Additionally, means standard deviations, median, minimum and maximum values for continuous variables will be presented for each visit, as will be the change from baseline. These descriptive statistics will also be presented for the primary endpoint.

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 Baseline data which will also be summarized where appropriate (e.g., change from Baseline 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).

Adverse events

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

The number (and percentage) of participants with treatment emergent adverse events (events that started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following way:

- by treatment, primary system organ class and preferred term.

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

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time, and if ranges are available, abnormalities will be flagged. Analysis of the vital sign measurements using summary statistics for the change from Baseline for each post-Baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from Baseline will only be summarized for patients with both, Baseline and post-Baseline values.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time, and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

9.4.3 Patient reported outcomes

See Section 9.3 for PRO related to primary objective and Section 9.4 for PROs related to secondary objectives.

[redacted]

9.6 Interim analysis

Not applicable.

9.7 Sample size determination

Although the primary endpoint is designed for simple superiority trial, there is a need to make stronger assumptions for sample size due to AMNOG requirements.

Considering the regulatory assumptions of AMNOG (IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2022), the measure of effect size is defined by Hedges´ g with the given formula:

$$Hedges´g = \frac{\mu_1 - \mu_2}{\sigma},$$

with μ_1 denoting the mean of the secukinumab arm, μ_2 denoting the mean of the placebo arm and σ denoting the pooled standard deviation.

For AMNOG assumption Hedges´g should be significant for a small effect (i. e. >0.2), which corresponds to a shifted null hypothesis:

$$H_0: \mu_1 - \mu_2 \leq 0.2 \cdot \sigma \text{ and } \quad H_1: \mu_1 - \mu_2 > 0.2 \cdot \sigma.$$

To demonstrate superiority of secukinumab compared with placebo with a 90% power on a two-sided, 5% significance level with a shifted null hypothesis, the following assumptions were applied: The expected mean in WORC score in the secukinumab arm is 53.3, the observed mean in the placebo arm observed in phase II study CAIN457X2201) was 35.9. Due to concomitant therapy, we expect the effect in WORC score in the placebo arm to be 40. Assuming the common standard deviation $\sigma = 25$ as observed in phase II study and using the superiority test we obtain a shifted null hypothesis:

$$H_0: \mu_1 - \mu_2 \leq 5 \quad \text{and} \quad H_1: \mu_1 - \mu_2 > 5.$$

Under these assumptions, we obtain a difference in means of 8.3 after considering the shifted null hypothesis. This would give us a sample size of 192 participants in each group. To compensate for some expected drop-outs and other protocol deviations, a total of 430 patients should be recruited into this trial.

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, IB and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC/HA and reviewed and approved by the IRB/IEC/HA before the study is initiated.

Any amendments to the protocol will require IRB/IEC/HA 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 oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU regulation 536/2014 for clinical studies (if applicable), EU 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 GCP, with applicable local regulations (including EU Directive 2001/20/EC or EU 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 procedures

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.

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

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.

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 prevails 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 Committee structure

10.1.4.1 Steering committee

The Steering Committee (SC) will be established comprising investigators in the trial and Novartis/Sponsor 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 steering committee will be defined in the steering committee 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 25 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.

Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data

Capture (EDC) 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 before transfer of the data to the CRO working on behalf of Novartis. After database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

The Investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

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

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 Medical Dictionary for Regulatory Activities (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 Interactive Response Technology (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 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 ICF 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 Novartis or a CRO/ working on behalf of Novartis. 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 EudraCT or CTIS public website. In addition, after study completion (defined as last participant 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 or CTIS public website, etc.).

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

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

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 including 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 HA, where required, it cannot be implemented.

Protocol amendments

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

Only amendments that are required for participant safety may be implemented immediately provided the HA 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

AAOS	American Academy of Orthopaedical Surgeons
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
anti-CCP	Anti-Cyclic Citrullinated Peptide
AP	Anterior-Posterior
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
axSpA	Axial Spondyloarthritis
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CMO & PS	Chief Medical Office & Patient Safety
CRP	C-reactive protein

COA	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computer Tomography
CTT	Clinical Trial Team
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EoS	End of Study
EoT	End of Treatment
eSource	electronic Source
EQ-5D-5L	EuroQol-5D
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Gramm
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-Glutamyl Transferase
h	Hour
HA	Health Authorities
HAQ-DI	Health Assessment Questionnaire Disability Index
hCG	human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
i.v.	Intravenous
IB	Investigator’s Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IL	Interleukin
IL-17/IL-17A	Interleukin 17 and Interleukin-17A
IRB	Institutional Review Board
IRT	Interactive Response Technology
L	Liter
LDL	Low Density Lipoprotein
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
µL	micro Liter
µSv	micro Sievert
MID	Minimal Important Difference
mL	milli Liter
mSv	milli Sievert
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PASI	Psoriasis Area and Severity Index
PFS	Pre-Filled Syringe
PaGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PMR	Polymyalgia Rheumatica
PRO	Patient Reported Outcome
PRP	Platelet Rich Plasma
PsA	Psoriatic Arthritis
PT	Preferred Term

QoL	Quality of Life
QuickDASH	Change in Disability of Arm, Shoulder and Hand Questionnaire
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RDO	Retrieved drop out
RF	Rheumatoid Factor
RNA	Ribonucleic Acid
ROM	Range-Of-Movement
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SF-36	Short Form 36
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SD	Standard Deviation
SoA	Schedule of Activities
SoC	Standard of Care
SpA	Spondyloarthropathies
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
Tmax	Time to maximum concentration
TNF	Tumor Necrosis Factor-α inhibitor
TNF-IR	Tumor Necrosis Factor-α inhibitor Incomplete Responders
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization
WORC	Western Ontario Rotator Cuff (score)

10.2.2 Glossary of terms

Assessment	A procedure used to generate data required by the study.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives.
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician, etc.
Coded Data	Personal Data, which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time.
Control drug	A study intervention (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
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessment or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
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 source data/documents 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 as defined in the protocol.

Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g., screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis and other oversight authorities, as appropriate.
Estimand	As defined in the ICH E9(R1) addendum, estimand is 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 participants 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 population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes.
Medication number	A unique identifier on the label of medication kits
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" terminology is used in the protocol whereas term "Subject" is used in data collection

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.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else.
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.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
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 medications or other intervention).
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 administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
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 SoC, 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 ICF.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

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

Clinically notable values will be forwarded to Novartis/CRO at the same time that they are sent to investigators. Any action based on these laboratory values should be discussed with Novartis/CRO personnel.

Table 10-1 Safety Analyses: Expanded Limits and Notable Criteria

	Final Harmonization	
Laboratory Variable	**Notable Criteria**	
	Standard Units	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	> 3 x ULN	> 3 x ULN
SGPT (ALT)	> 3 x ULN	> 3 x ULN
Bilirubin	> 2 x ULN	> 2 x ULN
Alkaline phosphatase	> 2.5 x ULN	> 2.5 x ULN
RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES		
Creatinine (serum)	> 2 x ULN	> 2 x ULN

eGFR	> 2 x ULN	> 2 x ULN
HEMATOLOGY VARIABLES		
Hemoglobin	20 g/L decrease from Baseline	
Platelet Count	< 100 x 10E9/L	
White blood cell count	< 0.8 x LLN	
Neutrophils	< 0.9 x LLN	

eGFR is calculated using the following formula:

$eGFRcr = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{(-1.209)} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if race is black]

where:

Scr = standardized serum creatinine in mg/dL

$\kappa = 0.7$ (females) or 0.9 (males)

$\alpha = -0.329$ (female) or -0.411 (male)

$\min(Scr/\kappa, 1)$ is the minimum of Scr/κ or 1.0

$\max(Scr/\kappa, 1)$ is the maximum of Scr/κ or 1.0

Age (years)

in accordance with **Levey, A., S., et al. 2009.** A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med.* 2009, Vol. 150, 9, pp. 604-612. doi: 10.7326/0003-4819-150-9-200905050-00006

10.4 Appendix 4: Participant Engagement

Not applicable.

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