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AIN457 / Secukinumab

Clinical Trial Protocol CAIN457X2201

A randomized, double-blind, placebo-controlled, parallel group, Phase II, 24-week study investigating the efficacy, safety and tolerability of AIN457 in patients with active overuse tendinopathy refractory to oral NSAIDs/acetaminophen, physiotherapy or corticosteroid injections

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

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 9.2 of the Clinical Trial Protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO & PS) within 24 hours after awareness of the SAE
- Notify the Novartis Medical Lead
- The fax number(s) and email addresses are located in the Site Operations Manual.

Table of contents

Site Operations Manual (SOM) 2
Notification of serious adverse events 2
Table of contents 3
List of tables 7
List of figures 7
List of abbreviations 8
Pharmacokinetic definitions and symbols 11
Glossary of terms 12
Amendment 2 (March 2018) 14
Amendment 1 (October 2017) 15
Protocol summary 16
1 Introduction 21
1.1 Background 21
1.2 Nonclinical safety data 23
1.3 Clinical data 23
1.3.1 Human safety and tolerability data 23
1.3.2 Human pharmacokinetic data 24
1.4 Study purpose 24
2 Objectives and endpoints 25
2.1 Primary objective(s) 25
2.2 Secondary objective(s) 25
2.3 Exploratory objective(s) 26
3 Investigational plan 27
3.1 Study design 27
3.2 Rationale for study design 28
3.3 Rationale for dose/regimen, route of administration and duration of treatment 30
3.4 Rationale for choice of comparator 31
3.5 Rationale for choice of background therapy 31
3.6 Purpose and timing of interim analyses/design adaptations 32
3.7 Risks and benefits 32
3.7.1 Blood sample volumes 33
4 Population 34
4.1 Inclusion criteria 34
4.2 Exclusion criteria 35
5 Restrictions for study subjects 39

5.1 Prohibited treatment....39
6 Treatment....40
6.1 Study treatment....40
6.1.1 Investigational and control drug(s)....40
6.1.2 Additional study treatment....40
6.2 Treatment arms....41
6.3 Treatment assignment and randomization....41
6.4 Treatment blinding....42
6.5 Treating the subject....43
6.5.1 Instructions for prescribing and taking study treatment....43
6.6 Emergency breaking of assigned treatment code....44
6.7 Treatment exposure and compliance....44
6.8 Recommended treatment of adverse events....44
6.9 Rescue medication....45
6.10 Concomitant treatment....45
6.10.1 Physiotherapy....45
7 Study completion and discontinuation....46
7.1 Study completion and post-study treatment....46
7.2 Discontinuation of study treatment....46
7.3 Withdrawal of informed consent....47
7.4 Lost to follow-up....48
7.5 Early study termination by the sponsor....48
8 Procedures and assessments....49
8.1 Assessment schedule....49
8.2 Informed consent procedures....52
8.3 Patient screening....53
8.4 Information to be collected on screening failures....53
8.5 Patient demographics/other baseline characteristics....53
8.5.1 Hepatitis screen, HIV screen....53
8.5.2 Alcohol test, drug screen....54
8.5.3 X-ray of the shoulder....54
8.5.4 Treatment exposure and compliance....54
8.6 Efficacy....54
8.6.1 The PRO efficacy measures, primary and secondary objectives:....54
8.6.2 Clinician reported outcome (CRO) efficacy measures collected in the trial for secondary objectives....57

8.6.3 Imaging efficacy measures collected in the trial for secondary and exploratory objectives are: 57
8.7 Safety 58
8.7.1 Physical examination 59
8.7.2 Vital signs 59
8.7.3 Height and weight 59
8.7.4 ECG 59
8.7.5 Tuberculosis screening 60
8.7.6 Ultrasound of the shoulder 60
8.7.7 Chest X-ray 61
8.7.8 Tolerability of investigational treatments 61
8.7.9 Laboratory evaluations 61
8.7.10 Pregnancy and assessments of fertility 62
8.7.11 Additional parameters 63
8.8 Pharmacokinetics 63
8.9 Other assessments 64

Commercially Confidential Information

8.9.3 Immunogenicity 64

Commercially Confidential Information

9 Safety monitoring 66
9.1 Adverse events 66
9.2 Serious adverse event reporting 67
9.2.1 Definition of SAE 67
9.2.2 SAE reporting 68
9.3 Liver safety monitoring 69
9.4 Renal safety monitoring 70
9.5 Reporting of study treatment errors including misuse/abuse 70
9.6 Pregnancy reporting 71
10 Data review and database management 71
10.1 Site monitoring 71
10.2 Data collection 72
10.3 Database management and quality control 72
10.4 Data Monitoring Committee 73
10.5 Adjudication committee 73

11 Data analysis 73
11.1 Analysis sets 73
11.2 Subject demographics and other baseline characteristics 74
11.3 Treatments 74
11.4 Analysis of the primary variable(s) 74
11.4.1 Primary Variable(s) 74
11.4.2 Statistical model, hypothesis, and method of analysis 74
11.4.3 Handling of missing values/censoring/discontinuations 74
11.4.4 Summary statistics of safety 75
11.4.5 Sensitivity analyses 75
11.5 Analysis of secondary variable(s) 75
11.5.1 Efficacy / Pharmacodynamics 76
11.5.2 Safety 76
11.5.3 Pharmacokinetics 76
11.5.4 Pharmacokinetic / pharmacodynamic correlation analysis 76
11.5.5 Other assessments 77
11.6 Analysis of exploratory variables 77

11.7 Sample size calculation 77
11.8 Power for analysis of key secondary variables 77
11.9 Interim analyses 78
12 Ethical considerations 78
12.1 Regulatory and ethical compliance 78
12.2 Responsibilities of the investigator and IRB/IEC 78
12.3 Publication of study protocol and results 79
12.4 Quality control and quality assurance 79
13 Protocol adherence 79
13.1 Protocol amendments 79
14 References 80
15 Appendix 1: Clinically notable laboratory values and vital signs 83

List of tables

Table 5-1 Prohibited medications 39
Table 6-1 Overview of study medication 40
Table 6-2 Blinding and unblinding plan 43
Table 8-1 Assessment schedule 49
Table 9-1 Guidance for capturing study treatment errors 70
Table 15-1 Safety Analyses: Expanded Limits and Notable Criteria 83

List of figures

Figure 3-1 Study design 28

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
anti-CCP	Anti-cyclic citrullinated peptide
AP	Anterior-posterior
AS	Ankylosing spondylitis
ASES	American shoulder and elbow surgeons shoulder score
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CK	Creatinine kinase
CMO & PS	Chief Medical Office & patient safety
CRF	Case report/record form (paper or electronic)
CRO	Contract research organization
CSR	Clinical study report
CT	Computerized tomography
CTC	Common toxicity criteria
CV	Coefficient of variation
ECG	Electrocardiogram
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of the Study
eSource	Electronic source

EQ5D	EuroQol-5D
EU	Europe
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
HAQ-DI	Health assessment questionnaire disability index

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

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IB	Investigators brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of 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
i.v.	Intravenous
LFT	Liver function test

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MedDRA	Medical dictionary for regulatory activities
µSv	MicroSievert
mSv	MilliSievert
MRI	Magnetic resonance imaging

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NSAIDs	Non-steroidal anti-inflammatory drugs
PASI	Psoriasis area and severity index
PCR	Polymerase chain reaction
PD	Pharmaco-dynamic(s)
PFS	Prefilled syringe
PGA	Patient global assessment
PhGA	Physician global assessment
PK	Pharmacokinetic(s)

PPD	Purified protein derivative
PRO	Patient reported outcome
PRP	Platelet rich plasma
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RBC	Red blood cell(s)
RC	Rotator cuff
RF	Rheumatoid factor
RNA	Ribonucleic acid

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SAE	Serious adverse event
s.c.	Subcutaneous
sCR	Serum creatinine
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SD	Standard deviation
SOM	Site operations manual
SpA	Spondylarthritides
SUSAR	Suspected unexpected serious adverse reactions

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TB	Tuberculosis
TBL	Total bilirubin
Tmax	Time to maximum concentration
TNF	Tumor necrosis factor-α inhibitor
TNF-IR	Tumor necrosis factor-α inhibitor incomplete responders
ULN	Upper limit of normal

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VAS	Visual analog scale
WBC	White blood cell(s)
WHO	World health organization
WoC	Withdrawal of consent
WORC	Western Ontario rotator cuff (score)

Pharmacokinetic definitions and symbols

Cmin	The lowest serum concentration observed during a dosing interval [mass / volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
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 sponsors and other oversight authorities, as appropriate.
Investigational drug	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”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest

Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)
Screen failure	A subject who is screened but is not treated or randomized
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
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.
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
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol summary

Protocol number	CAIN457X2201
Full Title	A randomized, double-blind, placebo-controlled, parallel group, Phase II, 24-week study investigating the efficacy, safety and tolerability of AIN457 in patients with active overuse tendinopathy refractory to oral NSAIDs/acetaminophen, physiotherapy or corticosteroid injections
Brief title	Study of efficacy, safety and tolerability of AIN457 in patients with active overuse tendinopathy
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	Cosentyx is an anti-IL-17 antibody, approved for the treatment of PsA and AS, and there is a plenitude of evidence of efficacy in treating the enthesitis in patients with these symptoms in both these indications. 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) has provided recent evidence indicating that IL-17-expressing tendon-resident immune cells are present in human overuse tendinopathy and IL-17 mRNA and protein expression levels are increased in early human tendinopathic samples. IL-17, being a mediator of tendon inflammation, disrepair of tendon matrix and tenocyte apoptosis is thus considered to be a key player in the pathogenesis of overuse tendinopathy. The study design addresses the primary objective of determining the efficacy of secukinumab in improving signs, symptoms and structure in patients with overuse rotator cuff tendinopathy.
Primary Objective(s)	To assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving clinical symptoms at week 14
Secondary Objectives	To assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving symptoms over time To assess the structural changes in the rotator cuff tendinopathy over time To assess PK/immunogenicity in secukinumab treated patients To confirm the safety and tolerability of AIN457 in overuse rotator cuff tendinopathy over time

Study design	This is a randomized, double-blind, placebo-controlled, multi-center, Phase II study of s.c. secukinumab 300 mg in approximately 100 randomized patients with overuse rotator-cuff tendinopathy without systemic inflammatory disease and refractory to NSAIDs/acetaminophen, physiotherapy or corticosteroids. The patient and investigator will be blinded throughout the study, while the sponsor will be blinded until after the analysis of the primary endpoint. The study consists of a 4-week screening period, a 2-week run-in period, a 12-week treatment period and a 12-week follow-up period after last treatment (Figure 3-1). The population will consist of patients with MRI-positive unilateral overuse (non-systemic inflammatory) shoulder tendinopathy, 18 - 65 years of age. The screening period will be used to assess eligibility and to start/continue patients on physiotherapy. In the run-in period the patient should have 2 weeks of stable NSAID/acetaminophen intake and standardized physiotherapy (defined in the SOM). Patients who meet the eligibility criteria at screening after the run-in period will go through baseline evaluations. Eligible subjects 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. Randomization will be stratified by the following 2 factors: Partial tear/no tear and previous steroid injection (yes/no), in order to achieve approximate balance between these factors in the treatment groups. The assessments to address the primary endpoint will be performed at 14 weeks (2 weeks after the last injection). Patients will come to the out-patient clinic approximately 2-4 hours prior to dosing for the evaluations. Dosing will be on-site, except for injections at 1 and 3 weeks, that can be done either on site or by a nurse at the patient's home. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring.
Population	The population will consist of male and female patients at least 18 years of age, but under or equal to 65 years of age at the time point of randomization with a MRI-positive diagnosis of overuse (non-systemic inflammatory) unilateral shoulder tendinopathy with symptoms present for at least 6 weeks but not more than 12 months.

Key Inclusion criteria	Patients eligible for inclusion in this study must fulfill all of the following criteria: • Written informed consent obtained prior to all study specific screening procedures, as close to the start of the screening period as possible • Male or non-pregnant, non-lactating female patients 18 to 65 years of age at randomization • Presence of unilateral rotator cuff tendinopathy with: a. Symptoms present ≥6 weeks, but <12 months prior to randomization b. Tendinopathy with no more than a 50% tear as established by ultrasound at screening and MRI at baseline: Sein MRI tendinopathy scoring system grade I-III; with no tear or partial tear [maximum 50% tendon thickness (Bauer tendon thickness score maximum 2); AP length maximum 10 mm (Bauer tendon length score max 2)]. Maximum 50% of patients with partial tear c. Pain in the affected shoulder (at rest or on movement) on at least 3 days out of 7 days in the past week prior to baseline and a score of ≥4 out of 10 on a VAS pain scale d. Positive “Painful Arc Test” on examination and/or nightly pain in the affected shoulder on at least 4 out of 7 days in the past week prior to baseline • The rotator-cuff tendinopathy must have been refractory to standard treatment defined as: • NSAIDs / acetaminophen • In the run-in period patients should be on a stable dose of NSAIDs and/or acetaminophen for at least 2 weeks prior to randomization, not exceeding – e.g.: Ibuprofen 1600 mg/d, naproxen 1000 mg, diclofenac 105 mg/d, or diclofenac sodium enteric-coated tablets 150 mg/d, or equivalent. • If patients cannot tolerate these doses, the maximal tolerable dose should be used, and may be augmented with acetaminophen/paracetamol, at doses not exceed local guidelines or 4 g/day, whichever is lower. This medication should also be at a stable dose for at least 2 weeks. • If patients have contraindications to NSAIDs or to acetaminophen, these treatments can be omitted (contraindication, drug and dose must be specified in the eCRF). • If patients were refractory to at least 2 weeks of previous treatment as specified in 4 i/ii, NSAIDs or acetaminophen treatment can be omitted. • Physiotherapy • In the run in period patients should have had 2 weeks of a standardized physiotherapy treatment before randomization. In Czech Republic, patients should have had at least 6 weeks of physiotherapy prior to randomization. This includes the 2 weeks of standardized physiotherapy in run in phase.

Key Exclusion criteria	• History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes • Rheumatologic, inflammatory diseases, including but not limited to: PsA, AS and RA • Previous shoulder surgery in affected shoulder • History of adhesive capsulitis/frozen shoulder or calcification in the tendon (in affected or contralateral shoulder) confirmed by X-Ray, historic X-Rays can be used if performed within 3 months of baseline • Symptomatic osteoarthritis of the shoulder (gleno-humeral, acromioclavicular) (in affected or contralateral shoulder confirmed by X-Ray, historic X-Rays can be used if performed within 3 months of baseline • Neck conditions, including but not limited to cervical spine syndrome, which in the opinion of the investigator, may explain the patient's symptoms • Previous platelet rich plasma injections within the last 12 months prior to randomization
Study treatment	• Group 1: Secukinumab 300 mg s.c. (2 x 150 mg) • Group 2: Placebo s.c. (2 injections)
Pharmacokinetic assessments	• PK/immunogenicity assessment
Efficacy/PD assessments	Patient Reported Outcomes (PROs) • The WORC score • The QuickDASH score • The ASES score • The EQ5D-5L score • Patient's global assessment of disease activity Clinician Reported outcome • Physician's global assessment of disease activity Imaging • Shoulder MRI Commercially Confidential Information
Key safety assessments	Key safety assessments: • Evaluation of AE/ SAE's • Physical examination • Vital signs • Height and weight • Tuberculosis screening: QuantiFERON TB-Gold test or PPD skin test • Chest X-Ray • Electrocardiogram • Local tolerability (Injection site reactions) • Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis) • Pregnancy and assessment of fertility Commercially Confidential Information • Immunogenicity

Other assessments	Commercially Confidential Information
Data analysis	The primary end-point (change from baseline in WORC score at Week 14) will be analyzed by repeated measures analysis of covariance including all WORC scores available. Change at Week 14 will be compared between treatments to address the primary objective. The baseline WORC score will be included as a covariate. The stratification factors partial tear/no tear and previous steroid injection (yes/no) will be included in the model as fixed effects. A 95% one-sided (90% two-sided) confidence interval for the treatment effect at Week 14 will be reported. Missing variables will be considered missing at random. Initially, models with an unstructured within-subject covariance and a separate mean for each treatment and time point will be fitted. These models may be reduced in number of covariance and mean parameters by model comparison using tools such as the BIC criterion for model fit.
Key words	Overuse tendinopathy, shoulder, rotator cuff, IL-17A-Ab

1 Introduction

1.1 Background

Overuse tendinopathy is a complex multi-faceted disease of the tendon, clinically diagnosed after gradual onset of activity-related pain, decreased function and sometimes with localized swelling of the tendon (Riley 2005, Riley 2008). Historically the terms 'tendinitis' and 'tendinosis' have interchanged with the term 'tendinopathy', however, these definitions are now included in the spectrum of human tendon disorders ('tendinopathy'). Tendinopathy is a common overuse injury in the athletic and working populations; it is the most common reason for consultation for a musculoskeletal complaint, corresponding to around 30% of all such consultations with a general practitioner (Forde et al 2005; Riley 2008).

The exact incidence of overuse tendon injuries is not known, but in sports medicine, they account for 30% to 50% of all injuries (Scott and Ashe 2006). Generally, for physical workers, the prevalence of musculoskeletal symptoms increases with duration of employment (Forde et al 2005).

Upper limb tendinopathy

A systematic review showed that the incidence of rotator cuff tendinopathy ranges from 0.3% to 5.5% per year and the annual prevalence from 0.5% to 7.4% (Littlewood et al 2013). The incidence is higher in physical workers and athletes (15-20%) and in the wheelchair populations (31-73%). It is typically seen in swimmers, baseball-, tennis-, volleyball players (Kaux et al 2011).

Tennis elbow (lateral epicondylitis) is another frequent tendinopathy and is common in athletes of all ages participating in sports involving overhead or repetitive arm actions (Hume et al 2006). Its incidence in tennis players is as high as 9% to 40% (Maffulli et al 2003; Scott and Ashe 2006). The condition affects approximately 1 to 3% of the general population. Another elbow tendinopathy is the golfer's elbow (medial epicondylitis), which is a typical complaint in javelin throwing, baseball and golf (Maffulli et al 2003; Scott and Ashe 2006).

Lower limb tendinopathy

Achilles tendinopathy is the most prevalent lower extremity tendinopathy, with a 5.9% frequency in sedentary people and around a 50% frequency in elite endurance athletes (Scott and Ashe 2006; Fredberg and Stengaard-Pedersen 2008).

About one third of sports injuries treated in sports clinics concern the knees and one quarter of athletes treated for a knee injury are diagnosed with tendinopathy (Maffulli et al 2003). The most common knee disorder is jumper's knee (insertional patellar tendonitis), and its incidence is reported to be in the range of 7% to 40% (Fredberg and Stengaard-Pedersen 2008; Scott and Ashe 2006).

Treatments

Current treatments for tendinopathy are rest, icepacks and physiotherapy (including therapeutic ultrasound, laser therapy, hyperthermia and extra corporeal shockwave therapy). Evidence to support the widespread use of these therapies in tendinopathies remains inconsistent (Alfredson and Cook 2007). Non-steroidal anti-inflammatory drugs (NSAIDS), or local corticosteroid injections can give transient pain relief, but the long term benefit is questionable (Mohamadi et al 2017; Coombes et al 2010). Even more, it has been shown that repetitive steroid injections have the potential to accelerate tendon degeneration increasing the risk of tendon rupture (Mohamadi et al 2017; Coombes et al 2010). Autologous platelet rich plasma (PRP) injections are being used, however the evidence for long term efficacy is weak, thus the benefits of PRP for tendinopathy remain controversial, with several trials showing no efficacy compared with saline (Krogh et al 2013; de Vos et al 2010).

Overall, overuse tendinopathy is a disease with high medical need without adequate treatment options.

Secukinumab (AIN457, Cosentyx®), interleukin-17A (IL-17A) neutralization

IL-17A is a central cytokine in multiple autoimmune and inflammatory processes.

Recent evidence indicates that IL-17-expressing tendon-resident immune cells are present in human overuse tendinopathy and IL-17 mRNA and protein expression levels are increased in early human tendinopathic samples. In human tenocytes, IL-17 regulates pro-inflammatory cytokines, key apoptotic mediators and tendon matrix changes towards a mechanically inferior type III collagen phenotype. IL-17 being a mediator of tendon inflammation, disrepair of tendon matrix and tenocyte apoptosis is thus considered to be a key player in the pathogenesis of overuse tendinopathy (Millar et al 2017).

Secukinumab is a selective high-affinity fully human monoclonal antibody that neutralizes IL-17A and is approved in more than 70 countries for the following indications: 1) Moderate to severe plaque psoriasis in adult patients, including postular psoriasis (Japan only); 2) adults with active psoriatic arthritis (PsA); 3) adults with active ankylosing spondylitis (AS) (Cosentyx prescribing information 2016).

Enthesitis is the term used to describe inflammation at tendon, ligament or joint capsule insertions. It applies to diseases associated with the spondylarthritides (SpA) including AS and PsA. Enthesitis can be inflammatory or mechanically induced; the two may share common features (McGonagle and Benjamin 2009). Neutralization of IL-17 has proven efficacy in inflammatory enthesitis in PsA and AS, as seen in studies with secukinumab: CAIN457F- 2305, 2306, 2310, and 2312. In study CAIN457F2312, enthesitis was evaluated in the subset of patients who had disease activity at baseline. In this patient population secukinumab significantly increased the percentage of patients with resolution of enthesitis compared with placebo (CAIN457F2312 CSR). Overall, the percentage of patients without resolution of enthesitis at Week 24 was 67.6%, 57.8%, 51.8%, 59.6%, and 78.5% for secukinumab 75 mg, 150 mg, 300 mg, secukinumab pooled, and placebo groups, respectively. These differences vs. placebo were also greater for the 150 mg and 300 mg dose groups vs placebo ($p=0.0108$ and $p=0.0025$, respectively), while 75 mg vs was similar ($p=0.1678$) to placebo.

Neutralization of IL-17 with secukinumab is thought to reduce tendon inflammation and to stop tendon matrix disrepair and degeneration. Secukinumab will therefore be tested as a disease-modifying therapy for overuse tendinopathy.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure or Core Data Sheet.

Data from this study are aimed at supporting the planning and design of the Phase III studies for global submission of secukinumab as a treatment option for patients with active tendinopathy.

1.2 Nonclinical safety data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

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1.3.2 Human pharmacokinetic data

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1.4 Study purpose

The purpose of this Phase II study is to determine the efficacy of secukinumab in treating patients with a diagnosis of overuse, non-systemic inflammatory rotator cuff tendinopathy and to confirm the safety and tolerability profile of secukinumab in a dose of 300 mg s.c. given at day 1 and weekly until and including week 4, thereafter additional injections at weeks 8 and 12.

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. Patients will be followed up without treatment from week 12 to week 24 to investigate long-term safety.

2 Objectives and endpoints

2.1 Primary objective(s)

Objective	Endpoint
• To assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving clinical symptoms at week 14	• The Western Ontario Rotator Cuff (WORC) patient reported outcome (PRO) score at week 14

2.2 Secondary objective(s)

Objective	Endpoint
• To assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving symptoms over time	• WORC score at Weeks 2, 4, 8, 12, 18 and 24 • Disability of Arm, Shoulder and Hand Questionnaire (QuickDASH) score at Weeks 2, 4, 8, 12, 14, 18 and 24 • American Shoulder and Elbow Surgeons Shoulder Evaluation Form (ASES) score at Weeks 2, 4, 8, 12, 14, 18 and 24 • EQ5D-5L score at Weeks 2, 4, 8, 12, 14, 18 and 24 • Pain score using a VAS scale (considering the last 24 hours) at Weeks 2, 4, 8, 12, 14, 18 and 24 • Patient global assessment (PGA) score using a VAS scale (considering the last 24 hours), at Weeks 2, 4, 8, 12, 14, 18 and 24 • Physician global assessment (PhGA) score using a VAS scale (considering the last 24hours), at Weeks 2, 4, 8, 12, 14, 18 and 24
• To assess the structural changes in the rotator cuff tendinopathy over time	• MRI Sein score at Weeks 8, 14 and 24
• To assess PK/immunogenicity in secukinumab treated patients	• PK/immunogenicity assessment at Day 1, Weeks 4, 12, 24
• To confirm the safety and tolerability of AIN457 in patients with overuse rotator cuff tendinopathy over time	• Safety and tolerability assessments over time: Incidence and severity of AEs and SAEs; routine safety laboratory parameters

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

This is a randomized, double-blind, placebo-controlled, multi-center, Phase II study of s.c. secukinumab 300 mg in approximately 100 randomized patients with overuse rotator-cuff tendinopathy without systemic inflammatory disease and refractory to NSAIDs/acetaminophen, physiotherapy or corticosteroids. The patient and investigator will be blinded throughout the study, while the sponsor will be blinded until after the analysis of the primary endpoint. The study consists of a 4-week screening period, a 2-week run-in period, a 12-week treatment period and a 12-week follow-up period after last treatment (Figure 3-1).

The population will consist of patients with MRI-positive unilateral overuse (non-systemic inflammatory) shoulder tendinopathy, 18 - 65 years of age. Symptoms should have been present for at least 6 weeks but not more than 12 months. The tendinopathy must have been refractory to NSAIDS/acetaminophen as defined in the inclusion criteria. On MRI, patients may have no tendon tear or a partial tendon tear (up to 50% thickness, in max. 50% of patients). The patients should also have had at least 2 weeks of a standardized physiotherapy treatment.

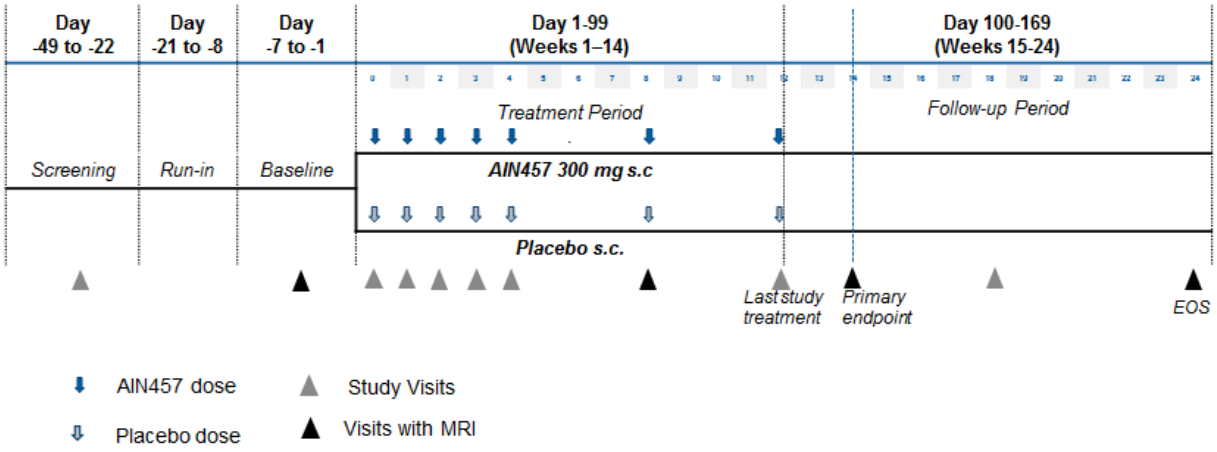
The screening period will be used to assess eligibility and to start/continue patients on physiotherapy. In the run-in period the patient should have 2 weeks of stable NSAID/acetaminophen intake and standardized physiotherapy (defined in the SOM). Patients who meet the eligibility criteria at screening after the run-in period will go through baseline evaluations.

Eligible subjects 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. Randomization will be stratified by the following 2 factors: Partial tear/no tear and previous steroid injection (yes/no), in order to achieve approximate balance between these factors in the treatment groups. The assessments to address the primary endpoint will be performed at 14 weeks (2 weeks after the last injection).

Patients will come to the out-patient clinic approximately 2-4 hours prior to dosing for the evaluations. Dosing will be on-site, except for injections at 1 and 3 weeks, that can be done either on site or by a nurse at the patient's home.

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

Figure 3-1 Study design



3.2 Rationale for study design

The study design addresses the primary objective of determining the efficacy of secukinumab in improving signs, symptoms and structure in patients with overuse rotator cuff tendinopathy. The study will enroll patients with inadequate response (determined by a VAS pain score ≥4) to physiotherapy or NSAIDs/acetaminophen or intolerance to NSAIDs/acetaminophen, using a double-blinded, randomized, parallel group design to minimize bias. At the time of inclusion, patients can be steroid-naïve or have inadequate response or intolerance to local steroid injection in the tendon, but last steroid therapy must have been >8 weeks prior to randomization. Patients must be naïve to IL-17 inhibition therapy.

The patient population with rotator cuff tendinopathy was chosen, as this is one of the most frequent tendinopathies. 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).

Currently, no Health Authority guideline exists for developing drugs for the overuse tendinopathy indication. The 14-week endpoint is chosen to allow the last injection at 12 weeks to take effect.

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, and a moment in time. One is specific for rotator cuff; two others are for arm and shoulder.

During the 2-week run-in period patients should take NSAIDs/acetaminophen at a stable and adequate (or maximally tolerable) dose, and still have inadequate control of symptoms at randomization. Alternatively NSAID should have been stopped due to intolerance. Patients who tolerate it will continue taking the NSAID regimen from the run-in period. Patients should not increase the NSAID/acetaminophen dose, but can choose to decrease the dose at any time. Dose adjustments are allowed after the primary endpoint at 14 weeks. During first 14 weeks of the study local steroid injection is not allowed. After assessment of the primary endpoint at week 14 patients may have 1 steroid injection during the last 10 weeks observation period. The stable NSAID dosing and avoidance of steroid injections are required in order not to have other variables than AIN457 influencing the effect on the tendinopathy.

The rationale for key design elements in this study include:

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

Double-blind: Blinding of subjects, investigators and sponsor up to the point of week 14, the primary endpoint, allows for an unbiased assessment of subjective readouts such as the efficacy parameters, especially the PROs and as well for adverse events evaluation. The blinding is maintained for patient and investigator beyond the primary endpoint until the end of the study to ensure reliable efficacy and safety measures. The sponsor will be unblinded after the primary endpoint analysis.

Placebo-controlled: A placebo arm is included in this study because it is not known whether secukinumab can improve tendinopathy, and because there is no disease modifying therapy available. However, standard of care with NSAIDs and physiotherapy will be given to both treatment groups throughout the study, and if required a steroid injected into the tendon can be given also in both groups. 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.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

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.

While secukinumab 150 mg and 300 mg regimens are both more efficacious than placebo, the 300 mg regimen provided the greatest efficacy across multiple PsA domains in tumor necrosis factor-α inhibitor (TNF) incomplete responder (TNF-IR) patients and showed higher efficacy on skin endpoints and physical function as measured by HAQ-DI in both TNF-naïve patients and TNF-IR patients.

Evidence of dose response was shown in TNF-IR patients favoring secukinumab 300 mg over 150 mg at the Week 24 efficacy endpoint used for the primary and secondary efficacy analyzes of CAIN457F2312 study. Indeed, ACR20/50/70 response rates at Week 24 in TNF-IR patients were higher with secukinumab 300 mg compared to 150 mg (45.5% vs 29.7%, 27.3% vs 18.9%% and 15.2% vs 10.8% respectively). This trend was maintained up to Week 52.

Furthermore, secukinumab 300 mg was more efficacious than 150 mg in achieving clinically meaningful improvements in skin disease, particularly with respect to clear/almost clear skin (PASI 90, IGA mod 2011 0/1) in patients with moderate to severe psoriasis (defined as ≥ 10% BSA). There was a clear dose response favoring secukinumab 300 mg in the higher thresholds of skin clearance. The difference between 300 mg and 150 mg regimens was more pronounced in the more difficult-to-achieve PASI 90 and IGA mod 2011 0/1 endpoints, with 21.9% and 27.4% more patients with ≥ 10% body surface area (BSA) compared to 8.2% and 3.3% more patients with < 10 % BSA reaching PASI 90 and IGA mod 2011 0/1 responses, respectively, at Week 24. Therefore, secukinumab 300 mg afforded greater improvement in plaque psoriasis than 150 mg, particularly in the achievement of clear/almost clear skin, in patients with moderate to severe psoriasis (≥ 10% body surface area).

In addition, pertaining to safety assessment, 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. The overall safety in the PsA population was consistent with prior extensive experience in psoriasis, and showed that secukinumab 300 mg and 150 mg are acceptable for chronic use in adult patients with active PsA.

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 weeks treatment duration was chosen as this is considered the maximum acceptable duration for resolution or partial resolution in subacute tendinopathy. The 12 weeks follow-up after the end of study treatment is included to generate follow-up data for potential relapse and to have treatment safety follow-up data in this indication.

3.4 Rationale for choice of comparator

A placebo arm is included in this study for the duration of the 12 weeks of treatment (7 doses), the placebo group will continue without treatment until week 24. 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 NSAID dosing is allowed, and one local steroid injection is permitted.

The regular assessments of disease activity ensures that subjects experiencing worsening of their disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time. In addition, the inclusion of a placebo group is in accordance with health authority guidelines, including (FDA 1999; EMA 2009), and the parallel-group, placebo controlled design is in alignment with Phase II/III trials of other biologics in a related therapeutic domain (PsA) as outlined in EMA guidelines (EMA 2009).

3.5 Rationale for choice of background therapy

Patients should have taken NSAIDs or acetaminophen at a stable dose for at least 2 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs or acetaminophen. Patients should continue on their NSAIDs/acetaminophen regimen at time of randomization. The dose of NSAID should remain stable until the timing of the primary endpoint at 14 weeks, however, dose reduction is allowed. After Week 14 dose adjustments are allowed. Local steroid injection will only be allowed after the primary endpoint, and only as one injection during the last 12 weeks observation period.

3.6 Purpose and timing of interim analyses/design adaptations

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3.7 Risks and benefits

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 . Ultimately, this should result in few cases of tendinopathy progressing to a tear and therefor lessen the need for surgery.

The placebo patients 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 subjects 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 Investigator's Brochure (IB).

The risks of secukinumab treatment identified from the clinical experience described in Section 1.3.1 are:

a) 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.
b) Neutropenia, mostly non-serious, transient, spontaneously reversible, grade 1-2, seldom associated with infections and did not lead to treatment discontinuation.
c) Hypersensitivity, primarily non-serious, mild to moderate urticaria, eczema or dermatitis.

The safety profile of secukinumab remains unchanged since the launch in 2015.

Please refer to the IB for a more detailed review of the pre-clinical and clinical information on secukinumab.

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 child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Risks of imaging procedures

For screening purposes, the patient should have a chest x-ray that is less than 3 months old. If they do not have this (or a historic CT scan or chest MRI), then a new chest x-ray must be performed in the posterior-anterior plane; the lateral plane is only done if acceptable per local practice and regulations. The amount of exposure for a patient chest X-ray is 100 µSv (https://www.radiologyinfo.org/en/pdf/safety-xray.pdf).

For screening purposes, a shoulder x-ray will be performed in anterior-posterior and lateral plane. This is often performed during the routine evaluation of patients with shoulder pain, but not always. Consequently, in some patients the x-rays may be obtained only for research purposes. The total amount of radiation exposure per patient from these X-rays will be about 100 µSv. The 200 µSv of radiation from both x-rays is equivalent to approximately 28 days of background exposure (approx. 0.3 µSv per hour at sea level). For effective radiation doses under 3 mSv, the risk is considered to be "minimal".

Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of patients.

The only imaging technique used in this study for follow-up purposes is MRI Commercially Confidential Information. 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 patient 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 a MRI image quality. For more information, see Section 4.2 exclusion criterion 11.

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There may be unknown risks of AIN457 which may be serious.

3.7.1 Blood sample volumes

A maximum of 500 mL of blood will be collected over a period of 24 weeks, from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central Laboratory Manual.

See Section 8.9.5 regarding the potential use of residual samples.

4 Population

The population will consist of male and female patients at least 18 years of age, but under or equal to 65 years of age at the time point of randomization with a MRI-positive diagnosis of overuse (non-systemic inflammatory) unilateral shoulder tendinopathy with symptoms present for at least 6 weeks but not more than 12 months.

The tendinopathy must have been refractory to NSAIDs and/or acetaminophen as defined in the inclusion criteria. The patients should also have had at least 2 weeks of a standardized physiotherapy treatment.

The tendinopathy must be MRI-positive, as indicated by a Sein MRI tendinopathy scoring system grade I-III, with no tear or partial tear (maximum 50% tendon thickness = Bauer tendon thickness score maximum 2; AP length maximum 10 mm, Bauer tendon length score maximum 2. Up to 50% of enrolled patients may have a partial tear. Patients will be stratified to four strata: Patients with or without a tendon tear and patients with or without previous local steroid treatment to the affected shoulder. Randomization will occur within these four strata.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Unless specified otherwise in the inclusion/exclusion criteria, subject selection is to be established by checking through all eligibility criteria at both screening and baseline, except for assessments that according to the Assessment schedule are performed at only one of these visits. In this case, it is acceptable to include the patient 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 patient from enrollment into the study.

4.1 Inclusion criteria

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

1. Written informed consent obtained prior to all study specific screening procedures, as close to the start of the screening period as possible
2. Male or non-pregnant, non-lactating female patients 18 to 65 years of age at randomization
3. Presence of unilateral rotator cuff tendinopathy with:
   a. Symptoms present ≥6 weeks, but <12 months prior to randomization
   b. Tendinopathy with no more than a 50% tear as established by ultrasound at screening (historic data acceptable if not older than 3 months) and MRI at baseline: Sein MRI tendinopathy scoring system grade I-III; with no tear or partial tear [maximum 50% tendon thickness (Bauer tendon thickness score maximum 2); AP length maximum 10 mm (Bauer tendon length score max 2)]. Maximum 50% of patients with partial tear

c. Pain in the affected shoulder (at rest or on movement) on at least 3 days out of 7 days in the past week prior to baseline and a score of ≥4 out of 10 on a VAS pain scale
d. Positive "Painful Arc Test" on examination and/or nightly pain in the affected shoulder on at least 4 out of 7 days in the past week prior to baseline

4. The rotator-cuff tendinopathy must have been refractory to standard treatment defined as:
   a. NSAIDs / acetaminophen
      i. In the run-in period patients should be on a stable dose of NSAIDs and/or acetaminophen for at least 2 weeks prior to randomization, not exceeding – e.g.: Ibuprofen 1600 mg/d, naproxen 1000 mg, diclofenac 105 mg/d, or diclofenac sodium enteric-coated tablets 150 mg/d, or equivalent.
      ii. If patients cannot tolerate these doses, the maximal tolerable dose should be used, and may be augmented with acetaminophen/paracetamol, at doses not exceed local guidelines or 4 g/day, whichever is lower. This medication should also be at a stable dose for at least 2 weeks.
      iii. If patients have contraindications to NSAIDs or to acetaminophen, these treatments can be omitted (contraindication, drug and dose must be specified in the eCRF).
      iv. If patients were refractory to at least 2 weeks of previous treatment as specified in 4 i/ii, NSAIDs or acetaminophen treatment can be omitted.
   b. Physiotherapy
      i. In the run-in and baseline period, patients should have had at least 2 weeks of a standardized physiotherapy treatment. In Czech Republic, patients should have had at least 6 weeks of physiotherapy prior to randomization. This includes the 2 weeks of standardized physiotherapy in run in phase.
5. If the patient had previous steroid treatment, it must be ≥8 weeks prior to randomization and ≤3 injections
6. If the patient had previous shock-wave therapy, it must be ≥8 weeks prior to randomization
7. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies must be negative at Screening

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are <u>not</u> 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 patients.

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days for small molecules/until the expected PD effect has returned to baseline for biologics, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes
3. Rheumatologic, inflammatory diseases, including but not limited to: PsA, AS and RA
4. Previous shoulder surgery in affected shoulder

5. History of adhesive capsulitis/frozen shoulder or calcification in the tendon (in affected or contralateral shoulder) confirmed by X-Ray, historic X-Rays can be used if performed within 3 months of baseline
6. Symptomatic osteoarthritis of the shoulder (gleno-humeral, acromioclavicular) (in affected or contralateral shoulder confirmed by X-Ray, historic X-Rays can be used if performed within 3 months of baseline
7. Neck conditions, including but not limited to cervical spine syndrome, which in the opinion of the investigator, may explain the patient's symptoms
8. Previous platelet rich plasma injections within the last 12 months prior to randomization
9. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g. Campath, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
10. Previous exposure to any biologic immunomodulating agents, including but not limited to TNFalpha inhibitors (including, but not limited to adalimumab, infliximab), or biologics targeting IL-17 (including, but not limited to secukinumab, ixekizumab or brodalumab) or the IL-17 receptor within the last 12 months prior to baseline
11. Patients taking high-potency opioid analgesics, including but not limited to, methadone, hydromorphone, and morphine
12. Any intraarticular/subacromial corticosteroid treatment within 8 weeks prior to randomization and more than 3 injections for the current tendinopathy. Oral, intramuscular or i.v. corticosteroid treatment within the last 12 months prior to randomization
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
14. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks after the last dose, or longer, if local regulations require it (e.g. 20 weeks in EU). Effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. 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 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 patients on the study, the vasectomized male partner should be the sole partner of that patient
    d. Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps. For UK: 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)
f. 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
g. In case local regulations deviate from the methods listed, local regulations apply and will be described in the ICF
h. Women are considered post-menopausal and not of child bearing potential if they have had at least 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 child bearing potential

15. Chest X-ray, CT or MRI scan with evidence of ongoing infectious or malignant process obtained at screening or within 3 months prior to screening and evaluated by a qualified physician
16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immune-compromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy
17. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes
18. Evidence of hypomagnesemia or other reason associated with risk of reduced activity of matrix metalloproteinases. Treatment with fluorquinolone antibiotics (mainly ciprofloxacin, moxifloxacin or similar drugs) associated with risk of magnesium chelation and reduced activity of matrix metalloproteinases.
19. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT/SGPT) alkaline phosphatase or serum bilirubin. The investigator should be guided by the following criteria:
    a. Any single parameter may not exceed 3 x upper limit of normal (ULN). A single parameter elevated up to and including 3 x ULN should be re-checked once more as soon as possible and in all cases, at least prior to enrollment/randomization, to rule out any possible laboratory error
    b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin
20. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 μmol/L).

21. Screening/baseline total white blood cell (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85 g/L).
22. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.
23. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines), or a positive Quantiferon test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated prior to enrollment.
24. Known infection with human immunodeficiency virus (HIV) Hepatitis B (HBV) or Hepatitis C (HCV) at screening or randomization.
25. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed), treated or untreated within the past 5 years prior to baseline regardless of whether there is evidence of local recurrence or metastases.
26. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
27. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
28. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
29. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
30. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.
31. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomization.
32. Inability or unwillingness to undergo MRI of the shoulder (e.g., patients with pacemakers, or metal fragments / foreign objects in the body that are not compatible with performing a MRI.

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

Refer to Section 8.3 (Patient Screening) for information regarding re-screening.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for study subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Prohibited treatment

Use of the treatments displayed in Table 5-1 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.

Table 5-1 Prohibited medications

Prohibited treatments	**Prohibition[1] /Washout period before randomization[2]**	Action to be taken
Any immunomodulating biologic drugs, including but not limited to TNFalpha inhibitors or other biologic drugs targeting IL-17 or IL-17 receptor*	Never	Discontinue study medication
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents*	Never	Discontinue study medication
cDMARD (e.g. MTX) including apremilast, tofacitinib*	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
Unstable dose of NSAIDs (including selective COX-2 inhibitors) and/or paracetamol/acetaminophen	2 weeks	Reduce dose as soon as possible, back to baseline dose. Dose decreases after randomization are allowed within the first 14 weeks Dose increases are only allowed after Week 14. All dose changes must be recorded
Analgesics other than NSAIDs, paracetamol/acetaminophen and low strength opioids PRN	2 weeks	Discontinue the forbidden medication. All medications must be recorded
High potency opioids	12 weeks	Discontinue study medication
Systemic corticosteroids	12 months	Discontinue study medication
Local steroid injections in the shoulder (until Week 14)	8 weeks and not more than 3 injections	Discontinue study medication
Intramuscular steroid injection	8 weeks	Discontinue study medication
Fluoroquinolone	8 weeks	Discontinue study medication

Prohibited treatments	Prohibition[1] /Washout period before randomization[2]	Action to be taken
Shock wave therapy	8 weeks	Discontinue study medication
Live vaccinations	6 weeks	Discontinue study medication
Platelet rich plasma injections	12 months	Discontinue study medication
Oral or topical retinoids	12 weeks	Discontinue study medication

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

[1] Never = medication is prohibited from any time point prior to study start and up to and including follow-up visit

[2] period in weeks refers to washout of prohibited medications during screening counted from randomization visit Administration of these agents requires study discontinuation.

6 Treatment

6.1 Study treatment

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

6.1.1 Investigational and control drug(s)

Table 6-1 Overview of study medication

Study drug name	Formulation	Unit dose	Packaging	Provided by
Secukinumab 300 mg (2 injections of 150 mg)	2 x 1 mL PFS	1 mL (150 mg)	Single -blind supply	Novartis
Placebo, 2 injections	2 x 1 mL PFS		Single-blind supply	Novartis

Patients will be given the injections by the site staff on site, except for injections at weeks 1 and 3, which will be given by a study nurse on site or at home, whichever is most convenient for the patient, in agreement with the investigator.

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

- Single blind secukinumab and placebo pre-filled syringe (PFS) will be labeled AIN457 150 mg/1 ml/Placebo for dosing up to and including Week 12.

For detailed instructions on storage of the investigational treatments, please refer to the SOM.

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a 1:1 ratio, with approximately 50 patients per arm.

- Group 1: Secukinumab 300 mg s.c. (2 x 150 mg)
- Group 2: Placebo s.c. (2 injections)

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

Subjects who complete the assessments associated with Week 14 visit should continue the study in a (treatment free) follow up period of 10 weeks up to 24 weeks.

6.3 Treatment assignment and randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject 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 Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization number is only used to identify which treatment the subjects have been randomized to receive. The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

Randomization will be stratified on the basis of

- Tendinopathy without tear / tendinopathy with partial tear.
- Steroid-naïve for the current RC injury / local steroid treatment for the current RC injury.

The stratification occurs in order to make sure that these two potential factors, which may impact response to treatment, are evenly distributed in the treatment groups.

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject, investigator and sponsor-blinded study. Subjects, investigators and sponsor will remain blinded to study treatment throughout the study, except where indicated below.

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

Site staff

All site staff (including study investigator and study nurse), except the unblinded pharmacist, will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.6).

Sponsor staff

All other 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 14. 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 14.

Following final database lock all roles may be considered unblinded. See Table 6-2 for an overview of the blinding/unblinding plan.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared with the team for after the primary endpoint analysis at Week 14.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting the primary endpoint analysis.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

Table 6-2 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Primary analysis at Week 14
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded pharmacist	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	UI	UI	UI	UI
Unblinded monitor	B	UI	UI	UI
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	UI

Key:
UI: Allowed to be unblinded on individual patient level
B: Remains blinded
NA: Not applicable to this study

6.5 Treating the subject

AIN457 will be administered to the subject via the s.c. route of administration. Patients will be given the injections by the site staff on site, except for injections at weeks 1 and 3, which will be given by a study nurse on site or by a study nurse at home, whichever is most convenient for the patient. See the Site Operations Manual for further details.

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

6.5.1 Instructions for prescribing and taking study treatment

Study treatment (2 x 150 mg s.c. secukinumab or matching placebo) will be administered by PFSs throughout the study.

S.c. administration with pre-filled syringes

Secukinumab solution for s.c. injection (150 mg in 1.0 mL active/placebo) will be provided in PFSs. Details of the injection is provided in the SOM. Permitted dose adjustments and interruptions of study treatment

Study treatment interruption should be avoided with the following exceptions:

Study treatment interruption is only permitted if, in the opinion of the investigator, a subject 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.

6.6 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject 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 subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study 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 at any time in case of emergency. The investigator will need to provide:

- Protocol number
- Study drug name (if available)
- Subject number.

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

6.7 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with AIN457, as detailed in Section 8.8.

Compliance to the treatment regimen is ensured by administration of the AIN457 at the study site at all visits as per Assessment schedule except for visits at weeks 1 and 3, when AIN457 will be administrated by a nurse at the patients' home. Information on the study treatment administration or any deviation from the dose regimen must be recorded in the Case Report Form (CRF). All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.8 Recommended treatment of adverse events

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

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

Rescue medication must not be used before completion of Week 14 assessments as outlined in Section 3.1.

Efficacy and safety will be assessed in detail at every study visit, and patients 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.

Changes in NSAIDs concomitant therapy is permitted after Week 14 assessments as per investigator's clinical judgment.

6.10 Concomitant treatment

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

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

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.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

6.10.1 Physiotherapy

Patients should be on the standard home-base physiotherapy for at least 2 weeks prior to randomization until study Week 14. Please refer for the details in provided separately Exercise Manual for patients.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety; no further study treatment will be made available after Week 14.

Study completion is defined as when the last subject completes their End of Study (EoS) 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.

Normally, all randomized and/or treated subjects should have a safety follow-up call conducted 60 days after last administration of study treatment; however the 60 days falls within the study 12-week follow-up period, where no treatment is given, therefore the safety follow up is part of the EoS.

All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual.

After study participation, the patients will continue to be treated at the investigators discretion according to local practice. The investigator must provide follow-up medical care for all subjects who prematurely withdraw from the study, or must refer them for appropriate ongoing care.

7.2 Discontinuation of study treatment

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- 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 subject's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting))
- Use of prohibited treatment as per recommendations in Table 5-1.
- Adverse events, abnormal laboratory values or abnormal test results that indicate a safety risk to the subject.

- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- The following deviations from the prescribed dose regimen for the study drug:
  - Missed 2 doses or more

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

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3, Withdraw of Informed Consent).The patients who discontinue the treatment should return to the clinic as soon as possible, after discontinuation of study drug, for EoS visit. At a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

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

If they fail to return for the EOS visit for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 7.4 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a subject:

- 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 and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

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 subject are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

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

7.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. 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 subject’s interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

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

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects 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. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule

Epoch	Screening			Treatment								Follow-up	
Visit Name	Screening	Run-in[2]	Baseline	Treatment								Follow-up	EOS
Visit Numbers[1]	1	2	3	101	102	103	104	105	106	107	199	201	299
Days	-49 to -22	-21 to -8	-7 to -1	1	8	15	22 ±1	29 ±1	57 ±2	85 ±2	99 ±2	127 ±7	169 ±7
Weeks of dosing	-	-	-	0	1	2	3	4	8	12	14	18	24
Informed consent	X												
Commercially Confidential Information													
Inclusion / Exclusion criteria	S		S										
Medical history/current medical conditions	X												
Prior medication for tendinopathy	X												
Hepatitis B, C or HIV serology (only in countries where required)	S		S										
Tuberculosis test[11]	S												
Demography	X												
Pregnancy and assessments of fertility[3]	X		X					X	X	X		X	X
Alcohol Test, Drug Screen	S												
T3, T4, TSH	X												

Epoch	Screening			Treatment								Follow-up	
Visit Name	Screening	Run-in[2]	Baseline	Treatment								Follow-up	EOS
Visit Numbers[1]	1	2	3	101	102	103	104	105	106	107	199	201	299
Days	-49 to -22	-21 to -8	-7 to -1	1	8	15	22 ±1	29 ±1	57 ±2	85 ±2	99 ±2	127 ±7	169 ±7
Weeks of dosing	-	-	-	0	1	2	3	4	8	12	14	18	24
Chest X-Ray[7]			S										
Randomization				X									
Study drug administration[4]				X	X	X	X	X	X	X			
Physiotherapy		S[13]	S										
Physical Examination[5]	S		S										S
Body Height[5]	X												
Body Weight[5]	X		X										X
Body Temperature[5]	X		X	X		X		X	X	X	X		X
Blood Pressure and Pulse Rate[5]	X		X	X		X		X	X	X	X		X
Electrocardiogram (ECG)[5]	S		S								S		S
Hematology[5]	X		X					X			X		X
Clinical Chemistry[5]	X		X					X			X		X
Urinalysis[5]	X		X								X		X
Lipid panel and glucose[5]			X								X		
Shoulder X-Ray[6, 12]			S										
Shoulder US	S												
Shoulder MRI			X[12]						X		X		X
Patient pain & NSAIDs diary		X											
Patient reported outcomes[5]			X	X		X		X	X	X	X	X	X
Pain VAS		X	X	X									
Clinician reported outcome (PhGA)[5]			X	X		X		X	X	X	X	X	X

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Epoch	Screening			Treatment								Follow-up	
Visit Name	Screening	Run-in[2]	Baseline	Treatment								Follow-up	EOS
Visit Numbers[1]	1	2	3	101	102	103	104	105	106	107	199	201	299
Days	-49 to -22	-21 to -8	-7 to -1	1	8	15	22 ±1	29 ±1	57 ±2	85 ±2	99 ±2	127 ±7	169 ±7
Weeks of dosing	-	-	-	0	1	2	3	4	8	12	14	18	24
PD blood (IL-17A)[5]				X				X		X			X
Commercially Confidential Information													
PK blood collection[5]				X				X		X			X
Commercially Confidential Information													
Immunogenicity[5]				X						X			X
Commercially Confidential Information													
Concomitant medications	X												
Adverse Events	X												
Comments	X												
Study completion information													X

[1] Visit structure given for internal programming purpose only
[2] Run-in to standardize physiotherapy and stabilize NSAIDS, no site visit required
[3] Serum pregnancy test required as Screening and EOS, for remaining visits: urine test
[4] At study days 8 and 22 study medication can be administered by study nurse at patients home
[5] Collected pre-dose if applicable
[6] Historic data accepted if obtained ≤3 months before baseline
[7] A chest X-ray (can be replaced by historic CT or MRI) is required if it was not performed and evaluated within 3 months prior to screening. The X-ray should be performed after it is certain the subject meets other inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation.
[8] To be done the night before and the night after each visit (except for EOS when it is done only before the visit).
[9] Commercially Confidential Information
[10]
[11] The PPD skin test can be performed at any time during the screening period, but it must be read within 72 hours and before randomization
[12] Assessments to be performed maximum 14 days before study Day 1
[13] Duration of the standardized physiotherapy might be prolonged if required by local regulations

S: collected as source data only

For all subjects who discontinue from the study, the investigator should ensure that the subject completes the end of treatment visit (EOS) 4 weeks after last study treatment of secukinumab. Every attempt should be made to obtain MRI images at the final visit, unless the MRI was taken within 8 weeks before discontinuation.

8.2 Informed consent procedures

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

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

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 patient source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the patient agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient 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 subject.

Ensure patients are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria).

Commercially Confidential Information

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

Refer to the SOM for a complete list of Informed Consent Forms included in this study.

8.3 Patient screening

It is permissible to re-screen a patient once if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

8.4 Information to be collected on screening failures

Subjects who discontinue from the study prior to randomization are considered screen failures.

The reason for not being randomized and demographics will be entered in the CRF. The CRF for adverse events (AEs) should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

All subjects 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.

8.5 Patient demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all patients and recorded in the eCRF include:

- Date of birth, age, sex, race, ethnicity
- Relevant tendinopathy and general medical history/current medical condition data until the start of study treatment, such as date of diagnosis of tendinopathy, previous tendinopathy therapies, especially pain medication and physiotherapy
- Potential corticoid steroid treatment and information on potential tear on MRI will be recorded to assess patients for eligibility and to stratify patients

Whenever possible, diagnoses and not symptoms will be recorded. Further details are outlined in the SOM.

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.

8.5.1 Hepatitis screen, HIV screen

Hepatitis B and/or hepatitis C and/or HIV serology testing are to be performed during screening period, only if required per local medical practice or local regulations prior to initiation of therapy.

If HIV test is seropositive, it should be confirmed by a second technique available at the laboratory site, e.g., 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.

8.5.2 Alcohol test, drug screen

All subjects will be screened for substances of abuse. These assessments will be documented in source records only and will not be entered into the CRF.

See the SOM for details.

8.5.3 X-ray of the shoulder

An X-ray of the shoulders will be taken at screening, if one was not taken within the last 3 months. It is recommended that shoulders X-ray is performed in anterior-posterior and lateral planes in order to evaluate patient's eligibility.

8.5.4 Treatment exposure and compliance

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

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

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

8.6 Efficacy

8.6.1 The PRO efficacy measures, primary and secondary objectives:

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

- The WORC score
- The QuickDASH score (in case available in local language/dialect)
- The ASES score
- The EQ5D-5L score
- Patient's global assessment of disease activity (VAS)
- Patient's assessment of tendinopathy pain intensity (VAS)

Daily assessments of pain intensity, as well as any changes in concomitant pain medication will be recorded in the patient diary.

All questionnaires will be available, in the local languages of the participating countries. The patients will be asked to fill in these PROs at the clinic at the visits specified in the Assessment schedule.

Subjects 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 subject to complete any missing responses. If subjects 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 subjects, including patients who prematurely discontinue prior to the study evaluation completion visit. However, if subjects refuse to complete PROs, this should be documented in study source records. Subject's refusal to complete study PROs are not protocol deviations.

Guidelines for administering the PRO questionnaires can be found in SOM.

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 subject. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 9.1 and Section 9.2 of the protocol. Investigators should not encourage the subjects to change the responses reported in the completed questionnaires.

8.6.1.1 The WORC score

The WORC score 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 so the best possible result is 0 (asymptomatic patient) while the worst possible result is 2100 (highly symptomatic). The WORC Index has a recall period of 1 week and is filled in by the patient at the clinic at visits specified in the Assessment schedule.

Details of the WORC are outlined in the SOM.

8.6.1.2 The QuickDASH score

Quick DASH should be performed in all countries for which local language/dialect is available. The Quick DASH is an abbreviated form of the DASH a patient reported outcome tool, which has been developed by the American Academy of Orthopedic Surgeons along with the Institute for Work & Health (Toronto, Ontario, Canada) (http://www.dash.iwh.on.ca/scoring). The Quick DASH Index is self-administered and uses 11 items to measure physical function and symptoms in patients 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 patient at visits specified in the Assessment schedule.

Details of the Quick DASH are outlined in the SOM.

8.6.1.3 The ASES score

The ASES score is developed by the Society of the American Shoulder and Elbow Surgeons for the assessment of shoulder function (Richards et al 1994). The ASES score is self-administered and has 17 questions in the areas of symptoms and functions. The severity of pain is graded on a 10 cm visual analog scale that ranges from 0 (no pain at all) to 10 (pain as bad as it can be). The recall period is the current point in time. The tool is filled in by the patient at visits specified in the Assessment schedule.

Details of the ASES are outlined in the SOM.

8.6.1.4 EuroQuol 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 patients. 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). Subjects 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 subject of particular health states and the generation of subject 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 EQ5D is filled in by the patient at Day 1 prior to drug administration and at visits specified in the Assessment schedule.

Details of the EQ5D are outlined in the SOM.

8.6.1.5 Patient’s assessment of tendinopathy pain intensity and change in pain medication

The patient will assess his/her pain in a PRO diary once per day rating the pain during the previous 24 hours. The patient’s assessment of pain will be performed using 100 mm visual analog scale (VAS) ranging from “no pain” to “worst possible pain” after the question “*Please rate the severity of your pain at its worst during the last 24 hours by marking an X on the line below*”.

Similarly, the patient should note down whenever he/she has changed the NSAID/acetaminophen intake.

8.6.1.6 Patient's global assessment of disease activity

The patient'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 patient's global assessment of disease activity is filled in by the patient at Day 1 prior to drug administration and at visits specified in the Assessment schedule.

8.6.2 Clinician reported outcome (CRO) efficacy measures collected in the trial for secondary objectives

Physician's global assessment of disease activity

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *" Considering all the ways the tendinopathy affects your patient, please indicate with a vertical mark (|) through the horizontal line how well his or her condition is today"*. To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that subject.

The physician's global assessment of disease activity is filled in by the investigator at Day 1 prior to drug administration and at visits specified in the Assessment schedule.

8.6.3 Imaging efficacy measures collected in the trial for secondary and exploratory objectives are:

8.6.3.1 MRI of the shoulder, Sein score and Bauer score

The MRI Sein score will be used primarily to grade supraspinatus tendinosis at screening using a modified 4-point scale (Sein et al 2007), and monitor changes in this grading over time as a treatment outcome (secondary objective). Tendinopathy will be characterized by thickened inhomogeneous rotator cuff tendon with increased signal intensity on all pulse MRI sequences, yet not as bright as the fluid on typical T2-weighted images. Since tendonisis and partial thickness cuff injuries are prevalent in sporting activity and in middle age, another grading system, the Bauer score, will be used as an exploratory endpoint for a differentiated assessment of supraspinatus partial tears and tendonosis (Bauer et al 2014). A 9-point tendinopathy grade will be generated out of this approach, including sub-scores for tendonisis (0-2), tear thickness (0-4) and AP tear size (0-3). Finally these images will also be used to measure thickness of the rotator cuff tendon and assess for presence of bursitis in the area of the rotator cuff.

Enhancement of the subacromial bursa will be assessed. Images will be scored on a scale of 0–2 depending on the maximum thickness of enhancing tissue: 0: no abnormal enhancement; 1: up to 3 mm thickness of enhancing tissue; 2: 3 mm or more enhancing tissue (Hodgson et al 2012).

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MR images will be acquired at 3T in multiple planes by using an imaging sequences optimized for tendon/surrounding tissue separation and adapted to the MRI system capabilities. All MRI scans will be sent for central reading and all results obtained post Baseline visit will remain blinded to the investigator, patient and sponsor until after the primary endpoint analysis at week 14. Detailed information can be located in the imaging manual. The coded MRI medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

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8.7 Safety

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
- Vital signs
- Height and weight
- Tuberculosis screening: QuantiFERON TB-Gold test or PPD skin test
- Chest X-Ray
- Electrocardiogram
- Local tolerability (Injection site reactions)
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)

- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- Immunogenicity

8.7.1 Physical examination

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.

8.7.2 Vital signs

This will include body temperature, BP and pulse rate measurements after 5 minutes rest in sitting position.

Clinically notable vital signs are defined in Appendix 1.

8.7.3 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.

8.7.4 ECG

In this study, local ECG will be used. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. A single 12 lead ECG is collected. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The original ECGs (on non-heat-sensitive paper or a certified copy on non-heat sensitive paper), appropriately signed, must be collected and archived at the study site. The ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

Clinically relevant abnormalities should be recorded on the relevant medical history/Current medical conditions eCRF page for the baseline ECG.

Clinically relevant abnormalities noted after the baseline ECG should be reported as AE (see Section 9).

8.7.5 Tuberculosis screening

Either a central laboratory immunological test (QuantiFERON TB-Gold) **or** a locally performed skin test must be performed at the screening visit to screen the subject population for latent tuberculosis infection. The results must be known prior to randomization to determine the subject's eligibility for the study.

Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that

- the subject has no evidence of active tuberculosis
- if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.

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.

Local skin test for Tuberculosis screening

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

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

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

8.7.6 Ultrasound of the shoulder

Ultrasound of the shoulder is done at screening, in order to assess eligibility unless US or MRI are available from within previous 3 month and clinical symptoms stabile, these examinations can be used for source data. B-mode US is utilized to rule out major structural damage to the tendon (i.e. more than 50% tear) or other shoulder pathologies

8.7.7 Chest X-ray

A chest x-ray (posterior-anterior plane) is required if it was not performed and evaluated within 3 months prior to screening. An additional x-ray in the lateral plane is only done if acceptable per local practice and regulations. Lateral plane x-ray will not be permitted in the UK for this study. The X-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The X-Ray might be replaced by historic CT or MRI scan if performed within 3 months prior to screening.

8.7.8 Tolerability of investigational treatments

Tolerability will be assessed by adverse events, laboratory values, injection site reaction and immunogenicity. The local tolerability at the site of s.c. injection of the study treatment will be assessed in case of any local reaction, until this has disappeared. The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the appropriate CRF capturing AEs, including the severity (mild, moderate, severe) and the duration of the adverse reaction.

8.7.9 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported 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.

Clinically notable laboratory findings are defined in Appendix 1.

8.7.9.1 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured.

8.7.9.2 Clinical chemistry

Serum chemistries will include sodium, potassium, BUN/urea, bicarbonate, calcium, phosphorous, total protein, calcium, albumin, uric acid, creatinine, CK, total bilirubin, AST (SGOT), ALT (SGPT), GGT and alkaline phosphatase; at all timepoints specified in the Assessment schedule.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and interferon-gamma release test done only at screening. FSH is only done at screening and only in patients who are reported post-menopausal at screening

8.7.9.3 Lipid panel and glucose

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol, triglycerides and glucose will be measured from a fasting blood sample.

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8.7.9.6 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed at site ad documented as source data.

If dipstick measurement results are positive (abnormal), results will be captured in the CRF. Microscopy must be assessed following an abnormal dipstick test with results captured in the CRF.

8.7.10 Pregnancy and assessments of fertility

Pregnancy testing

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 4.2).

A serum β-hCG test will be performed in all women at Visit 1 (screening). All women who are not surgically sterile at screening will have local urine pregnancy tests as indicated in Table 8-1. 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 subject must be discontinued from the trial. Additional pregnancy testing might be performed if requested per local requirements. Refer to Section 9.6 for details on Reporting Pregnancy. Pregnancy testing results are kept in the source data documentation.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

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

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

In the absence of the above medical documentation, FSH testing is required of any female subject who states that they are of non-child bearing potential, regardless of reported reproductive/menopausal status at screening/baseline

8.7.11 Additional parameters

Blood will be obtained at the first screening visit (Visit 1) for anti-CCP antibodies and the Rheumatoid Factor (RF)

8.8 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment. See Section 8.9.5 regarding the potential use of residual samples.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

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

8.9 Other assessments

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8.9.3 Immunogenicity

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken pre-dose at the scheduled time points as indicated in Table 8-1. Anti-secukinumab antibodies will be assessed in serum by MSD assay. Details of the analytical methods to assess anti-secukinumab antibodies in serum will be described in the bioanalytical data report.

In addition, if a subject discontinues from the study at any timepoint, he/she will need to provide a sample at the last visit. The actual sample collection date and exact time will be entered on the Immunogenicity Blood collection eCRF. Sampling problems will be noted in the Comment section of the eCRF.

A laboratory manual will be provided to investigators with detailed information on sample collection, handling and shipment. Tubes and preprinted labels will be provided by the central lab to the sites

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

9 Safety monitoring

9.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

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

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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Clinically notable vital signs are defined in Appendix 1.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

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
   - Yes or
   - No
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 9.2 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:

- No action taken (e.g. further observation only)
- Investigational treatment dosage increased/reduced
- Investigational treatment interrupted/withdrawn
- Concomitant medication or non-drug therapy given
- Hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)

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

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications.

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

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

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/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 the start of study drug
- 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
- Social reasons and respite care in the absence of any deterioration in the subject's general condition

- Is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the subject 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).

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 subject or might require intervention to prevent one of the other outcomes listed above. 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).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis.

Screen Failures & Run-In Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

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

Randomized Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject 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 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 subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis.

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

9.3 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in approximately 13,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the liver. Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned. For further information on standard liver function tests, see Appendix 1.

9.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests containing clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

9.5 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, patient/subject 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.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO & PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO & PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO & PS) Department. 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 the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued*, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (eCRF) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis or CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

Novartis staff and CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Details regarding patient diary, PRO, and CRO data collection will be provided in SOM.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication committee

Not required.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

The primary aim of this study is to assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving clinical symptoms at week 14

11.4.1 Primary Variable(s)

The primary variable, the WORC score, will be available at Baseline and weeks 2, 4, 8, 12 and 14

11.4.2 Statistical model, hypothesis, and method of analysis

The primary end-point (change from baseline in WORC score at Week 14) will be analyzed by repeated measures analysis of covariance including all WORC scores available. Change at Week 14 will be compared between treatments to address the primary objective. The baseline WORC score will be included as a covariate. The stratification factors partial tear/no tear and previous steroid injection (yes/no) will be included in the model as fixed effects. A 95% one-sided (90% two-sided) confidence interval for the treatment effect at Week 14 will be reported. Missing variables will be considered missing at random.

Initially, models with an unstructured within-subject covariance and a separate mean for each treatment and time point will be fitted. These models may be reduced in number of covariance and mean parameters by model comparison using tools such as the BIC criterion for model fit.

11.4.3 Handling of missing values/censoring/discontinuations

11.4.4 Summary statistics of safety

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

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

Adverse events

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

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

11.4.5 Sensitivity analyses

Not applicable.

11.5 Analysis of secondary variable(s)

Secondary variables include:

- Change from baseline in WORC score at weeks 2, 4, 8, 12, 18 and 24
- Disability of Arm, Shoulder and Hand Questionnaire (QuickDASH) score at weeks 2, 4, 8, 12, 14, 18 and 24
- American Shoulder and Elbow Surgeons Shoulder Evaluation Form(ASES) score at weeks 2, 4, 8, 12, 14, 18 and 24
- EQ5D score at weeks 2, 4, 8, 12, 14, 18 and 24
- Pain score using a VAS scale (considering the last 24 hours) at weeks 2, 4, 8, 12, 14, 18 and 24
- Patient global assessment (PGA) score using a VAS scale (considering the last 24 hours), at weeks 2, 4, 8, 12, 14, 18 and 24
- Physician global assessment (PhGA) score using a VAS scale (considering the last 24 hours), at weeks 2, 4, 8, 12, 14, 18 and 24
- MRI Sein score at weeks 8, 14 and 24

Secondary variables (except Sein score) will be summarized descriptively and analyses similar to the primary analysis will be performed.

The secondary endpoint (Sein MRI score at week 14) will be analyzed by ordinal categorical regression. A model with an additive treatment effect on the cumulative logistic scale will be used, and the common treatment effect estimated and reported together with 90% asymptotic two-sided confidence intervals. Baseline SEIN score will be included as a covariate and the stratification factors, partial tear/no tear and previous steroid injection (yes/no) will be included in the model as fixed effects.

11.5.1 Efficacy / Pharmacodynamics

Not Applicable

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

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

Adverse events

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

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

11.5.3 Pharmacokinetics

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11.5.4 Pharmacokinetic / pharmacodynamic correlation analysis

Not Applicable.

11.5.5 Other assessments

Immunogenicity

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

11.6 Analysis of exploratory variables

The statistical analysis for exploratory variables will be described in the RAP.

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11.7 Sample size calculation

From (de Witte et al 2012), one can infer an SD of change in the WORC score from baseline to 6 weeks of approximately 22 percentage points. By conservatively assuming a linear increase in the change score variability, the 14 week SD would by 22 multiplied by the square root of 1.53 (14/6); that is, 34 percentage points.

Assuming a clinically meaningful difference of 20 percentage points results in an effect size of 20/34=0.59. With this effect size, 40 subjects per group completing week 14 will provide power exceeding 80% to detect a significant difference between treatments by one-sided test at significance level 0.05.

11.8 Power for analysis of key secondary variables

To address the secondary MRI endpoint (Sein score at Week 14), the sample size of 40 subjects per group completing Week 14 will also provide approximately 80% power to detect an odds ratio at or above 50%, i.e., that the odds of a Sein score improvement is at least 50% higher in the treated group than in the placebo group, again by one-sided test at nominal significance level 0.05. This assumes a proportional cumulative odds model as described in (Whitehead 1993).

11.9 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

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

12.2 Responsibilities of the investigator and IRB/IEC

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

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality control and quality assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

13.1 Protocol amendments

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

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

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15 Appendix 1: Clinically notable laboratory values and vital signs

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

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 15-1 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
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	