NOVARTIS

Clinical Development

AIN457 / Secukinumab / Cosentyx®

**CAIN457FDE05 / NCT05569174**

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

# Statistical Analysis Plan (SAP)

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## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ClinRO | Clinician Reported Outcome |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Form |
| EoS | End of Study |
| EoT | End of Treatment |
| EQ-5D-5L | EuroQol-5D |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IRT | Interactive Response Technology |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| MMRM | Mixed-effect model for repeated measures |
| NRS | Numeric Rating Scale |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| PaGA | Patient Global Assessment |
| PRO | Patient Reported Outcome |
| PT | Preferred Term |
| QoL | Quality of Life |
| QuickDASH | Change in Disability of Arm, Shoulder and Hand Questionnaire |
| ROM | Range-Of-Movement |
| s.c. | Subcutaneous |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SF-36 | Short Form 36 |
| SD | Standard Deviation |

| | |
|---|---|
| SOC | System Organ Class |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |
| WORC | Western Ontario Rotator Cuff (score) |

# 1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis for the final clinical trial report (CSR) for study CAIN457FDE05 according to Section 9 of the clinical study protocol (CSP, version no. 02, Amended version) along with any additional analyses, specifications or deviations from this protocol planned before unmasking of the data.

Data capture will be performed using an electronic Case Report Form (eCRF). The SAP is based on the latest available version 2.0.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specifications (PDS) respectively.

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO). Statistical software SAS version 9.4 or higher will be used for generating TFLs.

## 1.1 Study design

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

The study consists of a Screening period (up to 6 weeks), a 2-week Run-in period, a 12-week Treatment period and a 12-week Follow-up period (see Figure 1-1). Treatment and Follow-up (24 weeks) period were blinded. The Screening period assessed eligibility. Participants who met the eligibility criteria at Screening continued to Run-in period and were randomized. In the Run-in period participants should have performed 2 weeks of home-based standardized physiotherapy. The Run-in period was defined as 14 days prior to Randomization and was commenced beforehand by a telephone visit. The study comprises a total of 13 visits. Eligible participants were randomized 1:1 to either receive secukinumab 300 mg s.c. or placebo s.c. at Baseline, week 1, 2, 3, 4, 8 and 12 (7 injections in total) (Figure 1-1).

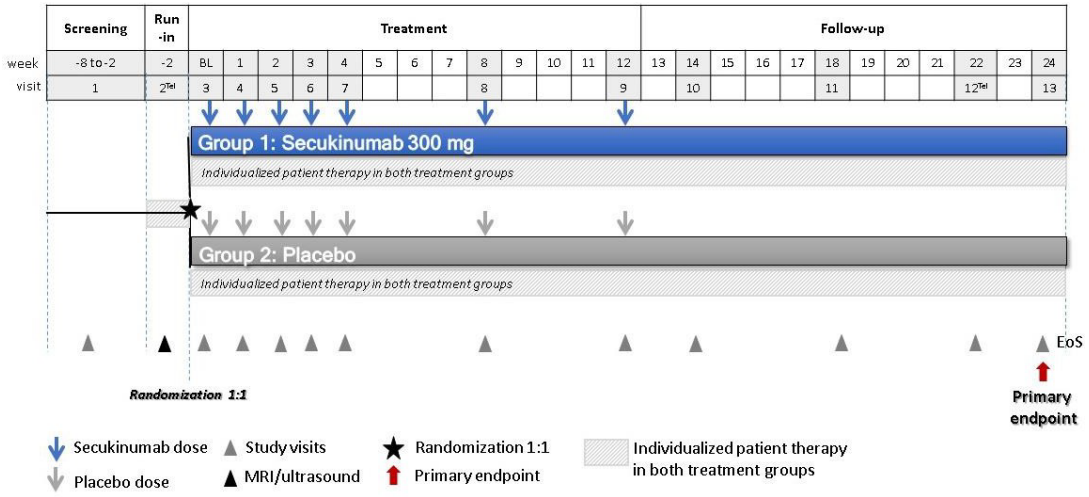


**Figure 1-1 Study design**

At Baseline visit, all eligible participants were randomized via Interactive Response Technology (IRT) to one of the treatment arms. For details see the IRT manual regarding the process and timing of treatment assignment and randomization of participants. Subsequently, the investigator entered the randomization number in the eCRF.

Screening for the CAIN457FDE05 study has been discontinued on 17-MAY-2024 due to the early termination of Secukinumab Phase 3 trials in Rotator Cuff Tendinopathy.

The recruitment activities of the study were stopped, as described in Amendment 2. Instead of planned randomization of 430 participants, 62 participants could be recruited (14.41%).

In total 62 participants were randomized. Under the previous assumptions for the sample size the power will be below 26%. Therefore, only a descriptive analysis will be performed.

## 1.2 Study objectives, endpoints and estimands

The study objectives and related endpoints are presented in Table 1-2.

**Tabelle 1-2 Study objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To demonstrate the superiority of 12 weeks of treatment with secukinumab 300 mg s.c. compared to placebo (both arms in combination with patient individualized conventional therapy), in participants with moderate to severe rotator cuff tendinopathy, based on change in Western Ontario Rotator Cuff index (WORC) score from Baseline to week 24. | Mean change in WORC patient reported outcome (PRO) score from Baseline to week 24 |

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

[redacted]

### 1.2.1 Primary estimand(s)

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

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

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

1. Population: Participants as defined by the inclusion/exclusion criteria to reflect the targeted rotator cuff tendinopathy population based on the FAS.
2. Variable: WORC score from Baseline to week 24
3. Treatment of interest: the randomized treatment (secukinumab 300 mg s.c. and placebo s.c.), both arms in combination with patient individualized conventional therapy
4. Intercurrent events:
   - Treatment discontinuations due to any reason:
     Treatment policy strategy: interested in treatment effect regardless of these events.
   - Other protocol deviations:
     Treatment policy strategy: interested in treatment effect regardless of these events.
5. Summary measure: Difference in mean change in WORC score from Baseline to week 24 between treatments.

### 1.2.2 Secondary estimand(s)

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

# 2 Statistical methods

## 2.1 Data analysis general information

The analysis will be conducted on all participant data after database lock for the study. The data will be analyzed by Novartis and/or by the designated Contract Research Organization (CRO).

All analyses will be performed using SAS® statistical software (Version 9.4 or a more recent version), unless otherwise noted.

Data will be summarized per treatment group.

For categorical variables, the absolute and relative frequencies of each category within a variable will be calculated. A row (category) denoted 'Missing' will be included in count tabulations if a non-zero count of missing values is present.

For continuous variables descriptive statistics, i.e. number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) will be presented.

Data measured several times during the study are analyzed by visit presenting also differences to baseline for numerical data and shift tables for categorical data.

All data will be listed by center and patient number, unless otherwise stated.

It is planned that the data from all centers that participate in this protocol will be used.

The analysis will include all data collected until study completion.

### 2.1.1 General definitions

#### 2.1.1.1 Investigational treatment

At the baseline (Base) visit, eligible participants will be randomly assigned in a 1:1 ratio to:

• Group 1: Secukinumab 300 mg s.c. or

• Group 2: Placebo s.c.

The following labels will be used for study treatment throughout the analysis: "Secukinumab 300mg s.c." and "Placebo".

Participants in both study arms will receive patient individualized conventional therapy consisting of home-based standardized physiotherapy and flexible dosing of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and/or paracetamol as needed (dose decrease and dose increase of NSAIDs/paracetamol relative to the optimized starting dose).

#### 2.1.1.2 Date of first administration of study treatment (Secukinumab/Placebo)

The date of first administration of Secukinumab/Placebo is the first recorded administration date with "Was injection administered?"=yes in the eCRF form "Study Drug Administration".

#### 2.1.1.3 Date of last administration of study treatment (Secukinumab/Placebo)

The date of last administration of Secukinumab/Placebo is the last recorded administration date with "Was injection administered?"=yes in the eCRF form "Study Drug Administration".

#### 2.1.1.4 Baseline

Baseline is referred to as "Day 1" of the study. It is defined as the date of first administration of study treatment for treated patients. If a patient is randomized but not treated then the baseline date is defined as the date of randomization.

The baseline value for efficacy and safety variables is the last available, non-missing, (scheduled or unscheduled) value collected prior to first administration of study treatment.

Some baseline assessments may be recorded on the day of the Baseline visit, assuming the respective assessment was conducted prior to administration of study treatment on Day 1 according to the protocol.

All data collected after the Baseline date are defined as post-baseline. The difference of measure between post-Baseline and Baseline is called change from Baseline. The change from Baseline will always be calculated as below:

post-Baseline value – Baseline value

#### 2.1.1.5 Study day

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. visit, lab samples, AEs). For events prior to study drug start date (e.g. time since diagnosis), study day will be negative and calculated as (event date – study drug start date). Negative study days will be applied to events during the screening period.

#### 2.1.1.6 Study period

The study consists of a 6-week "Screening period", a 2-week "Run-in period", a 12-week "Treatment period" and a 12-week "Follow-up period".

The "on-treatment period" used for safety analyses lasted from the date of first administration of study treatment to 84 days after the date of the last actual administration of any study treatment or end of treatment phase, whichever is later.

#### 2.1.1.7 Date of last available visit (date of last contact)

The date of last available visit is defined as the EOS date. "Last contact" is defined as the last documented date for a patient either within visits or unscheduled data sets (Adverse Event, Prior / Concomitant medication, Relevant Medical History / Current Medical Condition, etc) or date of patient's assessment documented on patient questionnaires.

#### 2.1.1.8 Data of re-screened patients

For re-screened patients, the data collected under the new patient number is used. However, in the event that data is missing but is available under the old patient number, these data can be used. This only applies to data that may be used as baseline data.

## 2.2 Analysis sets

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

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

### 2.2.1 Subgroup of interest

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

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

## 2.3 Patient disposition, demographics and other baseline characteristics

No inferential tests for differences in background and demographic characteristics will be performed.

### 2.3.1 Patient disposition

The following information will be presented for patient disposition (frequencies if not otherwise specified):

- Study duration
- Screening:
  Number of patients screened and rescreened as well as number of screening failures including reason for screening failure and number of patients discontinued during screening phase – for all screened patients
- Patient disposition:
  Number of patients randomized, completed study, discontinued study prematurely, completed treatment, discontinued treatment prematurely including reasons for

discontinuation
Note: For screening failures, the reason for study discontinuation is always set to "Screening failure" regardless of the documentation on the "Study Completion" form.

- Number of patients by center and treatment
- Analysis sets:
  Number of patients per analysis set – All screened/enrolled, FAS, SAF
- Protocol deviations:
  Number of patients with at least one important protocol deviation, and number of patients per PD-ID

All patient disposition data will be listed by treatment group, center, and patient number.

### 2.3.2 Demographics and other baseline characteristics

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

Medical history/ current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the FAS by primary system organ class (SOC), preferred term (PT), treatment group and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Study treatment / compliance

The Safety set will be used for the analyses of study treatment. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure to study treatment by treatment group will be summarized by means of descriptive statistics using the safety set. In addition, the number of patients with an exposure of at least 4 weeks, of at least 8 weeks, at least 12 weeks (EoT) will be displayed. Duration of exposure to the study treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (expressed as: Duration of exposure = Date of last known dose of study drug – Date of first dose of study drug + 1).

Compliance will be calculated based on documented study drug administrations in percent as number of injections performed divided by 7 (= visits with active injections) times 100% and displayed by treatment group.

Secukinumab/Placebo treatment data will be listed by treatment group, center, patient number, and visit for the Safety Set.

### 2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system, by treatment group for the Safety set.

Prior treatments will be defined as treatments taken and stopped prior to first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last intake of study treatment is a concomitant treatment, including those which were started pre-baseline and continued into the treatment period of the study. Post treatment will be defined as treatments that started after the last day of study treatment.

All prior,concomitant and post medications will be coded using the latest version of the WHO drug dictionary. Treatments were presented in alphabetical order, by ATC codes and grouped by anatomical main group. Tables also showed the overall number and percentage of patients achieving at least one treatment of a particular ATC.

All summaries will be on the safety set.

All prior and concomitant medication and procedures/non-drug therapies will be listed by center, and patient number.

The following descriptive statistics will be presented:

- Prior medication:
  - Number of patients with prior medications
  - Medications by WHO ATC class (alphabetically) and descending frequency (preferred name within ATC)
- Concomitant medication
  - Number of patients with concomitant medications
  - Medications by WHO ATC class (alphabetically) and descending frequency (preferred name within ATC)
- Post medication
  - Number of patients with post medications
  - Medications by WHO ATC class (alphabetically) and descending frequency (preferred name within ATC)
- Prior surgical and medical procedures:
  - Number of patients with prior procedures or non-drug therapies
  - Procedures and non-drug therapies by primary MedDRA SOC and PT
- Concomitant surgical and medical procedures
  - Number of patients with concomitant procedures or non-drug therapies
  - Procedures and non-drug therapies by primary MedDRA SOC and PT

### 2.4.3 Glucocortiod infiltration and pain medication

Treatment with glucocorticoids and pain medication during the course of the study will be shown for the comparison of the study phases before treatment (Screening period and Run-in period), during treatment (Treatment period) and after treatment (Follow-up period) by ATC classes and treatment. Medication was defined as relevant pain medication based on a coded medication listing in the blinded review meeting (see section 5.4 Subgroup GC-infiltration).

### 2.4.4 Inability to work

The course of inability to work will be displayed by visit and treatment, the reason for inability to work and the duration of inability to work will be displayed by treatment.

## 2.5 Analysis supporting primary objective(s)

Due to early termination of Secukinumab Phase 3 trials in Rotator Cuff Tendinopathy screening has been discontinued on 17-MAY-2024. Patients that have been screened until 17-MAY-2024 can be randomized and all randomized patients can complete the study. A number of 65 patients have been randomized, the resulting power under previous assumptions will be ca. 26%. Therefore only a descriptive analysis will be performed.

The primary objective of this trial is to demonstrate that the efficacy of 12 weeks of treatment with secukinumab 300 mg s.c. is superior to placebo (both arms in combination with patient individualized conventional therapy), in participants with moderate to severe rotator cuff tendinopathy, based on change from Baseline in WORC score at week 24. Participants will be analyzed according to the treatment they have been assigned to during the randomization procedure (FAS, see section 2.2).

### 2.5.1 Primary endpoint(s)

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

**WORC (**Kirkley, et al., 2003**)**

The Western Ontario Rotator Cuff (WORC) index is a patient reported outcome tool, uniquely developed for the rotator cuff diseases by Kirkley and co-workers. The WORC is self-administered and consists of 21 items divided into five domains: Physical symptoms (items 1-6), sports/recreation (items 7-10), work (items 11-14), lifestyle (items 15-18), emotions (items 19-21).

Items are scored by a 100 mm VAS. The best possible result is 0 (asymptomatic patient) and the worst possible result is 2100 (highly symptomatic). For ease of interpretation and in accordance with recommendations from instrument authors, the WORC index will be calculated for the total score as well as the five domains.

The average of the non-missing items will be used to calculate the domain index where there are two or fewer missing items for the physical symptoms domain and one or fewer missing

items for each of the sports/recreation, work, lifestyle and emotions domains. Each domain index will be computed by summing the non-missing item scores, dividing by the number of non-missing items and multiplying by the total number of items in the scale. For the WORC total index to be derived, scores for all five domains need to be present. The algorithms for calculating the index are as follows:

$$WORC\ Total\ index\ = 21 * \frac{sum\ of\ non-missing\ items}{number\ of\ non-missing\ items}$$

$$WORC\ Physical\ Symtoms\ index = 6 * \frac{sum\ of\ non-missing\ items}{number\ of\ non-missing\ items}$$

$$WORC\ Sports/Recreation\ index = 4 * \frac{sum\ of\ non-missing\ items}{number\ of\ non-missing\ items}$$

$$WORC\ Work\ index = 4 * \frac{sum\ of\ non-missing\ items}{number\ of\ non-missing\ items}$$

$$WORC\ Lifestyle\ index = 4 * \frac{sum\ of\ non-missing\ items}{number\ of\ non-missing\ items}$$

$$WORC\ Emotions\ index = 3 * \frac{sum\ of\ non-missing\ items}{number\ of\ non-missing\ items}$$

If there are no missing values, the index corresponds to the sum of the items. For index, higher values indicate worse (more symptomatic) status.

For each domain index, the total is subtracted from the maximum index and divided by the number of items, resulting in a percentage score of 0 to 100, where 0 represents the most symptomatic score and 100 represents no symptoms:

$$WORC\ Total\ percentage\ score = \frac{2100 - WORC\ Total\ index}{2100} * 100$$

$$WORC\ Physical\ Symptoms\ percentage\ score = \frac{600 - WORC\ Physical\ Symptoms\ index}{600} * 100$$

$$WORC\ Sports/\ Recreation\ percentagescore = \frac{400 - WORC\ Sports/\ Recreations\ index}{400} * 100$$

$$WORC\ Work\ percentage\ score = \frac{400 - WORC\ Work\ index}{400} * 100$$

$$WORC\ Lifestyle\ percentage\ score = \frac{400 - WORC\ Lifestyle\ index}{400} * 100$$

$$WORC\ Emotional\ percentage\ score = \frac{300 - WORC\ Total\ index}{300} * 100$$

### 2.5.2 Statistical hypothesis, model, and method of analysis

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

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

### 2.5.3 Handling of intercurrent events

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

### 2.5.4 Handling of missing values not related to intercurrent event

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

### 2.5.5 Sensitivity analyses

The primary endpoint will additionally be analyzed with an MMRM extended by the interaction baseline WORC score * visit.

Subgroup analyses will be conducted as supportive analyses to investigate possible subgroup-by-treatment interaction effects (see 2.2.1 Subgroup of interest).

### 2.5.6 Supplementary analyses

No further supplementary analyses were planned.

## 2.6 Analysis supporting secondary objectives

The analyses of secondary endpoints will be performed using the FAS once all patients had completed the Week 24 assessment. For evaluation of secondary efficacy outcomes, no formal statistical testing procedure is applied.

Secondary outcomes will be analyzed analogously to the primary endpoint where appropriate, e.g. means standard deviations, median, minimum and maximum values for continuous

variables will be presented for each visit, as will be the change from baseline. These descriptive statistics will also be presented for the primary endpoint

Some observed parameters were used in this study both as secondary objective and as explorative endpoint. In the SAP the parameters were defined in both sections as appropriate. In the tables, figures and listings (TFL) shells file tables were presented by parameter irrespective of this separation.

### 2.6.1 Secondary endpoint(s)

Secondary objectives and the corresponding secondary endpoints were presented in chapter 1.2

### 2.6.2 Statistical hypothesis, model, and method of analysis

Due to early termination of the study only a descriptive analysis will be performed.

### 2.6.3 Handling of intercurrent events

For the analysis of the secondary endpoint, all patients of the FAS will be included.

### 2.6.4 Handling of missing values not related to intercurrent event

For the analysis of the primary endpoint, all patients of the FAS will be included.

### 2.6.5 Sensitivity analyses

No additional sensitivity analyses are planned for secondary objectives.

### 2.6.6 Supplementary analyses

No additional supplementary analyses are planned for secondary objectives.

## 2.7 Safety analyses

Participants will be analyzed according to the study treatment received (see section 2.2 Analysis sets for further details) for the Safety Set (SAF).

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

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

### 2.7.1 Adverse events (AEs)

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

The number (and percentage) of patients with treatment emergent adverse events (events present during on-treatment period, see section 2.7.1 Adverse events (AEs)) will be summarized in the following way:

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

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

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

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by system organ class and PT.

In addition, all the treatment emergent AEs will be listed.The by-subjects listing will include, SOC/PT/Verbatim term, start date, end date, severity, relationship to study drug, whether or not it is a serious AE, action taken with study drug and outcome. Adverse events of special interest / grouping of AEs

No adverse events of special interest are defined.

### 2.7.2 Deaths

Deaths will be presented by treatment group, primary system organ class, preferred term and study period (on treatment, post treatment).
All deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first dose of study treatment until 30 days after the date of last treatment will be summarized. In addition, deaths occurring after the first dose of study treatment and before the date of last treatment will be summarized.

### 2.7.3 Laboratory data

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

### 2.7.4 Other safety data

#### 2.7.4.1 ECG and cardiac imaging data

Not applicable.

#### 2.7.4.2 Vital signs

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

## 2.8 Pharmacokinetic endpoints

Not applicable.

## 2.9 PD and PK/PD analyses

Not applicable.

## 2.10 Patient-reported outcomes (PRO)

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

Further patient-reported outcomes are the EQ-5D-5L, the Participant's globals assessment of disease activity (PaGA), the QuickDASH, the SF-36 v2.0, pain NRS score [redacted]

These PROs will be presented as a course (EQ-5D-5L, pain score, [redacted]) resp. change from baseline by visit and treatment for the Full Analysis Set.

For the SF-36, the score is calculated and provided by the license holder. For the presentation of the change from baseline, external data sets with the calculated score are therefore imported via the SAS program and used for the analysis.

## 2.11 Clinician reported outcomes (ClinRO)

The ClinROs Range of Movement (ROM), Painful Arc Test, Full/ empty cup test, Apley scratch test and shoulder/ arm strength will be displayed by visit and treatment, for both, the affected arm and the not affected arm, where applicable. The Full Analysis Set will be used.

## 2.12 Biomarkers

Not applicable.

[redacted]

## 2.14 Interim analysis

No interim analyses was planned nor conducted.

# 3 Sample size calculation

Due to early termination of Secukinumab Phase 3 trials in Rotator Cuff Tendinopathy screening has been discontinued on 17-MAY-2024. Patients that have been screened until 17-MAY-2024 can be randomized and all randomized patients can complete the study. Therefore, Amendment 2 has been implemented.

A number of 63 patients have been randomized, the resulting power under previous assumptions will be ca. 26%. Therefore only a descriptive analysis will be performed.

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

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

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

with $\mu_1$ denoting the mean of the secukinumab arm, $\mu_2$ denoting the mean of the placebo arm and $\sigma$ denoting the pooled standard deviation.

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

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

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

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

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

# 4 Change to protocol specified analyses

In the protocol, the calculation of the WORC percentage score was only specified for cases without missing values. This calculation has been extended to include formulas for the compensation of missing values.

# 5 Appendix

## 5.1 Imputation rules

Details on data imputation were already presented in the above sections. No additional information was needed.

### 5.1.1 Study drug

The eCRF was implemented in a way, that each injection date of study drug had to be complete. Thus no implementation rule was necessary.

### 5.1.2 AE date imputation

In case an AE belonged unambiguously to one study period, missing start date parts will be imputed in such a way, that the minimal possible start date resulted. In case an AE could be assigned to different study periods including on-treatment depending on the imputation of the missing start date parts (e.g. minimal possible date < date of randomization and maximal possible date > end of study treatment + 84 days, or minimal start date ≤ end of study treatment + 84 days and maximal start date > end of study treatment + 84 days) missing start date parts will be imputed such that the earliest on-treatment date resulted.

For missing end date parts date will be imputed as maximal possible date.

If this imputation results in a end date prior to start date, end date will be imputed as start date plus 1 day.

### 5.1.3 Concomitant medication date imputation

In case a therapy could unambiguously be assigned as concomitant to study drug missing date parts will be imputed in such a way, that the minimal possible start date resulted. In case a therapy could be assigned to different study treatment phases depending on the imputation of the missing start date parts (e.g. minimal possible start date < date of randomization and maximal possible start date ≥ date of randomization or minimal end date ≤ date of randomization and maximal end date ≥ date of randomization missing start date), parts will be imputed such that the maximal possible start date results and missing end date parts will be imputed such that the minimal possible end date results.

If this imputation results in a end date prior to start date, then either start date will be imputed as end date – 1 or end date will be imputed as start date plus 1 day, but such that the therapy is assessed as concomitant medication.

#### 5.1.3.1 Prior therapies date imputation

In case a therapy could unambiguously be assigned as prior to study drug missing date parts will be imputed in such a way, that the minimal possible start date results and the maximal end date results.

#### 5.1.3.2 Post therapies date imputation

In case a therapy could unambiguously be assigned as post study drug missing date parts will be imputed in such a way, that the minimal possible start date results and the maximal end date resulted.

#### 5.1.3.3 Other imputations

Duration since onset of symptoms in weeks will be calculated as [min(start of symptoms) – date of informed consent] / 7

Duration since onset of symptoms in weeks will be calculated as [date of informed consent - min(start of symptoms)] / 7

Duration since start of physiotherapy in weeks will be calculated as [date of informed consent - min(start of physiotherapy)] / 7

Duration since start of analgesic therapy in weeks will be calculated as [date of informed consent - min(start of analgesic therapy)] / 7

### 5.1.4 EQ-5D-5L Score

The EQ-5D-5L questionnaire was evaluated with the German value set described in (Ludwig et al, 2018). For each EQ-5D-5L dimension - Mobility (MO), Self-Care (SC), Usual activities (UA), Pain/ Discomfort (PD) and Anxiety/ Depression (AD) – the level 1 (“no problems”) is used as the reference category. The decrement of level 1 for each of the remaining 4 levels is represented by a coefficient so that a regression model is optained as follows:

$$\begin{aligned} Y = {} & \beta_0 + \beta_1 * MO2 + \beta_2 * MO3 + \beta_3 * MO4 + \beta_4 * MO5 \\ & + \beta_5 * SC2 + \beta_6 * SC3 + \beta_7 * SC4 + \beta_8 * SC5 \\ & + \beta_9 * UA2 + \beta_{10} * UA3 + \beta_{11} * UA4 + \beta_{12} * UA5 \\ & + \beta_{13} * PD2 + \beta_{14} * PD3 + \beta_{15} * PD4 + \beta_{16} * PD5 \\ & + \beta_{17} * AD2 + \beta_{18} * AD3 + \beta_{19} * AD4 + \beta_{20} * AD5 + \varepsilon \end{aligned}$$

The parameter estimates for the model including correction for heteroskedasticity are displayed in the following table:

| Independent variable | Parameter estimate (β) |
|---|---|
| MO2: slight problems | 0.026 |
| MO3: moderate problems | 0.042 |
| MO4: severe problems | 0.139 |
| MO5: unable | 0.224 |
| SC2: slight problems | 0.050 |

| | |
|---|---|
| SC3: moderate problems | 0.056 |
| SC4: severe problems | 0.169 |
| SC5: unable | 0.260 |
| UA2: slight problems | 0.036 |
| UA3: moderate problems | 0.049 |
| UA4: severe problems | 0.129 |
| UA5: unable | 0.209 |
| PD2: slight problems | 0.057 |
| PD3: moderate problems | 0.109 |
| PD4: severe problems | 0.404 |
| PD5: extreme problems | 0.612 |
| AD2: slight problems | 0.030 |
| AD3: moderate problems | 0.082 |
| AD4: severe problems | 0.244 |
| AD5: extreme problems | 0.356 |

## 5.2 AEs coding/grading

AE were coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary. Severity of AE was assessed by the physician and documented in the electronic case report form (eCRF). No additional grading will be performed.

## 5.3 Laboratory parameters derivations

Laboratory parameters will be analyzed using the grading from the central lab (high, normal and low). Additionally, expanded limits and notable abnormalities of key laboratory tests were defined in CSP Appendix 3 Table 10-1. However, contrary to the definition in the CSP, the defined upper limit is not used for the parameter eGFR, but a lower limit of 60 ml/min/1.73qm, i.e. all values < 60 are shown as notable clinical values.

## 5.4 Subgroup GC-infiltration

The classification into the subgroup categories “GC infiltration” and “no GC infiltration” took place in the blinded review meeting and is recorded in the document “CAIN457FDE05_GC_infiltration_14FEB2025.csv”. This file will be read into the analysis data via SAS program and used to define the subgroup.

## 5.5 Statistical models

### 5.5.1 Analysis supporting primary objective(s)

Change from Baseline in WORC score will be analyzed using a MMRM model with treatment group and analysis visits (up to week 24) as factors and baseline WORC score as continuous covariates. Treatment group by analysis visit will be included in the model. For sensitivity analysis, additionally baseline WORC score by analysis visit will be included. An unstructured covariance structure is assumed for this model. The significance of the treatment effects for

secukinumab 300 mg s.c. at each visit will be determined from the comparison performed between secukinumab 300 mg s.c. and placebo at the appropriate analysis visit.

The following SAS sytax can be used:

```
PROC MIXED data=datafilename;
  CLASS treatmentvar subjvar visitvar;
  MODEL changevar=treatmentvar visitvar baselinevar
                  treatmentvar*visitvar [baselinevar*visitvar] / ddfm=kr;
  LSMEANS treatmentvar*visitvar / diff cl;
  REPEATED visitvar / type=un subject=subjvar;
  ODS OUTPUT LSMeans=lsmeans
             Diffs=diffs;
RUN;
```

In case the MMRM model does not converge, the following sequential steps can be used:

1. Change `ddfm=kr` to `ddfm=bw`. If still no convergence, perform step 2.
2. Change `type=un` to `type=cs`.

### 5.5.2 Analysis supporting secondary objective(s)

Not applicable

## 6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

Ludwig K, Graf von der Schulenburg JM, Greiner W. German Value Set for the EQ-5D-5L. PharmacoEconomics, 2018.

# 7 Approval signatures

This Statistical Analysis Plan was subject to critical review and has been approved after review by:

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