NOVARTIS

Clinical Development

AIN457

CAIN457O12301 / NCT05722522

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

Statistical Analysis Plan (SAP)

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14-Mar-2023	Initial version	Creation of final version	N/A – First version	NA
6-May-2024		Update due to the discontinuation of the study	Due to feasibility reasons, purely descriptive analyses will be performed for primary and secondary endpoints.	1.2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.12, 2.13
27-Nov-2024	Dry-run		Specification of details	

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List of abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body Mass Index
BSL	Baseline
CMQ	Customized MedDRA Query
CRF	Case Report/Record Form (paper or electronic)
CRS	Case Retrieval Sheet
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBL	Database Lock
DMS	Document Management System
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	Gamma Glutamyl Transferase
HDL	High Density Lipoprotein
ICE	Intercurrent Event
IG	Immunogenicity
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LDL	Low Density Lipoprotein
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LLQ	Lower Level of Quantification
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MI	Multiple Imputation
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drug
PAP	Psychometric Analysis Plan
PD	Pharmacodynamic(s)
	Protocol Deviation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PoC	Proof of Concept

PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
PSD	Physical Symptom Domain
PT	Preferred term
Q4w	Quaque (every) four weeks
QAP	Qualitative Analysis Plan
QoL	Quality of Life
RAS	Randomized Analysis Set
RCT	Rotator Cuff Tendinopathy
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
s.c.	subcutaneous
SD	Standard Deviation
SF	Short Form
SoC	Standard of Care
SOC	System Organ Class
SMQ	Standardized MedDRA Query
TBL	Total Bilirubin
ULN	Upper Limit of Normal
ULQ	Upper Level of Quantification
VAS	Visual Analog Scale
vs.	Versus
WORC	Western Ontario Rotator Cuff Index
[redacted]	[redacted]

1 Introduction

The scope of this plan includes the primary and secondary analyses. The purpose of this amendment is to modify the analysis plan to reflect the early termination status of the study. At the time of termination, 21 patients had been randomized and 2 patients had completed the study. Patients who were screened by May 7, 2024 were permitted to continue in the study per protocol to study completion.

1.1 Study design

CAIN457O12301 is a randomized, double-blind, placebo-controlled Phase III study over 24 weeks in participants with moderate to severe Rotator Cuff Tendinopathy (RCT), refractory to Standard of Care (SoC) (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) course as per local standard practice, if not intolerant or contraindicated, and a course of physiotherapy over a period of 8 weeks).

A screening period of up to maximum of 56 days will be used to assess participant eligibility. During the 2-week run-in period prior to the Baseline (BSL) visit, the participant will need to have 2 weeks of stable NSAID intake and standardized physiotherapy.

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

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

Randomization will be stratified by tear status (no tear/partial tear).

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

Study Period 1 (Baseline to Week 16)

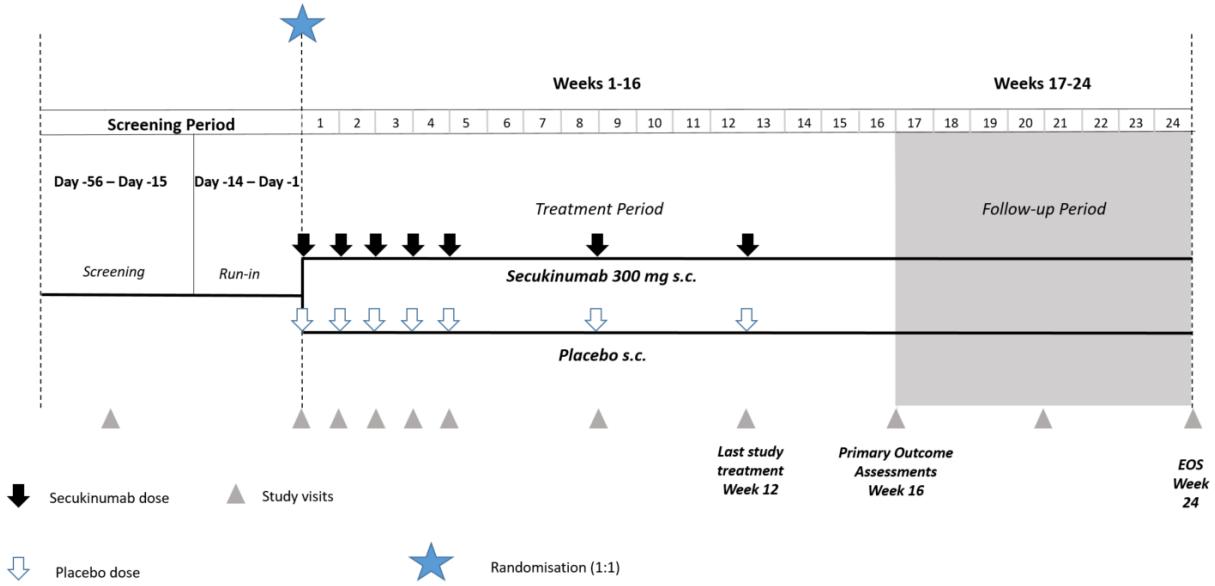
Participants should continue on stable NSAID pain medication and a standardized physiotherapy regimen. Reduction in NSAID dose is permitted after BSL, but participants must not increase above dose established during run-in. Use of corticosteroid injections is not permitted during this time.

Study Period 2 (Follow up period)

A follow-up period (Study period 2) of 8 weeks after the end of the treatment period is planned to assess the maintenance of effect and collect follow-up safety data up to Week 24.

Participants should continue on stable NSAID therapy and physiotherapy during this period. Reduction in NSAID dose is permitted, but participants must not increase above dose established during run-in. Corticosteroid injections are also not permitted after Week 16.

Figure 1-1 Study Design



1.2 Study objectives, endpoints and estimands

The purpose of this study is to demonstrate the efficacy and safety of secukinumab 300 mg s.c. in participants with moderate to severe RCT.

Due to the early termination of the study, purely descriptive analyses will be performed for primary and secondary endpoints. Exploratory endpoints will not be analyzed.

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

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Demonstrate that the efficacy of secukinumab 300 mg s.c., is superior to placebo, in improving physical shoulder symptoms in participants with moderate to severe RCT at Week 16	• Change from BSL in the WORC PSD score at Week 16
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in achieving a clinically meaningful response in improving physical shoulder symptoms in participants with moderate to severe RCT at Week 16	• Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in WORC PSD at Week 16
• Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in participants with moderate to severe RCT at Week 16 as measured by RCT-related QoL	• Proportion of participants who achieve an improvement (increase) of at least 50 points from BSL in the WORC total score at Week 16
• Demonstrate that the efficacy of secukinumab 300 mg s.c. is superior to placebo, in improving upper extremity in participants with moderate to severe RCT at Week 16	• Change from BSL in Patient-Reported Outcomes Measurement Information System (PROMIS) - Short Form (SF) Upper Extremity score at Week 16

Objective(s)	Endpoint(s)
• Demonstrate the efficacy of secukinumab 300 mg s.c. is superior to placebo, to improve physical symptoms at Week 24	• Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in WORC PSD at Week 24 • Change from BSL in WORC PSD score at Week 24
• Evaluate the pharmacokinetics (PK) of secukinumab 300 mg s.c., in the population of participants with moderate to severe RCT	• Secukinumab serum concentrations on Day 1 and Week 4 and Week 16
• Evaluate safety, immunogenicity and tolerability of 300 mg s.c. secukinumab, in participants with moderate to severe RCT	• Safety and tolerability demonstrated by assessing: • AEs and SAEs (incidence, severity, and relationship with study drug) • Incidence of clinically significant changes in laboratory parameters and vital signs • Incidence of binding and neutralizing anti-drug antibodies (ADAs) at Day 1 and Week 16

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis and/or a designated clinical research organization (CRO). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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

Missing values will not be imputed and are not included in calculations of summary statistics.

Efficacy and safety data for the 16-week placebo-controlled period or the entire study as appropriate will be presented by the following two treatment groups:

- Secukinumab 300 mg regimen
- Placebo regimen

2.1.1 General definitions

2.1.1.1 Study treatment

Study treatment is any drug administered to the study participants as part of the required study procedures, including investigational drug (i.e., Secukinumab 300 mg) and control drug (i.e., placebo).

2.1.1.2 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as *Study Day 1* or *Day 1*.

Of note, if there has been no drug administration, the randomization day is defined as *Day 1*.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose] + 1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis). Per protocol, participant informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose.

For efficacy analyses (except for WORC PSD, [redacted]), baseline is the last assessment (including unscheduled visits) obtained (on or) before the randomization (day). All assessments obtained after randomization (day) are considered as post-baseline unless otherwise specified. For WORC PSD, [redacted] baseline is the [redacted]

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before the first dose (day) of study treatment. All assessments obtained after the first dose (day) of study treatment are considered as post-baseline unless otherwise specified.

Of note, baseline will be derived based on the randomization day or first dose day, exact randomization/dosing time is not considered. If a scheduled baseline assessment value is missing, the screening value will be used instead.

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the CRF.

The participant's exposure will be calculated considering the last dose + 84 days or last visit whichever occurs earlier.

For safety analysis, on-treatment is defined as assessments within last dose + 84 days.

2.2 Analysis sets

The following analysis sets will be used in this study:

The **Randomized Analysis Set (RAS)** consists of all randomized participants.

The **Full Analysis Set (FAS)** comprises all participants in the RAS, excluding mis-randomized patients.

Mis-randomized participants are defined as cases where IRT contacts were made by the Investigator/qualified site staff either prematurely or inappropriately to confirmation of the patient's final randomization eligibility and treatment was not administered to the patient.

According to the intent-to-treat principle, participants will be analyzed according to the treatment they have been assigned to at randomization. If the actual randomization stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses.

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

2.2.1 Subgroup of interest

Due to the early termination of the study, subgroup analysis will not be performed.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of participants screened will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of participants in the RAS who completed the study periods, and who discontinued the study prematurely (including the reason for discontinuation) will be presented by study period for each treatment group and all participants. A listing will also be provided with detailed reasons for treatment discontinuation.

For each protocol deviation (PD), the number and percentage of participants for whom the PD applies will be tabulated.

2.3.2 Demographics and other baseline characteristics

The following common background and demographic variables will be summarized:

Continuous variables:

- Age
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

For BMI, height and body weight, the last value prior to randomization is used. If there is no weight or height recorded prior to administration of the study drug, BMI will be missing.

Categorical variables:

- Sex
- Race

- Ethnicity

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

- Time since first diagnosis of RCT (weeks), time since symptoms started (weeks), tear status (no tear/partial tear), WORC total score, WORC PSD score, [redacted] PROMIS SF UE score, [redacted], affected arm (Dominant arm/Non-dominant arm), pain medication during screening (No/Yes).

Time since diagnosis of RCT (weeks) will be calculated using the following formula:

Time since diagnosis = (inform consent date –first diagnosis date + 1)/7

Time since current symptoms of RCT (weeks) will be calculated using the following formula:

Time since current symptoms = (inform consent date – current symptoms date + 1)/7

The first diagnosis date of RCT will be imputed according to the imputation rules in Section 5.1.4.

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all participants (total) in the RAS. The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants (total) in the RAS.

2.3.3 Medical history

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the Medical dictionary for regulatory activities (MedDRA) dictionary. They will be summarized by treatment group, system organ class (SOC) and preferred term (PT) of the MedDRA dictionary.

Summaries for RCT specific medical history will be provided for the following parameters:

- Time since first diagnosis of RCT (weeks)
- Total number of prior episodes of tendinopathy
- Prior affected shoulder (left/right/bilateral)
- Time since current symptoms of tendinopathy started (weeks)
- Current affected shoulder (left/right)
- Dominant shoulder (left/right)

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

2.4.1 Study treatment / compliance

The analysis of study treatment data will be based on the SAF.

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

Duration of exposure will be defined as the time from first dose of study treatment to the end of study period. The end of study period will be defined as the last dose + 84 days or last visit whichever occurs earlier. For participants who discontinued and have their last visit earlier than last dose + 84 days, the end of study exposure will be the date of the last study visit in the follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min (last visit date, last dose date + 84 days) - first dose date + 1

Duration of exposure (years) = duration of exposure (days) / 365.25

Duration of exposure (100 subject years) = duration of exposure (years) / 100

The analyses of duration of exposure described above will be done for the entire study treatment period.

2.4.1.1 Analysis visit window

Analysis visit windows will be used for the data that is summarized by visit; they are based on the study visit and evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which analysis visit windows were created to cover the complete range of days within the study. Visit windows will vary depending on the frequency of the analysis visit. The analysis visit windows are defined in Table 2-1. In the tables, the days are counted since the first dose of the study treatment (i.e., *Study Day 1*).

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a participant is delayed and occurs on Day 46 instead of on Day 29, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a participant may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

In general, if two consecutive visits V_t and V_s are x days apart ($t < s$), when x is even, the upper limit for V_t will be $V_t + x/2$ and the lower limit for V_s will be $(V_s - x/2) + 1$; when x is odd, $x/2$ is rounded down to integer y, then the upper limit of the visit window for V_t will be $V_t + y$ and the lower limit for the visit V_s will be $V_s - y$. The algorithm needs to ensure that visit windows are not overlapping and there are no gaps, such that each assessment can be uniquely allocated to one visit window, e.g., if Week 8 visit is scheduled at day 57, Week 12 visit is scheduled at day 85 and Week 16 visit is scheduled at day 113, then the visit window for week 12 extends from Day 72 to Day 99.

Of note, participants are allowed to have gaps in visits.

Table 2-1 Analysis visit windows

Analysis Visit	Target Day	Analysis Visit Window	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Baseline	1*	≤ 1	≤ 1	[redacted]			≤ 1	≤ 1	≤ 1
Week 1	8	2-11							
Week 2	15	12-18	2-22						2-22

Analysis Visit	Target Day	Analysis Visit Window	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Week 3	22	19-25		[redacted]					
Week 4	29	26-43	23-43				2-71		23-43
Week 8	57	44-71	44-71						44-71
Week 12	85	72-99	72-99						72-99
Week 16	113	100-127	100-127				72-183	2-183	100-141
Week 20	141	128-155	128-155						
Week 24	169	156-183	156-183						142-183

Group 1: WORC Total, PROMIS SF UE, [redacted] WORC PSD, [redacted]
Group 2: [redacted]
Group 3: [redacted], Clinical Chemistry, Hematology
Group 4: [redacted]
Group 5: PK blood collection
Group 6: Immunogenicity
Group 7: Vital Signs
* The first day of administration of randomized study treatment (first dose) is defined as Day 1.

2.4.1.2 Multiple assessments within visit windows

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for *multiple assessments* within a particular visit window. The following rules will be used to determine the appropriate measurement to be summarized in the event of multiple assessments within a visit window (See Table 2-2).

For baseline assessment definition see Section 2.1.1.3. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-2 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.3.
Post-baseline efficacy	All data except for PRO	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used.

Timing of measurement	Type of data	Rule
		If two measurements are taken on the same day, then select the first one using eCRF visit number. If two measurements have been taken on the same day and same visit then select the worst.
Post-baseline efficacy	PRO data	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements have been taken on the same day, select the worst. If two measurements have the same value, select the first one using eCRF visit number.
Post-baseline safety	Summary visit information (e.g., lab, etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after) the first one will be used. If two measurements are taken on the same day then select the first one (using the time). If two measurements are taken on the same date/time then use the first visit number (assuming this is the planned visit). If two measurements are taken on the same date/time/eCRF visit number then use the average of two assessments.
Post-baseline safety	Notable abnormalities (e.g., vital signs) and CTCAE grading for laboratory values	The most extreme measurement in the window will be used. Note this means a participant can have a notably high and notably low measurement within an analysis period.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using the Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized in separate tables by treatment group for the SAF. Concomitant treatments will be displayed by study period as appropriate.

Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the 1st level of the ATC codes). Tables will show the overall number and percentage of participants receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and within 84 days after last dose will be a concomitant medication, including those which were started before first dose of study treatment and continued into the period where study treatment is administered.

Prior or concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date. See Section 5.1.3 for details.

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

Prior non-drug therapies and procedures are defined as non-drug therapies and procedures done prior to first dose of study treatment. Any non-drug therapies and procedures done between the day of first dose of study treatment and within 84 days after last dose will be defined as concomitant non-drug therapies and procedures, including those which were started before first dose of study treatment and continued into the period where study treatment is administered.

The number and percentage of participants receiving prior and concomitant RCT therapy will be presented by randomized treatment group.

[redacted]

2.5 Analysis supporting primary objective(s)

Due to the premature study discontinuation, purely descriptive analyses will be performed for the primary endpoint. Analysis of the primary endpoint will be done based on FAS.

2.5.1 Primary endpoint(s)

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

2.5.2 Statistical hypothesis, model, and method of analysis

WORC PSD change from baseline over time will be presented by treatment group using a summary table. Superiority testing will be omitted.

2.5.3 Handling of missing values

Missing values will not be imputed.

2.5.4 Sensitivity analyses

No sensitivity analyses are planned.

2.6 Analysis supporting secondary objectives

Due to the premature study discontinuation, purely descriptive analyses will be performed for secondary endpoints. Analysis on secondary endpoints will be done based on FAS.

2.6.1 Secondary endpoint(s)

The secondary efficacy variables include:

- Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in WORC PSD at Week 16
- Proportion of participants who achieve an improvement (increase) of at least 50 points from BSL in the WORC total score at Week 16
- Change from BSL in PROMIS SF UE score at Week 16

- Proportion of participants who achieve an improvement (increase) of at least 40 points from BSL in WORC PSD at Week 24
- Change from BSL in WORC PSD score at Week 24

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary objectives will be analyzed in a purely descriptive manner. Categorical variables will be presented in frequency tables. PROMIS change from baseline over time will be presented by treatment group using a summary table. No testing strategy will be applied.

2.6.3 Handling of missing values

Missing values of secondary endpoints will not be imputed.

2.6.4 Sensitivity analyses

Not applicable.

2.6.5 Supplementary analyses

Not applicable.

2.7 Safety analyses

All safety analyses will be based on the SAF and performed on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a participant received the wrong treatment during the entire study.

For those participants who did not receive the randomized treatment, i.e., who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors.

Safety summaries will include only data from the on-treatment period except for 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).

The on-treatment period lasts from the date of first administration of study treatment up to last administration + 84 days.

2.7.1 Adverse events (AEs)

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

The number (and percentage) of participants with treatment emergent adverse events will be summarized in the following ways:

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

Confidence intervals for the crude rate will be derived as described in Section 5.4.

Treatment emergent adverse events are defined as events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity on or after dosing based on preferred term and within last dose + 84 days (inclusive).

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

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

Adverse events reported will be presented in descending frequency according to its incidence in the AIN457 300 mg group starting from the most common event. AEs will be summarized by presenting the number and percentage of participants having any AE, having an AE in each primary system organ class and having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable. Of note, AEs by severity will be provided by SOC in the study report and AEs by severity and PTs may be provided if required at ad-hoc basis.

The MedDRA version (version 27.0 or above) used for reporting the study will be described in a footnote.

In addition, exposure time-adjusted incidence rates including 95% confidence intervals will be provided for the entire study period following the guideline as below:

- Primary SOC level for AE and SAE
- RMP risks
- PT level for SAE
- Overall PT level for AE and SAE
- Other selected AEs on lower levels (e.g., PT), if appropriate

Algorithms for date imputations are provided in Section 5.1.2.

Non-treatment emergent adverse events will be flagged on the overall AE listing. These adverse events occurred before the first dose of the study treatment or after 84 days post the last dose.

An overview of the safety analyses (i.e., crude incidence, exposure time-adjusted incidence) which will be performed for adverse events and other binary safety variables (e.g., labs and vital signs) for each analysis period is described in Table 2-3.

Table 2-3 Overview of analyses on some safety endpoints

Analysis period	AEs & SAEs	RMP risks	AEs by severity	Study drug related AEs	Notables (vitals/lab)
Entire Study	• crude incidence • exposure time adjusted incidence	• crude incidence • exposure time adjusted incidence	• crude incidence	• crude incidence	• crude incidence

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on **on-treatment/treatment emergent** adverse events which are not serious adverse events with an incidence greater than *z*% and on **on-treatment/treatment emergent** serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population. Here threshold value *z* is set to 2 (%) but it may be updated following review of the dry run outputs.

If for a same participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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 SOC and PT.

A listing of participants with anaphylaxis (including signs and symptoms) will be provided.

2.7.2 Deaths

Separate summary and listing will be provided for deaths.

2.7.3 Laboratory data

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

The general guideline for laboratory summaries (including Vital signs in Section 2.7.4.1) are as below:

- All the summary of lab outputs (newly occurring notables, maximum changes, by visit summary statistics) will consider the "on-treatment" data. i.e., all assessments up to last dose + 84 days.
- All records are displayed in the listing with the on-treatment flag. i.e., occurred up to last dose + 84 days- yes or no, as well as eCRF visits and epoch.

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and clinical chemistry).

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for participants with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) (i.e., numeric part is missing in the database) will be imputed as LLQ or ULQ value, respectively. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">").

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline within treatment period will be analyzed analogously.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-4: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose.

Table 2-4 CTCAE (v4.03) grades for laboratory parameters to be analyzed

CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	See Note 1 below
Platelet count decreased	<LLN – 75.0 ×10e9 /L	<75.0 - 50.0 ×10e9 /L	<50.0 – 25.0 ×10e9 /L	<25.0 × 10e9 /L
White blood cell decreased	<LLN - 3.0 × 10e9 /L	<3.0 - 2.0 × 10e9 /L	<2.0 - 1.0 × 10e9 /L	; <1.0 × 10e9 /L
Neutrophil count decreased	<LLN - 1.5 × 10e9 /L	<1.5 - 1.0 × 10e9 /L	<1.0 - 0.5 × 10e9 /L	<0.5 × 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 × 10e9/L	<0.8 - 0.5 × 10e9 /L	<0.5 - 0.2 × 10e9 /L	<0.2 × 10e9 /L
Creatinine increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 6.0 × ULN	>6.0 × ULN
TBL increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
GGT increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
ALT increased	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
AST increased	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
ALP increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

Note 1: Grade 4 Hemoglobin events are defined as life-threatening anemia events and will not be displayed in the table, as a numerical range is not provided in the CTCAE.

Of note, baseline will be defined as last assessment prior to first dose. Participants with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

The number and percentage of participants with clinically CTCAE grade newly occurring or worsening after baseline (treatment emergent) will be presented. Absolute and relative frequencies will be derived for non-overlap groups: CTCAE grade 1, CTCAE grade 2, CTCAE grade 3, and CTCAE grade 4.

Newly occurring or worsening liver enzyme abnormalities will also be summarized (crude incidence as described in above, including 95% confidence intervals) based on the event criteria given in Table 2-5:

Table 2-5 Liver-related events

Parameter	Criterion
ALT	>3×ULN; >5×ULN; >8×ULN;>10×ULN, >20×ULN
AST	>3×ULN; >5×ULN; >8×ULN >10×ULN; >20×ULN
ALT or AST	>3×ULN; >5×ULN; >8×ULN >10×ULN; >20×ULN
TBL	>1.5×ULN, >2×ULN, >3×ULN,
ALP	>2×ULN, >2.5×ULN, >3×ULN. >5×ULN
ALT or AST & TBL	ALT or AST>3×ULN & TBL >2×ULN; ALT or AST >5×ULN & TBL >2×ULN; ALT or AST >8×ULN & TBL >2×ULN; ALT or AST >10×ULN & TBL >2×ULN
ALP & TBL	ALP >3×ULN & TBL >2×ULN ALP >5×ULN & TBL >2×ULN
ALT or AST & TBL & ALP	ALT or AST>3×ULN & TBL >2×ULN & ALP ≤2×ULN **(Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3×ULN & TBL >2×ULN & ALP >2×ULN may not result in severe DILI.

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g., a participant with ALT = 6.42×ULN is counted for ALT > 3×ULN and ALT> 5×ULN.

Individual participant data listings will be provided for participants with newly occurring or worsening abnormal laboratory data. Data of participants with newly occurring or worsening liver enzyme abnormalities or renal abnormalities (as defined in the protocol) will be listed in an additional listing.

2.7.4 Other safety data

2.7.4.1 Vital signs

The summary of vital signs will only include treatment emergent data, which are defined as those vital sign measurements after the first dose of study treatment and up to last dose + 84 days.

Analysis in vital sign measurement using descriptive 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 participants with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The number and percentage of participants with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-6:

Table 2-6 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

2.7.4.2 Compound specific safety evaluation

Safety topics of interest, such as risks defined in the RMP or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in CREDI at the path Cabinets/CREDI Projects/A/AIN457A/Integrated Medical Safety.

The crude incidence and exposure-adjusted incidence rates for RMP risks will be summarized.

Important note: For the evaluation of RMP risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

2.8 Pharmacokinetic endpoints

AIN457 serum concentration data will be listed by treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the Lower Limit of Quantification (LLOQ) and reported as zero.

Concentrations below LLOQ will be imputed by 0 in summary statistics. No pharmacokinetic parameters will be calculated in this study as sparse sampling does not allow valid estimation by non-compartmental analysis.

2.9 PD and PK/PD analyses

2.9.1 Immunogenicity

Each anti-drug anti-body (ADA) sample is assessed in a three-tiered ADA testing approach. All ADA samples are analyzed in the initial screening assay (first tier). Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier).

Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb).

Any ADA sample collected after 84 days of the last dose of AIN457 will not be used for summaries or derivations and will only be included in the listing.

The following summaries of ADA subject status (n and %) will be provided by visit using the safety set:

- Subjects with ADA-positive sample at baseline
- Subjects with ADA-positive NAb sample at baseline (if applicable)

A listing of ADA subject status will also be provided.

2.10 Patient-reported outcomes

Patient reported outcomes will be evaluated based on FAS.

WORC Total

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

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

The average of the non-missing items will be used to calculate the raw domain score where there are two or fewer missing items for the physical symptoms domain and one or fewer missing items for each of the sports/recreation, work, lifestyle, and emotions domains. Each domain raw score will be computed by summing the non-missing item scores, dividing by the number of non-missing items and multiplying by the total number of items in the scale. For the WORC total score to be derived, scores for all five domains need to be present. The algorithms for calculating the raw scores are as follows:

WORC Total raw score = 21 × (sum of non-missing items/number of non-missing items)

WORC Physical Symptoms raw score = 6 × (sum of non-missing items/number of non-missing items)

WORC Sports/Recreation raw score = 4 × (sum of non-missing items/number of non-missing items)

WORC Work raw score = 4 × (sum of non-missing items/number of non-missing items)

WORC Lifestyle raw score = 4 × (sum of non-missing items/number of non-missing items)

WORC Emotions raw score = 3 × (sum of non-missing items/number of non-missing items)

For raw scores, higher scores indicate worse (more symptomatic) status.

Specifically, for each the raw aggregate score, the total is subtracted from the maximum score and divided by the number of items, resulting in a scale of 0 to 100, where 0 represents the most symptomatic score and 100 represents no symptoms:

[redacted]

WORC Physical Symptom domain

The WORC PSD comprises 6 questions (with a maximum score of 60 [redacted] possible) that capture the key symptoms experienced by participants with RCT relating to pain, weakness, stiffness, and mechanical symptoms. A score of 0 is the best outcome in terms of physical symptoms and a score of 60 is the worst possible score.

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

WORC PSD will be collected by a separate questionnaire in the e-diary which is completed by the participant at home. [redacted]

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

PROMIS SF UE measures self-reported capability of Physical Function. Participants will complete this questionnaire on site and will be asked a series of 7 questions rating their ability to perform a range of physical activities related to daily life that would be impacted by shoulder function. Each response is scored from 5 (Without any difficulty) to 1 (Unable to do). The 7 scores are added to give a total score out of 35. The lowest possible raw score is 7; the highest possible raw score is 35. Total raw score will be translated into a T-score (see Appendix 5.6) for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. There is no recall period for this questionnaire.

[redacted]

2.12 Other Exploratory analyses

Due to the premature study discontinuation, exploratory objectives and endpoints will not be analyzed.

3 Sample size calculation

3.1 Primary endpoint(s)

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

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

3.2 Secondary endpoint(s)

The estimated power with the chosen sample size based on data from the POC study are summarized in Table 3-1 and Table 3-2.

Table 3-1 Summary of power for continuous secondary endpoints

Endpoint	Mean difference	SD	Power
PROMIS SF UE[1] at Week 16	1.2	3	84%
WORC PSD at Week 24	14	30	95%

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

Table 3-2 Summary of power for binary secondary endpoints

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

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

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

4 Change to protocol specified analyses

Analyses changed as noted in change history due to the early termination of the study.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

- The last day in the month and
- The end day of the corresponding epoch

5.1.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), 31DECYYYY, date of death).
2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death).
3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

Before imputing AE start date, find the AE start reference date as below

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
- Else AE start reference date = treatment start date

1. If the AE start date 'year' value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date 'year' value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE 'month' is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Impute concomitant medication (CM) end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.4 First diagnosis date imputation

1. If the first diagnosis day/ month are missing and the year is non-missing:
   a. If the year part of the first diagnosis date is equal to the year part of the inform consent date, then the imputed first diagnosis date is set to the year start point (01JanYYYY).
   b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).
2. If the first diagnosis day is missing and the month/year are non-missing:
   a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date, then the imputed first diagnosis date is set to the month start point (01MONYYYY).
   b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

5.1.5 Other imputations

5.1.5.1 Laboratory data

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">").

5.2 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote. Safety topics of interest, such as risks defined in the Safety Profiling Plan, topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

5.3 Laboratory parameters derivations

See Table 2-4 and Table 2-5.

5.4 Statistical models

5.4.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, confidence intervals will be derived as well based on the score method including continuity correction (Newcombe 1998):

With z as (1-α/2)-quantile of the standard normal distribution (SAS: z = probit(1-α/2), n as total number of participants (i.e., number of participants in the denominator), p as estimated crude incidence (number of participants with event / n) and q = 1-p

Then the lower limit is

$$L = 100 \times \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is

$$U = 100 \times \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

In addition, if L > p then L = p and if U < p then U = p.

For binary response variables the placebo-adjusted response rates including 95% confidence interval will be derived.

SAS code for risk difference:

proc freq data=;

tables *response* treatment* / riskdiff;

run;

Note the response value should be sorted with '1' ahead of '0'.

5.4.2 Crude incidence and related risk estimates

5.4.2.1 Crude incidence and 100*(1-α)% confidence interval

For n participants, each at risk to experience a certain event with probability π, the crude incidence is estimated as p=x/n, where x is the number of participants with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With z as (1-α/2)-quantile of the standard normal distribution (SAS: z = PROBIT(1-α/2), n as total number of participants (i.e., number of participants in the denominator), and p as estimated crude incidence (number of participants with event / n) it is q=1-p.

Then the lower limit is

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

In addition, if L > p then L = p and if U < p then U = p.

If appropriate, an exact 100*(1-α)% confidence interval (Clopper-Pearson, 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

5.4.2.2 Odds ratio and 100*(1-α)% confidence interval

For an investigational drug group with n_1 participants at risk, independent from the control group (e.g., placebo or comparator) with n_0 participants at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio is estimated as

$\frac{p_1/(1-p_1)}{p_0/(1-p_0)}$ with $p_1 = x_1/n_1$ and $p_0 = x_0/n_0$. A conditional exact 100*(1-α)% confidence interval can be obtained by using the SAS procedure PROC FREQ with statement EXACT OR. However, to be able to adjust for covariates odds ratios will primarily be obtained from PROC LOGISTIC.

5.4.2.3 Risk difference and 100*(1-α)% confidence interval

For an investigational drug group with n_1 participants at risk, independent from the control group (e.g., placebo or comparator) with n_0 participants at risk, of whom x_1 and x_0 experience a certain event, the risk difference is estimated as p_1-p_0 with $p_1 = x_1/n_1$ and $p_0 = x_0/n_0$.

Exact unconditional confidence limits for the risk difference can be obtained with SAS procedure PROC FREQ and option RISKDIFF in the TABLES statement, specifying the RISKDIFF option also in the EXACT statement.

5.4.3 Exposure adjusted incidence rate and related risk estimates

5.4.3.1 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n participants in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be

modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as $\lambda=D/T$, where $T=\sum_{j=1}^{n} t_j$ and D is the number of participants with at least one event. Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai 1993):

Lower confidence limit $L=\frac{0.5c_{\alpha/2,2D}}{T}$ for $D>0$, 0 otherwise,

Upper confidence limit $U=\frac{0.5c_{1-\alpha/2,2D+2}}{T}$

Where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

5.5 Rule of exclusion criteria of analysis sets

Exclusion due to protocol deviation will be handled through the population attribute of the related estimand. The rules for participant classification in the analysis sets are based on criteria in Table 5-3.

Table 5-3 Criteria leading to exclusion

Analysis Set	Criteria that cause participants to be excluded
RAS	Not randomized
FAS	Not in RAS Mistakenly randomized and no double-blind study drug taken
SAF	No double-blind study drug taken
PK analysis set	Not in SAF No valid PK (AIN457) concentration measurement PD with impact on PK data

5.6 Computation of T-score for PROMIS SF UE

Please use the following table to convert Raw PROMIS value into T-score.

Raw summed score	T-Score	Raw summed score	T-Score
7	16.3	22	33.9
8	19.3	23	34.7
9	21.1	24	35.6
10	22.6	25	36.6
11	23.9	26	37.5
12	25.0	27	38.6
13	26.1	28	39.7
14	27.0	29	40.9

15	27.9	30	42.3
16	28.8	31	43.9
17	29.7	32	45.6
18	30.5	33	47.7
19	31.4	34	50.9
20	32.2	35	58.2
21	33.0		

6 Reference

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26; 404–413.

Garwood F (1936). Fiducial limits for the Poisson distribution. Biometrika, 46; 441–453.

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

Newcombe, RG. (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17: 857-872.

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867