NOVARTIS

Clinical Development

AIN457 (Secukinumab)

CAIN457ADE16 / NCT04737330

A two-year multi-center Phase 3 study to investigate the efficacy and safety of secukinumab in adult patients with active, moderate to severe thyroid eye disease (ORBIT), with a randomized, parallel-group, double-blind, placebo-controlled, 16-week treatment period, and a follow-up/retreatment period

Statistical Analysis Plan (SAP)

Author: CRO Biometrician, [redacted]

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15-Nov-2022	Prior to DB lock	Review of TFL shells	Analysis sets and definition of treatment groups changed; treatment sequence added; Study treatment related (S)AEs will not be analyzed separately	2.1.1; 2.2; 2.5.2; 2.8.1
25-Apr-2023	Prior to DB lock	Update due to discontinuation of the study	Due to feasibility reasons, purely descriptive analyses will be performed for primary and secondary endpoints. Adverse events of special interest (AESI) renamed to RMP risks.	1.2, 2.1.1, 2.5 to 2.14, 3, 4

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List of abbreviations

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AST	Asparate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
CAS	Clinical Activity Score
COVID-19	Coronavirus Disease 2019
CREDI	Clinical Regulatory Documentation and Information System
CRO	Contract Research Organization
CRS	Case Retrieval Sheet
DBP	Diastolic Blood Pressure
DBTP	Double-Blind Treatment Period
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
EUGOGO	European Group on Graves' Orbitopathy
FAS	Full Analysis Set
FDA	Food and Drug Administration
fT3	free T3
fT4	free T4
FUP	Follow-Up
GO-QoL	Grave's Orbitopathy Quality of Life
IP	Investigational Product
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
NR	Non-responder
PD(s)	Protocol Deviation(s)
PFS	Prefilled Syringe
PRO(s)	Patient Reported Outcome(s)
PT	Preferred Term
RMP	Risk Management Plan
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD-OCT	Spectral Domain Optical Coherence Tomography
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic-Oxaloacetic Transaminase

SOC	System Organ Class
TEAE(s)	Treatment-Emergent Adverse Event(s)
TED	Thyroid Eye Disease
TFLs	Tables, Figures, Listings

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analysis according to Section 12 of the study protocol v02 for AIN457 (secukinumab) Study CAIN457ADE16 dated 15-Mar-2022. 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, 28 patients had been randomized, 25 patients had completed the double-blind treatment period, and 23 patients had entered the follow-up period.

1.1 Study design

This is a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in patients with moderate to severe thyroid eye disease (TED). This study consists of the following 3 periods (see Figure 1-1):

Screening period (Week -6 to Baseline)

Patients' eligibility will be assessed during the Screening Period, which will occur for a maximum of 6 weeks. In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visits to the study sites, the Screening Period may be extended to a maximum of 8 weeks before Baseline.

Double-blind treatment period (DBTP) (Baseline to Week 16)

Eligible patients will be randomized in a 1:1 ratio to one of the following double-blinded treatment arms:

- Arm 1: Secukinumab 300 mg s.c. at Baseline, Week 1, 2, 3, 4, 8, 12 (n=35)
- Arm 2: Placebo s.c. at Baseline, Week 1, 2, 3, 4, 8, 12 (n=35)

Patients will be stratified according to current smoking status (up to 20% smokers per arm), since smoking has a well-known impact on treatment efficacy in TED.

Follow-up/open-label retreatment period (Week 16 up to Week 108)

- Proptosis responders (see definition below) at Week 16 will be followed for relapse up to Week 68. If these patients relapse, they will be offered a course of open-label secukinumab at the time of relapse (see "proptosis relapsers" definition below).
- Proptosis non-responders (see definition below) at Week 16 will be offered the option of open-label secukinumab treatment (with maintenance of blind of initial randomized treatment) for a duration of 16 weeks, i.e., up to Week 32 with last dose at Week 28, as follows:

  Open-label secukinumab 300 mg s.c. at Week 16, 17, 18, 19, 20, 24 and 28. Thereafter (i.e., from Week 32), patients will be followed up for a further 24 weeks [redacted].

  For patients who are proptosis non-responders and who do not receive open-label secukinumab treatment, a follow-up visit (End of Study [EOS]) 8 weeks after the Week 16 visit should be scheduled. At this EOS visit, the assessments associated with the Week 24 visit (for responder) should be performed.

- Proptosis relapsers (see definition below) during the follow-up period (from Week 16 onward to Week 68) will be offered the option of retreatment with open-label secukinumab for a duration of 16 weeks (with maintenance of blind to initial randomized treatment) at the time of relapse as follows:

  Open-label secukinumab 300 mg s.c., at time of relapse, then at 1, 2, 3, 4, 8 and 12 weeks. [redacted]

  For patients not receiving open-label secukinumab treatment, a follow-up visit (EOS) 8 weeks after the Week 16 visit should be scheduled, if not yet completed. At this EOS visit, the assessments associated with the Week 24 visit (for responder) should be performed.

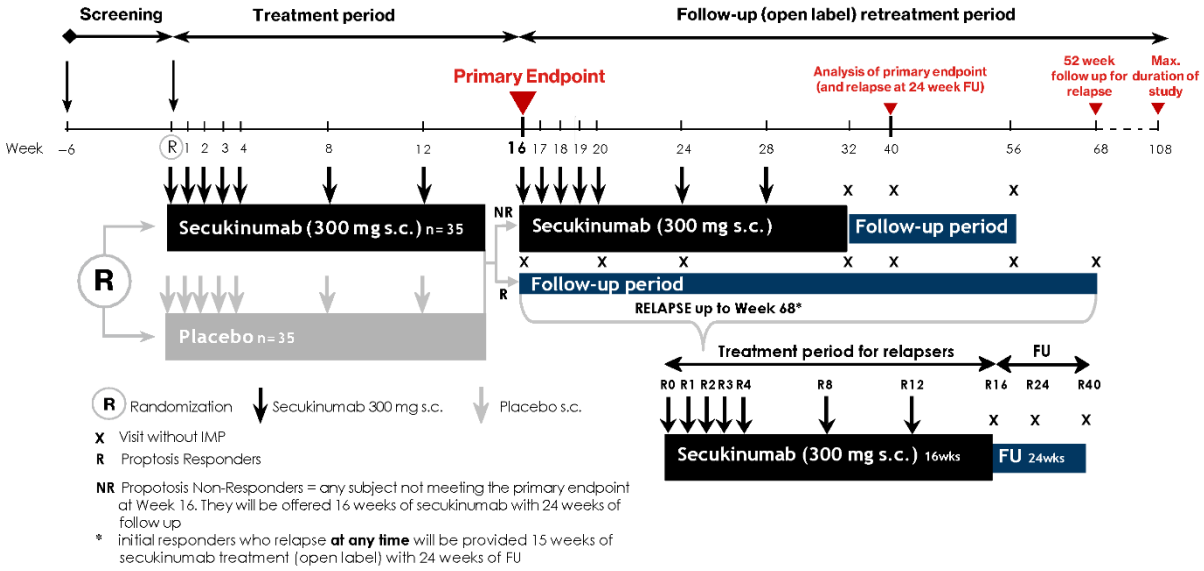
In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visits, special efforts should be made to conduct the Week 16, R16 and NR16 visits on-site, if feasible. If it is not feasible to conduct these visits on-site, visits to the patient´s home, or a virtual visit if a home visit is not feasible, should be attempted.

Definitions of proptosis responder, non-responder and relapser

- **Proptosis responder:** Patients achieving response in reduction of proptosis at Week 16 defined as follows: reduction of ≥ 2 mm from Baseline in the study eye without deterioration (≥ 2 mm increase from Baseline) of proptosis in the fellow eye.
- **Proptosis non-responder:** Patients not achieving response in reduction of proptosis at Week 16 with "response" defined as follows: reduction of ≥ 2 mm from Baseline in the study eye without deterioration (≥ 2 mm increase from Baseline) of proptosis in the fellow eye.
- **Proptosis relapser:** Patients who are "proptosis responders" as defined above, and then relapse based on proptosis [redacted] with relapse defined as follows: increase in proptosis of ≥ 2 mm compared to Week 16 in the study eye or deterioration of proptosis (≥ 2 mm increase compared to Week 16) in the fellow eye at any time during 52-week follow-up period.

In case of worsening of the disease during study treatment, patients may receive alternative treatment for TED at the discretion of the investigator and will be discontinued from the study treatment.

Figure 1-1 Study design



1.2 Study objectives and endpoints

The purpose of this study is to demonstrate the efficacy and safety of secukinumab 300 mg s.c. in adults with active, moderate to severe TED.

Due to non-efficacy (no responders at the time of premature study discontinuation), 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 the table below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary objective	**Primary endpoint**
1) To demonstrate that secukinumab is superior to placebo with regard to the **overall responder rate** after 16 weeks of treatment.	1) Proportion of patients achieving overall response defined as: ≥ 2 point reduction in clinical activity score (CAS) AND ≥ 2 mm reduction in proptosis from Baseline in the study eye, provided there is no corresponding deterioration in CAS or proptosis (≥ 2 point or 2 mm increase, respectively) in the fellow eye after 16 weeks of treatment.
Secondary objectives	**Secondary endpoints**
2.1) To demonstrate that secukinumab is superior to placebo with regard to the **CAS responder rate** after 16 weeks of treatment.	2.1) Proportion of patients achieving response in reduction of CAS at Week 16 defined as follows: reduction of ≥ 2 points from Baseline in the study eye

Objective	Endpoint
	without deterioration (≥ 2 point increase) of CAS in the fellow eye.
2.2) To demonstrate that secukinumab is superior to placebo with regard to the **proptosis responder rate** after 16 weeks of treatment.	2.2) Proportion of patients achieving response in reduction of proptosis at Week 16 defined as follows: reduction of ≥ 2 mm from Baseline in the study eye without deterioration (≥ 2 mm increase) of proptosis in the fellow eye.
2.3) To demonstrate that secukinumab is superior to placebo with regard to reduction in diplopia after 16 weeks of treatment.	2.3) Proportion of patients achieving response in diplopia at Week 16 defined as follows: Baseline diplopia > 0 and a reduction of ≥ 1 grade with no corresponding deterioration (≥ 1 grade worsening) in the fellow eye at Week 16.
2.4) To demonstrate that secukinumab is superior to placebo with regard to reduction in CAS after 16 weeks of treatment.	2.4) Mean change from Baseline to Week 16 in CAS in the study eye.
2.5) To demonstrate that secukinumab is superior to placebo with regard to reduction in proptosis after 16 weeks of treatment.	2.5) Mean change from Baseline to Week 16 in proptosis in the study eye.
2.6) To demonstrate that secukinumab is superior to placebo with regard to improvement in disease severity after 16 weeks of treatment.	2.6) Mean change in EUGOGO disease severity from Baseline to Week 16.
2.7) To demonstrate that secukinumab is superior to placebo with regard to improvement in GO-QoL after 16 weeks of treatment.	2.7) Mean change from Baseline to Week 16 in GO-QoL score.
Safety (secondary) endpoint	**Safety (secondary) endpoint**
2.8) To evaluate the safety of secukinumab 300 mg s.c. compared to placebo.	2.8) Frequency of AEs, TEAEs, AEs resulting in treatment discontinuation, SAEs.

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.

Statistical analysis of all data will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA) version 9.4 or higher.

General descriptive statistical rules

Categorical data will be presented as frequencies and percentages. In general, missing values are not considered for calculation of percentages (i.e., adjusted percentages are calculated) if not otherwise specified.

For continuous data, the number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented.

Unless otherwise stated, summary tables/figures/listings (TFLs) will be presented for each treatment arm in the respective analysis set.

General information on treatment arm handling, decimal places and other output-related information will be specified in TFL shells accompanying this analysis plan.

2.1.1 General definitions

Study treatment

Novartis will supply the investigational medication listed below:

- 2 × secukinumab 150 mg PFS, s.c.
- 2 × matching placebo 0 mg PFS, s.c.

Eligible patients will be randomized in a 1:1 ratio to one of the double-blinded treatment arms.

Treatment groups

- Randomized treatment:
  - AIN457 300 mg: All patients randomized to secukinumab.
  - Placebo: Patients randomized to placebo.
- Treatment sequence:
  - **AIN457 – AIN457**: Patients randomized to secukinumab and switched to open-label secukinumab treatment in follow-up period (“AIN457 non-responder”).
  - **Placebo – AIN457**: Patients randomized to placebo and switched to open-label secukinumab treatment in follow-up period (“placebo non-responder”).

Frequency of administration

Baseline to Week 16 (Double-blind):

- Secukinumab (300 mg): Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12
- Placebo: Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12

Week 16 to end of study (EOS) (Open-label):

- Non-responders at Week 16: Secukinumab (300 mg) at Week 16, Week 17, Week 18, Week 19, Week 20, Week 24 and Week 28;
- Responders at Week 16 who relapse thereafter: Secukinumab (300 mg) at time of relapse, then 1, 2, 3, 4, 8 and 12 weeks from time of relapse.

Stratification factor

Patients will be stratified according to current smoking status (up to 20% smokers per arm), since smoking has a well-known impact on treatment efficacy in TED.

2.1.1.1 Study dates

Screening/ Baseline

Screening period will occur for a maximum of 6 weeks (Day -42 to -1). Baseline is defined as the day with the last assessment on or before first dose. At Baseline all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms.

Randomization (enrollment) date in DBTP

Randomization (enrollment) date in double-blind treatment period (DBTP) is the date on which a subject is assigned to one of the treatments through IRT in DBTP.

First IP dose date

The first investigational product (IP) dose date is the date on which a subject is administered the first dose of IP following randomization.

Last IP dose date

The last IP dose date for each subject is defined as the latest date IP is administered (including study medication in the open-label retreatment phase).

Subject-level end of treatment (EOT) date

The EOT date (including the open-label retreatment phase) for each subject is defined as the minimum of (last dose date + 84 days) and EOS date.

Subject-level end of study (EOS) date

The EOS date for each subject is defined as the last date on which the subject participated in the study. The date will be recorded on the Disposition electronic case report form (eCRF) page.

2.1.1.2 Visit and analysis window

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to a study visit.

The nearest study day window will be utilized to define study visit for laboratory, vital signs, number of doses received, ophthalmological assessments and GO-QoL collected during office visits before dose is administered.

In case of multiple assessments within an analysis window, the day the closest to the scheduled visit day will be used.

Unscheduled visits will only be used when there is no measurement from the scheduled visit in the defined window. In case of multiple assessment values among the same type of visit (i.e., scheduled vs. unscheduled) within the same analysis window, the closest to the scheduled visit

day will be used. In case of equal distances (e.g., same day), the latest assessment value will be used.

For assessments that are not scheduled at all visits (e.g. hematology assessments) the derivation formula is:

- Lower limit = upper limit of previous visit +1.
- Upper limit = integer value of (target day + target day of next visit)/2.

Table 2-1 Study visit windows during DBTP

Study visit	Target day	Study day
DBTP		
Baseline	1	≤1
Week 1	8	2 – 11
Week 2	15	12 – 18
Week 3	22	19 – 25
Week 4	29	26 – 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 – 127

Table 2-2 Study visit windows during open-label treatment and follow-up for non-responders

Study visit	Target day	Study day
Week NR 16*	113	100 – 116
Week NR 17	120	117 – 123
Week NR 18	127	124 – 130
Week NR 19	134	131 – 137
Week NR 20	141	138 – 155
Week NR 24	169	156 – 183
Week NR 28	197	184 – 211
Week NR 32	225	212 – 253
Week NR 40	281	254 – 337
Week NR 56	393	338 – 448

*Only applicable for assessments that have not been performed at Week 16 visit in non-responders.

2.1.1.3 Demographics and other baseline characteristics

Smoking status

- "Smoker": a subject is defined as smoker if "Has the subject ever smoked"= "Yes" and "Usage" = "Current".
- "Non-Smoker": a subject is defined as non-smoker if "Has the subject ever smoked"= "No" OR "Has the subject ever smoked"= "Yes" and "Usage" = "Former".

TED history

- "Time (years) between onset of TED symptoms and Baseline" will be calculated as the difference between date of Baseline visit and date of onset of TED symptoms.
- "Time (years) between first diagnosis of TED and Baseline" will be calculated as the difference between date of Baseline visit and date of first diagnosis of TED.

Prior or concomitant medications (including previous TED treatments)

- Prior or concomitant medications will be grouped into categories "ophthalmic medications" and "non-ophthalmic medications". Non-ophthalmic medications are those with "laterality" = "not applicable".

2.1.1.4 Efficacy endpoints

Graves'orbitopathy – Quality of life questionnaire (GO-QoL)

The GO-Quality of life questionnaire (GO-QoL) comprises 2 subscales assessed separately. These 2 subscales are as follows:

- The consequences of double vision (diplopia) and decreased visual acuity on visual functioning and
- The psychological consequences of a changed appearance.

Total scores on each subscale will be calculated in the eCRF. Scoring rules used in the eCRF are defined in Appendix C (Section 5.7).

For other efficacy endpoints no specific definition is needed.

2.1.1.5 Safety endpoints

Discontinuation of treatment due to AE

Discontinuation of treatment due to AE is determined by the information given on the Adverse events eCRF page (action taken="Drug withdrawn"). "Death" as a reason for treatment discontinuation will be summarized separately.

Treatment-emergent adverse events (TEAEs)

Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that occurred on or after the first dose of study treatment up to 84 days following the last dose of study treatment. In addition, AEs registered prior to start of double-blind treatment are considered as treatment-emergent if they have increased severity based on preferred term any time after the first dose of study treatment.

Serious adverse events (SAEs)

SAEs are determined by the flag on the Adverse Events eCRF page.

Treatment-related adverse event

Treatment-emergent adverse event is defined as treatment-related, if the investigator considered it as having a reasonable possibility to be related to study treatment, which is reflected in the eCRF with a corresponding flag.

Duration of exposure to AIN457 or Placebo (DBTP)

For calculations of exposure duration, last/ first dose date refers to receiving dose (prefilled syringe) > 0.

The duration of exposure to study treatment or placebo is computed as:

For patients completing the DBTP:

- Week 16 visit date – first dose date + 1.

For patients who discontinue treatment during DBTP:

- min (last dose date +84 days, Week 16 visit date) – first dose date + 1.

Duration of exposure to AIN457 (during entire study period)

For calculations of exposure duration, last/ first dose date refers to receiving dose (prefilled syringe) > 0. Duration of exposure will be defined as the time from first dose of study treatment to the time of treatment switch (for subjects who switch treatment) or minimum of (last dose of the treatment + 84 days) and (last visit date). Patients who switch treatment during the study (e.g., from placebo to active treatment) will have exposure to both medications using the appropriate start and stop dates (full details are described in Section 3.1 of the protocol [i.e. study protocol v01 dated 24-Aug-2021]).

2.2 Analysis sets

Mis-randomized patients who never received any study drug are considered as screen failures and are not included in the analysis sets.

Efficacy analysis

- The **Full analysis set (FAS)** will consist of all patients to whom study treatment (AIN457 or placebo) has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment they have been assigned to.

Safety analysis

The **Safety analysis set (SAF)** will consist of all patients who received at least one dose of study treatment during the treatment period. Patients will be analyzed according to the study treatment received.

Table 2-3 Treatment groups for safety analysis

Analysis period	Treatment group label
DBTP (up to Week 16)	AIN457 Placebo
Entire study period	AIN457[1] Placebo[2] Any AIN457[3]

1 All patients randomized to secukinumab: This includes responders who receive no treatment after Week 16 and secukinumab non-responders or relapsers who go on open-label secukinumab.

2 Patients randomized to placebo with no open-label treatment in follow-up period. Any AEs reported in placebo patients prior to switching to AIN457 are also counted in this group.

3 Any AIN457 does not refer solely to just patients randomized to AIN457. It includes all patients who received at least one dose of secukinumab in DBTP or open-label follow-up. AEs occurring in placebo patients after switching to AIN457 are counted in this group.

2.2.1 Subgroup of interest

No subgroup analyses are planned.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Randomized

Subjects are considered randomized if they have been assigned a randomization number.

Mis-randomized

Subjects are considered as randomized in error (=mis-randomized) if they were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects will be treated as Screen Failures.

Screen failures

Subjects are considered as screen failure if they do not meet one or more criteria that where required for participation in the study.

Completing the DBTP

Subjects are defined as completing the DBTP if they complete all visits including Week 16 assessments. Subjects are defined as DBTP discontinuers if the Subject Status is not ticked as “Completed” for the blinded treatment disposition or if they missed any visit.

Completing the study

Subjects are defined as completing the study if they complete all visits including the follow-up visit (EOS)**.** It will be derived from Study Disposition Form.

Patient disposition for the DBTP and follow-up period will be presented based on the FAS.

A corresponding summary will include number and percentage of patients (treatment group specific and overall). The primary reason for premature study discontinuation will be displayed by randomized treatment and overall.

The total number of patients screened and the number of screen failures will be summarized. The number of patients within each of the analysis sets used in the study will be given.

Protocol deviations (PDs) will be summarized separately for PDs not related to coronavirus 2019 (COVID-19) and for PDs related to COVID-19. For PDs not related to COVID-19, the number of patients with at least one PD will be presented (based on FAS) and the results of the PDs will be grouped using the broad categories (Selection criteria not met (Study eligibility); Withdrawal criteria met, but subject not withdrawn; Treatment deviation; Prohibited Concomitant Medication; Other). For PDs related to COVID-19, the number of patients with at least one PD will be presented (based on FAS) and the results of the PDs will be grouped by category of COVID-19 PD and type of relationship to COVID-19.

A complete list of the PDs can be found in the Edit Check Specifications document in the Clinical Regulatory Documentation and Information System (CREDI).

2.3.2 Demographic variables 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.

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

2.3.3 Medical history

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

2.3.4 TED and thyroid medical history

Disease history collected at Screening contains information on the TED and thyroid medical history. Descriptive analyses will be done for time since onset of TED symptoms, time since first diagnosis of TED and underlying thyroid condition based on the FAS.

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

2.4.1 Study treatment / compliance

Descriptive statistics for exposure to study treatment will be provided based on the SAF.

The duration of exposure to study treatment will be summarized by treatment group.

In addition, the number of treatment syringes will be presented by treatment group in frequency tables by visit and cumulatively.

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 summarized according to the anatomical therapeutic chemical (ATC) classification system (ATC level 1 and preferred name), by treatment group for the SAF.

Separate presentations will be provided for ophthalmic and non-ophthalmic medications.

Concomitant medications and significant non-drug therapies during the double-blind treatment period and during the follow-up period will be displayed separately.

TED and thyroid treatment history (previous and ongoing treatments for TED) will be included in the tables for prior/ concomitant ophthalmic medications.

2.5 Analysis of the primary objective

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

2.5.1 Primary endpoint

The primary endpoint is the proportion of patients achieving overall response.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint will be presented by treatment group using a frequency table. Superiority testing will be omitted.

2.5.3 Handling of missing values/censoring/discontinuations

The primary endpoint should in principle be available for all patients who do not discontinue the trial prior to the discontinuation by the sponsor. Missing values will not be replaced.

2.5.4 Sensitivity analyses

No sensitivity analyses are planned.

2.5.5 Subgroup analyses

No subgroup analyses are planned.

2.6 Analysis of the secondary objective

2.6.1 Secondary endpoint

The secondary objectives and endpoints are given in Table 1-1.

Analysis of secondary endpoints will be done based on the FAS.

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary objectives will be analyzed in a purely descriptive manner: summary statistics by visit and change to baseline. No testing strategy will be applied.

2.6.3 Handling of missing values/censoring/discontinuations

Missing values of secondary endpoints will not be replaced.

2.6.4 Subgroup analyses

Not applicable.

2.7 Analysis of exploratory objectives

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

2.8 Safety analyses

Summaries may be performed separately for initial (Baseline to Week 16) period and entire study period (including follow-up). Week 16 is chosen due to the fact that patients may be switched to another treatment at this time. Use of data up to and including the last visit before first switch opportunity provides an unbiased comparison between AIN and placebo; data collected beyond Week 16 are included in analyses which summarize the entire study period.

All listings and tables will be presented by treatment group. Safety summaries include only data from the on-treatment period and follow-up period with the exception of Baseline data that will also be summarized where appropriate (e.g., change from Baseline summaries). The on-treatment period is defined as date of first treatment to (date of last treatment + 84 days).

In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided.

In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs) for the DBTP and the entire study period.

Missing data will not be imputed for safety endpoints.

2.8.1 Adverse events (AEs)

In the frame of safety analysis the following treatment-emergent AE types will be considered:

- Any AE
- Study treatment related AE
- AE leading to study treatment discontinuation
- Serious AE (SAE)
- Study treatment related SAE
- SAE leading to study treatment discontinuation
- Death

- RMP risks

All AE tables will be summarized by treatment group.

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code all AEs to a system organ class (SOC) and a preferred term (PT).

An overview table of the number and percentage of patients having each type of AE will be given. Crude incidence and exposure adjusted incidence rates will be provided (see Section 5.4.3 [safety analysis]).

Tables with number and percentage of patients having particular AE summarized by treatment group, SOC and PT will be provided for all AEs listed above except for death. Summaries will be provided for each AE type separately.

For AE type 'any AE' tables with number and percentage of patients having particular AE summarized by treatment group, SOC, PT and maximum severity will be provided.

The SOCs will be presented in the alphabetic order and PTs will be ordered within the SOCs by decreasing order of frequency in the secukinumab treatment group.

If a patient reported more than one AE with the same PT, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

All AEs, deaths, SAEs and AEs leading to permanent treatment discontinuation and leading to study discontinuation and AEs related to COVID-19 will be listed separately. In addition an ocular AE listing with laterality will be provided.

Table 2-4 Overview of analyses on some safety endpoints

Analysis period	AEs & SAEs	AEs by maximum severity	Study treatment related AEs	Notables for vitals, lab criteria
Day 1 – Week 16	•Crude incidence	•Crude incidence	•Crude incidence	•Crude incidence
Entire study phase	•Crude incidence Exposure time adjusted incidence	•Crude incidence	•Crude incidence	•Crude incidence

2.8.1.1 Adverse events of special interest / grouping of AEs

Safety topics of interest, such as risks defined in the Risk Management Plan (RMP), are defined in the Case Retrieval Sheet (CRS) that is stored in CREDI. For the evaluation of RMP risks, primary and secondary MedDRA SOCs will be considered.

2.8.2 Deaths

Deaths – including on treatment and post treatment deaths – will be listed by treatment group including the start date of the study treatment, the last date on study treatment, the death date and the reason for death. Deaths from the on-treatment period will be flagged.

2.8.3 Laboratory data

All laboratory data (hematology, clinical chemistry, urinalysis and thyroid-related parameters) from the on-treatment period will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics for clinical notable laboratory values will be provided by treatment and visit.

The following clinical notable laboratory values are defined:

Liver function and related variables	
ALT (SGPT)	> 3 × ULN
AST (SGOT)	> 3 × ULN
Total bilirubin	> 2 × ULN
Alkaline phosphatase	> 2 × ULN
Renal function and electrolyte variables	
Creatinine (serum):	> 1.5 × ULN
Hematology variables	
Hemoglobin	≥ 20 g/dL decrease from Baseline
Platelet count	< LLN
White blood cell count:	< 0.8 × LLN
Neutrophils	< 0.9 × LLN
Eosinophils	> 1.1 × ULN
Lymphocytes	> 1.1 × ULN
Urinalysis variables	
Protein urine dipstick	++* (* ++ is ≥ 100 mg/dL)

2.8.4 Other safety data

2.8.4.1 ECG

A standard 12-lead electrocardiogram (ECG) will be performed at Screening (source data) and will be reviewed locally. ECG data will not be analyzed.

2.8.4.2 Vital signs

Notable vital signs abnormalities will be analyzed by treatment group for the DBTP and the entire study period. A frequency table will be provided.

Normal blood pressure will be defined as systolic blood pressure (SBP) of 90 to < 120 mmHg, and diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined in the protocol. Notable blood pressure findings will be hypertension (SBP of ≥ 140 mmHg and/or diastolic blood pressure [DBP] of ≥ 90 mmHg) or hypotension (SBP of < 90 mmHg and/or a DBP of < 60 mmHg).

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm). Notable pulse rate abnormality will be a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

2.8.4.3 Pregnancy

Serum pregnancy test results will be listed for women of childbearing potential.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

The only patient reported outcome (PRO) assessed in the study is the GO-QoL. Summary statistics will be provided by treatment and visit.

2.12 Biomarkers

Not applicable,

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

Due to premature study discontinuation, no interim analysis is planned.

3 Sample size calculation

A final number of 28 patients is expected to be randomized by the time of study discontinuation.

Therefore, all analyses will be performed and interpreted in a purely descriptive manner.

4 Change to protocol specified analyses

Due to premature study discontinuation, purely descriptive analyses will be performed for primary and secondary endpoints. Exploratory endpoints will not be analyzed.

5 Appendix

5.1 Imputation rules

5.1.1 Concomitant medication date imputation

Incomplete day

Incomplete start day will be imputed as MAX(date of study day 1, *earliest possible start date*).

Incomplete end day will be imputed as MIN(EoS, *latest possible end date*).

Earliest possible start/end date is calculated on the eCRF page and refers to the first day of the corresponding month. *Latest possible start/end date* is calculated on the eCRF page and refers to the last day of the corresponding month.

Incomplete day/month

Incomplete start day/month will be imputed as MAX(date of study day 1, 01-Jan of the year entered).

Incomplete end day/month will be imputed as MIN(EoS, 31-Dec of the year entered).

Incomplete day/month/year

Incomplete day/months/year will not be imputed.

If the imputed end date is less than the existing start date, use the start date as the imputed end date.

5.1.2 Prior medications/ therapies date imputation

Prior medications/ therapies are those with an end date prior to the treatment phase (first drug administration).

Incomplete day

Incomplete start day will be imputed as earliest possible start date.

Incomplete end day will be imputed as MIN (date of the day prior to study day 1, latest possible end date).

Incomplete day/month

Incomplete start day/month will be imputed as01-Jan of the year entered.

Incomplete end day/month will be imputed as MIN(31-Dec of the year entered, date of the day prior to study day 1).

Incomplete day/month/year

Incomplete start date will be imputed as very early date, e.g., 01JAN1900.

Incomplete end date will be imputed as a date of the day prior to study Day 1.

For “Date of onset of TED symptoms” and “date of first diagnosis of TED”, the date will be imputed in the same way as prior medication/ therapies start date.

5.1.3 Post therapies date imputation

Not applicable.

5.1.4 Other imputations

Not applicable.

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Severity of adverse events is graded by investigator (mild, moderate, severe) and documented in the eCRF.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Safety analysis

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

For n subjects, 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 subjects with the event.

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

With z as $(1-\alpha/2)$-quantile of the standard normal distribution (SAS: z=PROBIT(1-α/2), n as total number of subjects (i.e., number of subjects in the denominator), and p as estimated crude incidence (number of subjects 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:

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

Note: if $p < L$ then $L = p$ and if $p > U$ then $U = p$.

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

It will be assumed that for each of n subjects in a clinical trial the time tj (j=1,…,n) to the first occurrence of a certain treatment emergent event is observed, or if the event was not experienced, the (censored) time to the end of the observation period or last dose plus 84 days whichever occur earlier. The sequence of first occurrence of an event will be modelled to follow approximately a Poisson process with constant intensity Θ. The parameter Θ will be estimated as λ= D/T, where T is the sum of t_1 to t_n and D is the number of subjects with at least one event.

Conditionally on T, an exact 100* (1-α)% CI 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)% CI for D/T will be derived as follows (Sahai 1993; Ulm 1990):

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.

Table 5-1 Examples for calculating exposure time for incidence rates (IR)

1st treatment / total exposure time	2nd treatment / total exposure time	AE event onset (in days from study start)	Exposure for IR
Placebo / 100 days	AIN457 / 200 days	Day 50 (during 1st treatment)	Placebo: 50 days
		Day 110 (10 days into 2nd treatment)	AIN457: 10 days Any AIN: 10 days

5.5 Rule of exclusion criteria of analysis sets

Exclusion criteria of analysis sets are complementary to those used for corresponding analysis set definitions (see Section 2.2 [Analysis Sets]).

5.6 Appendix A: Calculation rules

Not applicable.

5.7 Appendix C: Patient-reported Outcome Scoring rules/Forms/Instruments

GO-QoL scoring (calculation rule used in eCRF)

Questions are scored as follows:

- "Yes severely / very much" → 1 point
- "Yes a little" → 2 points
- "No not at all" → 3 points

Subscores are derived on the following logic:

1. Calculation of two **raw score**s from 8 to 24 points: adding points for the questions of each subscale (question 1 to 8 and 9 to 16). For questions 1 and 2, the answers `no driver's license' or `never learned to ride a bike' are scored as a missing value.
2. Transforming raw scores to **total scores** from 0 to 100 according to the formula:
    - If response is provided to fields 1 to 8 then Score 1 = [(raw score - 8)/16] *100
    - If response is provided for at least 4 fields then Score 1 ={[(raw score - #)/(2 * #)]*100}, where # is the number of completed items.
    - If response to 5 fields is missing then derive 'Score 1' as missing value.

5.8 Disclosure reporting

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> AEs which are not SAEs with an incidence greater than 5% and on <on-treatment/treatment emergent> SAEs and SAE suspected to be related to study treatment will be provided by Cohort, treatment, system organ class and preferred term on the SAF.

If for a same patient, 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 AE's 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.

6 References

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

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.

Ulm K (1990) A simple method to calculate the confidence interval of a standard mortality ratio. American Journal of Epidemiology, 131(2); 373-375.