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Novartis Research and Development

AIN457/Secukinumab

Protocol 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

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
axSpA	Axial Spondyloarthritis
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CAS	Clinical Activity Score
CD	Cluster of Differentiation
CI	Confidence Interval
ClinRO	Clinician Reported Outcomes
Cmax	Maximum Concentration
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CO	Country Organization
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
[redacted]	[redacted]
DON	Dysthyroid Optic Neuropathy
ECG	Electrocardiogram
ECM	Extracellular Matrix Components
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EUGOGO	European Group on Graves' Orbitopathy
EOS	End of Study
EOT	End of Treatment
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
fT3	free T3 (tri-iodothyronine)
fT4	free T4 (thyroxine)
GBCA	Gadolinium-based contrast agent
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GD	Graves' Disease
GGT	Gamma-Glutamyl Transferase
GO	Graves' orbitopathy
GO-QoL	Grave's orbitopathy quality of life
h	Hour

HA	Health Authority/Authorities
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-17A	Interleukin 17A
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver function test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
nr-axSpA	Non-radiographic Axial Spondyloarthritis
NSF	Nephrogenic systemic fibrosis
PA	posteroanterior
PD	Pharmacodynamic(s)
PFS	Prefilled Syringe
PK	Pharmacokinetic(s)
PsA	Psoriatic Arthritis
PsO	Psoriasis
pt	prothrombin time
PT	Preferred Term
QFT	QuantiFERON TB-PLUS test
QMS	Quality Management System
QoL	Quality of Life
RBC	Red Blood Cell(s)
SAE(s)	Serious Adverse Event(s)

SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
sCR	Serum Creatinine
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event(s)
TED	Thyroid Eye Disease
Th17	T-helper 17 cell
TNFα	Tumor Necrosis Factor Alpha
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized patients	Mis-randomized patients are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Patient information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.

Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient
Screen failure	A patient who did not meet one or more criteria that were required for participation in the study
Source data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or electronic source (eSource)
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient.
Study treatment	Any drug or combination of drugs or intervention administered to the study patients as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the patient permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 2 (February 2022)

Amendment rationale

The main purpose of this amendment is to provide clarification of wording for inclusion criterion 6 and for the requirement of patients to be fasting prior to laboratory assessments. [redacted] Furthermore, information was added that live vaccinations should not be given until 12 weeks after last study treatment administration to comply with current Novartis standards.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined font for insertions.

- Section 5.1 (Inclusion criteria): Wording of inclusion criterion 6 was amended to clarify that central lab retests are allowed for the fT3 and fT4 values during the Screening Period.
- Section 6.2.2 (Prohibited medication and procedures): Addition of the information that live vaccinations should not be given until 12 weeks after last study treatment administration.
- Section 8 (Visit schedule and assessments): Clarification added that patients should be reminded to be fasting before visits with laboratory assessments.
- Tables 8-1 and 8-2 (Assessment schedule):
  - Clarification of laboratory assessments that require fasting of the patients prior to the visit.
  - Clarification that the thyroid laboratory test can be performed at an unscheduled visit during the study, inclusive also of the screening period, at investigator´s discretion.
- Section 8.4.1 (Laboratory evaluations): Information was added for the test categories “Chemistry” and “Thyroid” that the listed parameters need to be assessed from fasting blood samples.
- [redacted]

IRBs/IECs

The changes described in this amendment provide clarification of wording for certain aspects of the protocol. The amendment does not require IRB/IEC and HA approval prior to implementation.

Amendment 1 (August 2021)

Amendment rationale

The main purpose of this amendment is to add additional ophthalmological assessments to the study protocol [redacted]. Exclusion criterion #13 was specified by the addition of a wash-out period for the prior use of oral corticosteroids. For patients who prematurely discontinue the study or study treatment, the follow-up assessment 12 weeks after last administration of study treatment was amended to an End of Study (EOS) visit which includes safety and efficacy assessments and will be recorded in the eCRF in order to increase data consistency and to comply with current Novartis standards.

Furthermore, minor clarifications and corrections of certain aspects and procedures as well as changes to correct formatting errors and administrative inconsistencies were made where applicable.

At the time of the amendment, no patients had been screened for inclusion.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red/blue font for deletions and red/blue underlined font for insertions.

- List of abbreviations was updated.
- [redacted]
- Sections 2.1 (Primary estimands) and 2.2 (Secondary estimands): Wording was amended for more clarity.
- Figure 3.1 (Study design):
  - Addition of visits without Investigational Medicinal Product (IMP) and relapse visits to the figure.
  - Addition of a short description for Week 108 on the timeline.
- Section 4.2 (Rationale for dose/regimen and duration of treatment): Wording on PK modeling was specified.
- Section 5.1 (Inclusion criteria):
  - “in the study eye” was added for inclusion criterion 3.
  - “for race and gender” was removed from inclusion criterion 3.
  - Timepoint for blood withdrawal was added for inclusion criterion 6.
- Section 5.1 (Exclusion criteria):
  - Addition of a wash-out period of 4 weeks for the prior use of oral corticosteroids for exclusion criterion 13.
- Table 6-2 (Prohibited medications/treatments/procedures):
  - Addition of a wash-out period of 4 weeks for the prior use of oral corticosteroids.
- Section 6.4 (Treatment blinding): Wording was amended for more clarity.
- Sections 6.7, 8 and 8.4: Timepoint for visits in the event of a major healthcare disruption was amended.
- Sections 8 (Visit schedule and assessments) and 9.1.1 (Study treatment discontinuation and study discontinuation): Renaming of “final visit” to “study discontinuation visit” for participants who prematurely discontinue the study.
- Tables 8-1 and 8-2 (Assessment schedule):
  - Renaming of unscheduled visit.
  - Clarification of assessments that can be performed at the unscheduled visit at investigator´s discretion.

  - Specification of visit day for Week 24 visit.
  - Removal of patient history.
  - Renaming of “Routine laboratory tests” to “Hematology and blood chemistry”.
  - [redacted]
  - CAS, proptosis measurement, diplopia grading and Graves’ Orbitopathy quality of life (GO-QoL) were changed from “optional” to “mandatory” assessments for Week 24 Visit.
  - Addition of “Contact Interactive Response Technology (IRT)”.
  - Clarification which assessments are documented in source data instead of the eCRF.
- Section 8.2 (Patient demographics/other baseline characteristics): Addition of patient race and ethnicity data to patient demographics that will be collected and analyzed in the study.
- Section 8.3 (Efficacy): Additional ophthalmological assessments were added.
- [redacted]
- Section 9.1 (Study treatment discontinuation and study discontinuation) and 9.2 (Study completion and post-study treatment): The visit to assess safety 12 weeks after last administration of study treatment for patients who prematurely discontinue the study or study treatment was replaced by an EOS visit that should be recorded in the eCRF.
- Section 12 (Data analysis and statistical methods): Specification of data analysis and methods. Addition of a definition for the Randomized Set.
- [redacted]
- The reference format in the text was updated.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Health Authorities (HA). The changes described in this amendment require IRB/IEC and HA approval prior to implementation. In addition, a revised informed consent that takes into account the changes to the protocol described herein will be submitted to the IRB/IEC for approval.

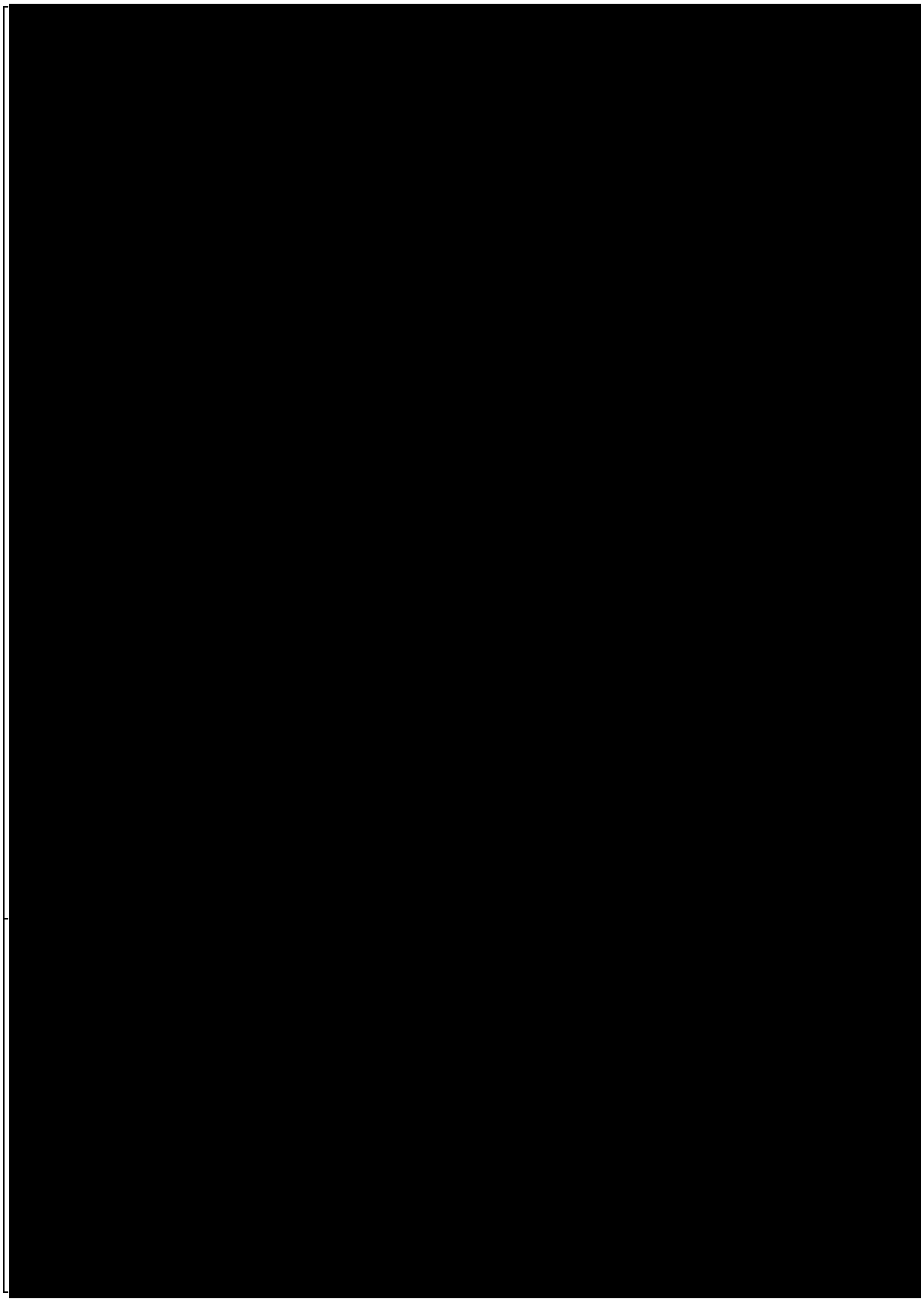
Summary of previous amendments

None

Protocol summary

Protocol number	CAIN457ADE16
Full Title	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
Brief title	A study of the efficacy and safety of secukinumab 300 mg in patients with thyroid eye disease (TED)
Sponsor and Clinical Phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Thyroid eye disease (TED) is a rare autoimmune, inflammatory disorder of the orbit and represents the most common extra-thyroidal manifestation of Graves' disease (GD). Several lines of evidence suggest an important role of interleukin-17A (IL-17A) in the pathogenesis of TED; increased levels of IL-17A have been detected in the serum and tears of patients with TED and IL-17A levels correlate with clinical activity of the disease. T-helper 17 cells (Th17 cells) (as well as other cellular sources of IL-17A, e.g., Tc17 cells) have been shown to infiltrate the orbital tissue of affected patients, producing IL-17A. IL-17A stimulates fibroblast activation, leading to retrobulbar tissue expansion and orbital fibrosis, which causes significant functional impairment. Secukinumab is a recombinant high-affinity fully human monoclonal anti-IL-17A antibody currently approved for the treatment of 3 inflammatory/ autoimmune diseases: moderate to severe plaque psoriasis (PsO), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) (ankylosing spondylitis (AS) and non-radiographic axSpA). The purpose of this study is to demonstrate the efficacy and safety of secukinumab 300 mg subcutaneous (s.c.) in adults with active, moderate to severe TED.
Primary objective	The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) expressed different preferences regarding the primary and secondary objectives and endpoints and their ordering. Therefore, this study will have 2 different analysis strategies and corresponding primary, secondary [redacted] objective and endpoint definitions; Plan A is intended for submission in Europe (EU) and other applicable countries and Plan B is intended for submission in the United States (US) and other applicable countries. **Plan A** • To demonstrate that secukinumab is superior to placebo with regard to the overall responder rate after 16 weeks of treatment, where the overall responder rate is defined as a ≥ 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.

	Plan B • To demonstrate that secukinumab is superior to placebo with regard to proptosis responder rate after 16 weeks of treatment, where the proptosis responder rate is defined as a reduction of ≥ 2 mm from Baseline in the study eye without deterioration (≥ 2 mm increase) of proptosis in the fellow eye.
Secondary objectives	**Plan A** • To demonstrate that secukinumab is superior to placebo with regard to the CAS responder rate after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to the proptosis responder rate after 16 weeks of treatment. • To demonstrate that secukinumab is superior to placebo with regard to reduction in diplopia after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to reduction in CAS after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to reduction in proptosis after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to improvement in disease severity after 16 weeks of treatment. • To demonstrate that secukinumab is superior to placebo with regard to improvement in Graves' Orbitopathy-quality of life (GO-QoL) after 16 weeks of treatment. § • To evaluate the safety of secukinumab compared to placebo.§ § Secondary objectives common to Plan A and Plan B.
	Plan B • To demonstrate that secukinumab is superior to placebo with regard to CAS responder rate after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to overall responder rate after 16 weeks of treatment. • To demonstrate that secukinumab is superior to placebo with regard to reduction in diplopia after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to reduction in CAS after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to reduction in proptosis after 16 weeks of treatment. § • To demonstrate that secukinumab is superior to placebo with regard to improvement in GO-QoL after 16 weeks of treatment. § • To evaluate the safety of secukinumab 300 mg compared to placebo. § § Secondary objectives common to Plan A and Plan B.
[redacted]	



[redacted]

Study design	This is a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in adult patients with moderate to severe TED. This study consists of the following 3 periods: **Screening period (Week -6 to Baseline)** Participants' eligibility will be assessed during the Screening period, which will occur for a maximum of 6 weeks. **Treatment period (Baseline to Week 16)** Eligible patients will be randomized in a 1:1 ratio to one of the following double-blinded treatment arms: 1. Arm 1: Secukinumab 300 mg s.c. at Baseline, Week 1, 2, 3, 4, 8, 12 (n = 35) 2. 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 8 weeks after the Week 16 visit should be scheduled. At this follow-up Visit, the assessments associated with the Week 24 visit (for responders) 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 since time of relapse. Thereafter, patients will be followed up for a further 24 weeks (i.e., 40 weeks after start of retreatment) to assess [redacted] safety. For patients not receiving open-label secukinumab treatment a follow-up visit 8 weeks after Week 16 visit should be scheduled, if not yet completed. At this follow-up Visit, the assessments associated with visit Week 24 (for responder) should be performed. **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) 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) 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) in the fellow eye at any time during 52-week follow-up period. In case of worsening of the disease, patients may receive alternative treatment for TED at the discretion of the investigator and will be discontinued from the study treatment. The primary endpoint analysis will be performed as an interim analysis once all patients have reached Week 40, which will include the primary efficacy endpoint (Week 16), efficacy of retreatment for initial non-responders and [redacted] during 24 weeks of follow-up. The final analysis will be performed when the last patient has reached the end of trial. Other interim analyses may be performed in accordance with HA requirements.
Population	Male or female patients with active, moderate to severe TED.

Key inclusion criteria	• Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed.
	• Male or non-pregnant, non-lactating female patients ≥ 18 years of age.
	• Clinical diagnosis of active, moderate to severe TED (**not** sight-threatening) in the study eye at Baseline associated with 2 or more of the following:
	  • Lid retraction ≥ 2 mm
	  • Moderate or severe soft tissue involvement
	  • Exophthalmos ≥ 3 mm above normal
	  • Inconstant or constant diplopia
	• Onset of TED symptoms fewer than 12 months prior to Baseline.
	• CAS ≥ 4 (on a 7-point scale, with a score of ≥ 3 indicating active TED) in the more severely affected (study) eye at Screening and Baseline. Note: Proptosis is the primary qualifier for selection of the study eye. In case both eyes show a similar degree of proptosis, other inflammatory signs and symptoms (CAS) should be taken into account by the investigator for the selection of the study eye.
	• Peripheral euthyroidism or mild hypo-/hyperthyroidism defined as free T3 (fT3) and free T4 (fT4) < 30% above/below normal limits at Screening. Every effort should be made to correct the mild hypo-/hyperthyroidism promptly and to maintain the euthyroid state until the end of this study.
	Note: Central lab retests will be allowed during the Screening Period if fT3 and fT4 values are outside the above-mentioned cut-off criteria.
	• Orbital MRI assessment available confirming the diagnosis of TED for patients initially presenting with hypo- or euthyroidism (without treatment for hyperthyroidism) before or at the time of TED diagnosis (to rule out other potential causes of orbital signs and symptoms.

Key exclusion criteria	• Improvement in CAS of ≥ 2 points and/or improvement in proptosis of ≥ 2 mm in the study eye between Screening and Baseline. • Signs of sight-threatening TED defined by optic neuropathy or severe corneal injury. • Patients, in the opinion of the investigator, requiring immediate or urgent medical treatment with glucocorticoids for TED. • Patients requiring immediate surgical ophthalmological intervention or planning corrective surgery/irradiation during the course of the study. • Decreased best corrected visual acuity (BCVA) as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect within the last 6 months. • Any other ophthalmic and/or orbital disease or condition that might interfere with the assessment of TED. • Previous orbital radiotherapy. • Previous ophthalmological/orbital surgery for TED (e.g., orbital decompression).

	• Previous use of biological agents for the treatment of TED. • Previous use of systemic, non-biologic, immunomodulatory agents for the treatment of TED (e.g., mycophenolate or cyclosporine). • Previous exposure to secukinumab or other biologic drugs directly targeting IL-17A or the IL-17 receptor (e.g., ixekizumab, brodalumab). • Previous treatment with rituximab, tocilizumab or teprotumumab. • Previous use of systemic corticosteroids for the treatment of TED, except for oral corticosteroids with a cumulative dose equivalent to < 1 g oral prednisone/prednisolone if the corticosteroid was discontinued at least 4 weeks prior to Baseline. • Previous treatment with any cell-depleting therapies including but not limited to anti-cluster of differentiation 20 (CD20) or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19). • Use of other investigational drugs within 5 half-lives of enrollment or within 30 days, whichever is longer. • Previous or ongoing use of prohibited treatments (see Section 6.2.2 of main protocol). Respective washout periods detailed in this section have to be adhered to. • History of hypersensitivity to any of the study drug constituents. Refer to Section 5.2. for full exclusion criteria list.

<table>
<tr><td>Study treatment</td><td>The investigational treatment is secukinumab 300 mg that will be supplied as 2 x 150 mg prefilled syringes (PFS). The control will be placebo to secukinumab, which will also be supplied as 2 x PFS.
<table>
<tr><th>Study treatment</th><th>Dose form</th><th>Route and frequency of administration</th></tr>
<tr><td>Baseline to Week 16 (Double-blind)</td><td></td><td></td></tr>
<tr><td>Secukinumab 300 mg</td><td>2 × 150 mg PFS</td><td>s.c. at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12.</td></tr>
<tr><td>Placebo</td><td>2 x 0 mg PFS</td><td>s.c. at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12.</td></tr>
<tr><td>Week 16 to end of study (EOS) (open-label)</td><td></td><td></td></tr>
<tr><td>Secukinumab 300 mg</td><td>2 x 150 mg PFS</td><td><u>Non-responders at Week 16</u>:
s.c. at Week 16, Week 17, Week 18, Week 19, Week 20, Week 24 and Week 28.

<u>Responders at Week 16 who relapse thereafter</u>:
s.c. at time of relapse, then 1, 2, 3, 4, 8 and 12 weeks from time of relapse.</td></tr>
</table>
PFS = prefilled syringe, q4w = every 4 weeks, s.c. = subcutaneous</td></tr>
<tr><td>Efficacy assessments</td><td>• CAS
• Proptosis
• Diplopia grading
• Ophthalmological assessments including subjective symptoms (e.g., epiphora, photophobia), Worth test, ocular motility, best corrected visual acuity (BCVA), visual field tests, pupil examination, swinging flashlight test, color vision assessment (Ishihara color plates), lid retraction, intraocular pressure (Goldman), fluorescein staining of the cornea, slit lamp examination, spectral domain-optical coherence tomography (SD-OCT) assessment of the macula and papilla and optic nerve assessment (only nonmydriatic)
[redacted]
• Disease severity assessment</td></tr>
<tr><td>Key safety assessments</td><td>• Physical examination
• Vital signs (systolic blood pressure, diastolic blood pressure (DBP), pulse)
• Adverse event (AE) assessments</td></tr>
</table>

	• Laboratory (hematology, clinical chemistry, urinalysis and Thyroid-related parameters) assessments
Other assessments	• GO-QoL assessment [redacted]
Data analysis	**Plan A** The primary endpoint is the proportion of patients achieving overall response at Week 16 defined as follows: ≥ 2 point reduction in 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. **Plan B** The primary endpoint is the 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 after 16 weeks of treatment. The null hypothesis to be rejected is that the difference in marginal response rates for patients with secukinumab vs. patients with placebo = 0 after 16 weeks. Let pj denote the probability of a response at 16 weeks for treatment group j, j=0, 1 where • 0 corresponds to placebo • 1 corresponds to secukinumab The following hypotheses will be tested: H0: p1 = p0 versus HA: p1 $\neq$ p0 The primary analysis will be performed comparing treatments with respect to the primary endpoint in a logistic regression model with treatment group and stratum (= smoking status) as factors and Baseline proptosis as covariate. Difference in marginal response proportions between treatments and its 95% confidence interval (CI) will be imputed using the marginal standardization method, details will be provided in the Statistical Analysis Plan (SAP). The primary analysis will be based on the Full Analysis Set (FAS) and will be performed when all patients have completed the Week 16 assessment.
Key words	CAS, diplopia, Graves' disease, TED, Graves' orbitopathy, proptosis, secukinumab

1 Introduction

1.1 Background

Thyroid eye disease (TED) also known as Graves' orbitopathy (GO) or Graves' ophthalmopathy, is a rare, autoimmune, inflammatory disorder of the orbit (Kahaly et al 2018). It represents the most common extra-thyroidal manifestation of Graves' disease (GD), which is characterized by autoimmune-induced hyperthyroidism. TED also occurs in hypothyroid (Hashimoto's) or euthyroid patients. Its prevalence is 2.9 to 4.5 cases per 10 000 people with a strong predominance for female patients (Perros et al 2017). Thyroid eye disease is characterized by exophthalmos, eyelid retraction, periorbital edema, swelling/redness of the eyelids, impaired ocular motility with consecutive strabismus or diplopia and impaired visual function. In very severe cases, TED can cause serious ophthalmologic complications such as corneal breakdown or dysthyroid optic neuropathy (DON), which can be sight-threatening. TED may severely affect patients' quality of life (QoL) from the highly visible and stigmatizing impact of symptoms on patients' facial expressions to highly bothersome symptoms such as retrobulbar pain, impaired visual function and diplopia (Kahaly et al 2005, Ponto et al 2013).

The **severity** of the disease is typically graded into mild, moderate to severe or sight-threatening (i.e., 'very severe') (Bartalena et al 2016), and is defined based on the degree of lid retraction, soft tissue involvement, proptosis, diplopia, corneal exposure and optic nerve involvement. Most patients have mild TED (~66%), approximately 29 to 33% have moderate to severe TED, and ~2% have very severe TED (Perros et al 2017). The natural course of TED consists of 2 phases: an active, inflammatory stage, followed by a post-inflammatory so-called inactive phase of the disease with in many cases remaining functional impairment (Bartley 2011, Barrio-Barrio et al 2015). TED activity is defined by the Clinical Activity Score (CAS), a validated scoring system that quantitatively measures the degree of active inflammation of the orbit (Mourits et al 1997).

Regarding the **pathogenesis** of TED, various immune cells (such as T cell subsets, B cells, monocytes, natural killer cells and macrophages) infiltrate the orbital space during the active phase of the disease. B and T cells become autoreactive and recognize orbital fibroblasts, the main target cell of the autoimmune attack, expressing the relevant antigens, the thyroid stimulating hormone (TSH) receptor and insulin-like growth factor 1 receptors. B cells produce autoantibodies and T cells secrete various cytokines/chemokines (e.g., IL-4, IL-13, IL-17A, tumor necrosis factor alpha [TNFα]) attracting further immune cells and reinforcing inflammatory processes. These processes jointly promote activation and proliferation/differentiation of orbital fibroblasts, with consecutive synthesis and deposition of large amounts of extracellular matrix components like glycosaminoglycans or collagens in the orbital space. Expansion of the orbital tissue leads to retrobulbar pressure increase with impaired venous drainage and consecutive proptosis. Inflammatory signs and symptoms include chemosis, eyelid swelling and periorbital edema. Swelling of the extraocular muscles leads to impairment in ocular motility. Furthermore, fibrosis of the orbital space results in long-term functional impairment such as restricted eye motility and strabismus (Wiersinga 2017, Huang et al 2019, Taylor et al 2020). In very severe cases the pressure increase in combination with the inflammatory processes can result in DON, which is potentially sight-threatening (Gorman 1998).

The current treatment of moderate to severe cases is mainly based on high-dose intravenous (i.v.) corticosteroids, as well as second line options, such as orbital radiation or cyclosporine each in combination with corticosteroids or rituximab (both off-label). All these treatment options show limited efficacy with very little impact on the key clinical feature, proptosis, and with well-known side effects. In many patients the condition does not improve and in some patients even progresses. A significant portion of patients require rehabilitative eye surgery after the active phase of the disease to treat remaining functional impairments, such as strabismus, eyelid retraction or exophthalmos. Approximately 25-30% of patients with TED do not respond adequately or relapse after completion of corticosteroid treatment. Furthermore, corticosteroids often only marginally improve long-term outcome of TED (Ing et al 2019). Given the associated risks, the guidelines recommend that this treatment be administered in experienced centers that can carefully monitor for toxicity and safely manage serious adverse events (SAEs), including monitoring of liver enzymes, glucose levels and blood pressure (Bartalena et al 2016). In addition, psychiatric side effects such as insomnia or dysphoria can occur, often at the beginning of high-dose corticosteroid therapy, for which patients should also be monitored. Proton pump inhibitors are recommended to prevent gastric ulcer, and contraindications such as inadequately controlled diabetes, significant hepatic dysfunction or relevant cardiovascular or psychiatric morbidity have to be taken into consideration.

Thus, there is a high need to identify new therapeutic strategies for TED. Teprotumumab, a fully human monoclonal antibody that acts by inhibiting the insulin-like growth factor 1 receptor has been approved in January 2020 for the treatment of TED in the United States by the FDA (Smith et al 2017, Douglas et al 2020).

There is an increasing amount of evidence showing the significant role of IL-17A in the immunopathogenesis of TED. IL-17A levels have been shown to be highly increased in the serum and lacrimal fluid (i.e., tears) of patients with TED, correlating with disease activity (Huang et al 2012, Kim et al 2012, Ujhelyi et al 2012, Wei et al 2014, Fang et al 2016a,). Th17 cells producing IL-17A, as well as other sources of IL-17A (such as Tc17 cells, γδ T cells or natural killer cells) have been shown to infiltrate the orbital space of active TED patients (Fang et al 2016b, Fang et al 2017, Hai et al 2019). IL-17A promotes orbital inflammation and has been shown to induce the proliferation and differentiation of orbital fibroblasts into (myo)fibrocytes and to stimulate their production of extracellular matrix components (ECM) (Fang et al 2016a, Fang et al 2016b, Fang et al 2017, Fang et al 2019, Huang et al 2019, Taylor et al 2020). Fibroblast activation and ECM production are key processes in the pathogenesis of TED, causing retrobulbar tissue expansion as well as orbital fibrosis and consecutive functional impairment. Thus, IL-17A is an attractive target for therapeutic intervention in patients with active TED.

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the immunoglobulin G1/kappa isotype. It is approved for the treatment of moderate to severe plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) with robust and clinically meaningful efficacy demonstrated. The safety profile of secukinumab has been established not only in a large clinical trial program across various indications (including long-term extension trials of up to 5 years), but also in 5 years of real world experience in clinical practice outside clinical trials (Deodhar et al 2019). Based on the role of IL-17A and Th17 cells in TED, secukinumab could offer a new therapeutic approach for patients with TED.

1.2 Purpose

As mentioned above, IL-17A plays a significant role in the immunopathogenesis of TED, an autoimmune, inflammatory disorder of the orbit. Secukinumab is a recombinant high-affinity fully human monoclonal anti-IL-17A antibody currently approved for the treatment of three autoimmune/inflammatory diseases with IL-17A central in their etiology. 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.

2 Objectives and endpoints

This study has 2 analysis strategies in accordance with FDA and European Medicines Agency (EMA) advice. Plan A is intended for submission in Europe and other applicable countries and Plan B is intended for submission in the United States and other applicable countries. The main difference between Plan A and Plan B is the definition of the primary objective, whereby the primary objective of Plan A is included as secondary objective in Plan B and vice versa. Furthermore, the assessment of the EUGOGO disease severity is included as a secondary objective in Plan A [redacted]

The objectives and related endpoints are presented for Plan A (EU submission) in Table 2-1, and for Plan B (FDA submission) in Table 2-2.

Table 2-1 Plan A - Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To demonstrate that secukinumab is superior to placebo with regard to the overall responder rate after 16 weeks of treatment.	• Proportion of patients achieving overall response defined as follows: ≥ 2 point reduction in 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. See Section 2.1 for primary estimand.
Secondary objectives	**Endpoints for secondary objectives**
• To demonstrate that secukinumab is superior to placebo with regard to the CAS responder rate after 16 weeks of treatment. §	• 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 without deterioration (≥ 2 point increase) of CAS in the fellow eye. §
• To demonstrate that secukinumab is superior to placebo with regard to the proptosis responder rate after 16 weeks of treatment.	• 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.
• To demonstrate that secukinumab is superior to placebo with regard to	• Proportion of patients achieving response in diplopia at Week 16 defined as follows:

Objectives	Endpoints
reduction in diplopia after 16 weeks of treatment. §	Baseline diplopia > 0 and a reduction of ≥ 1 grade with no corresponding deterioration (≥ 1 grade worsening) in the fellow eye at Week 16. §
• To demonstrate that secukinumab is superior to placebo with regard to reduction in CAS after 16 weeks of treatment. §	• Mean change from Baseline to Week 16 in CAS in the study eye. §
• To demonstrate that secukinumab is superior to placebo with regard to reduction in proptosis after 16 weeks of treatment. §	• Mean change from Baseline to Week 16 in proptosis in the study eye. §
• To demonstrate that secukinumab is superior to placebo with regard to improvement in disease severity after 16 weeks of treatment.	• Proportion of patients with improvement in EUGOGO disease severity (see Section 8.3.5) between Baseline and Week 16.
• To demonstrate that secukinumab is superior to placebo with regard to improvement in GO-QoL after 16 weeks of treatment. §	• Mean change from Baseline to Week 16 in GO-QoL score. §
• To evaluate the safety of secukinumab compared to placebo.§	• Frequency of AEs, TEAEs, AEs resulting in treatment discontinuation, SAEs. §

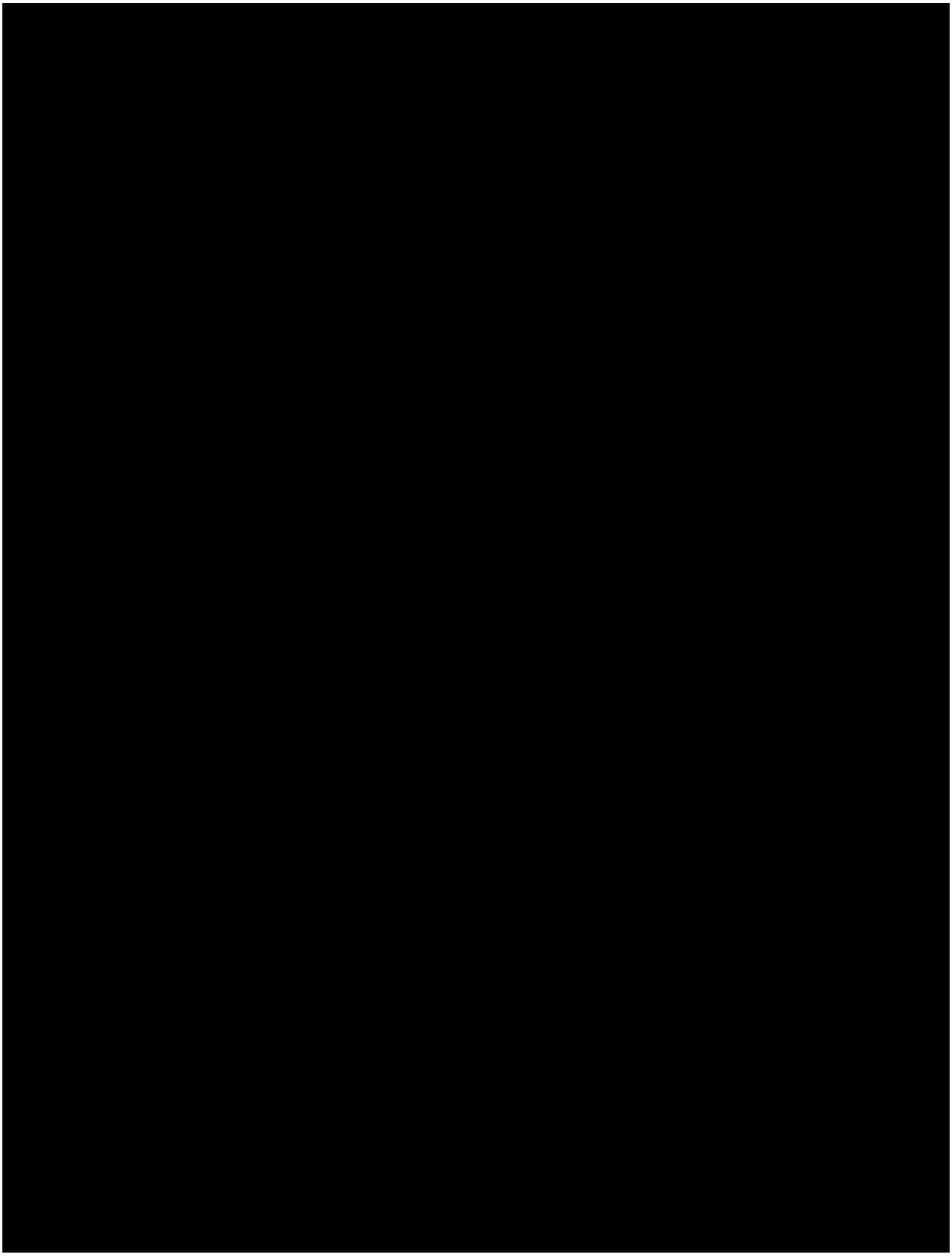
[redacted]

§ Secondary [redacted] objectives common to Plan A and Plan B.
AE(s)=adverse events, CAS=clinical activity score, fT3= free T3 (tri-iodothyronine), fT4= free T4 (thyroxine), GO-QoL = Graves' Orbitopathy quality of life, [redacted],
TEAE(s)=treatment-emergent AE(s), TSH=thyroid stimulating hormone

Table 2-2 Plan B - Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To demonstrate that secukinumab is superior to placebo with regard to proptosis responder rate after 16 weeks of treatment.	• 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. See Section 2.1 for primary estimand.
Secondary objectives	**Endpoints for secondary objectives**
• To demonstrate that secukinumab is superior to placebo with regard to CAS responder rate after 16 weeks of treatment. §	• 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 without deterioration (≥ 2 point increase) of CAS in the fellow eye. §
• To demonstrate that secukinumab is superior to placebo with regard to overall responder rate after 16 weeks of treatment.	• Proportion of patients achieving overall response at Week 16 defined as follows: ≥ 2 point reduction in 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.
• To demonstrate that secukinumab is superior to placebo with regard to reduction in diplopia after 16 weeks of treatment. §	• 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. §
• To demonstrate that secukinumab is superior to placebo with regard to reduction in CAS after 16 weeks of treatment. §	• Mean change from Baseline to Week 16 in CAS in the study eye. §
• To demonstrate that secukinumab is superior to placebo with regard to reduction in proptosis after 16 weeks of treatment. §	• Mean change from Baseline to Week 16 in proptosis in the study eye. §
• To demonstrate that secukinumab is superior to placebo with regard to improvement in GO-QoL after 16 weeks of treatment. §	• Mean change from Baseline to Week 16 in GO-QoL score. §
• To evaluate the safety of secukinumab 300 mg compared to placebo. §	• Frequency of AEs, TEAEs, AEs resulting in treatment discontinuation, SAEs. §

[redacted]



§ Secondary [redacted] objectives common to Plan A and Plan B.
AE(s)=adverse events, CAS=clinical activity score, fT3= free T3 (tri-iodothyronine), fT4= free T4 (thyroxine), GO-QoL = Thyroid eye disease quality of life, [redacted], TEAE(s)=treatment-emergent AE(s), TSH=thyroid stimulating hormone

2.1 Primary estimands

Plan A

The clinical question of interest is:
What is the effect of secukinumab 300 mg s.c. versus placebo on proportion of participants achieving overall response in reduction of CAS **and** proptosis at Week 16 in participants with active, moderate to severe TED, irrespective of adherence to treatment but without another treatment or procedure for TED in case of worsening of the disease?
The primary estimand is described by the following attributes:

1. Population of interest: defined through appropriate inclusion/exclusion criteria to reflect the targeted TED population
2. Variable of interest: overall response in reduction of CAS and proptosis at Week 16
3. Treatment of interest: the randomized treatment (secukinumab 300 mg s.c. and placebo s.c.). Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of intercurrent events:

- Treatment discontinuations/disruptions for any reason will be ignored (treatment policy strategy). The retrieved response status after treatment discontinuation will be used for the analysis.
- Other treatment given for TED, or procedure performed for TED in case of worsening of the disease: participants will be counted as non-responders (composite strategy)

The summary measure: difference in marginal response proportions between the treatments.

Plan B

The clinical question of interest is:
What is the effect of secukinumab 300 mg s.c. versus placebo on proportion of participants achieving response in reduction of proptosis at Week 16 in participants with active, moderate to severe TED, irrespective of adherence to treatment but without another treatment or procedure for TED in case of worsening of the disease? The primary estimand is described by the following attributes:

- Population of interest: defined through appropriate inclusion/exclusion criteria to reflect the targeted TED population
- Variable of interest: proportion of participants demonstrating response in reduction of proptosis at Week 16
- Treatment of interest: the randomized treatment (secukinumab 300 mg s.c. and placebo s.c.). Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of intercurrent events:

- Treatment discontinuations/disruptions for any reason: will be ignored (treatment policy strategy) The retrieved response status after treatment discontinuation will be used for the analysis.
- Other treatment given for TED, or procedure performed for TED in case of worsening of the disease: participants will be counted as non-responders (composite strategy)

The summary measure: difference in marginal response proportions between the treatments.

2.2 Secondary estimands

The clinical questions of interest for dichotomous secondary objectives are:

- What is the effect of secukinumab 300 mg s.c. versus placebo on proportion of participants achieving response (i.e., reduction of CAS, reduction of proptosis, reduction of CAS and proptosis, reduction of diplopia or improvement in EUGOGO disease severity) at Week 16 in participants with active, moderate to severe TED, irrespective of adherence to treatment but without another treatment or procedure for TED in case of worsening of the disease?

The clinical questions of interest for continuous secondary objectives are:

- What is the effect of secukinumab 300 mg s.c. versus placebo on change from baseline (i.e., in CAS, proptosis or GO-QoL score) at Week 16 in participants with active, moderate to severe TED, regardless of study treatment discontinuation and other treatment or procedure for TED in case of worsening of the disease?

The secondary estimands relating to dichotomous endpoints (response rates) are defined analogous to the primary estimand, but for the variable of interest.
The secondary estimand relating to continuous endpoints (mean change from Baseline to Week 16) is described by the following attributes:

1. Population of interest: defined through appropriate inclusion/exclusion criteria to reflect the targeted TED population
2. Variable of interest: change from baseline to Week 16 in the variable of interest

3. Treatment of interest: the randomized treatment (secukinumab 300 mg s.c. and placebo s.c.). Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of intercurrent events:

- Treatment discontinuations/disruptions for any reason: ignore (treatment policy strategy)
- Other treatment given for TED, or procedure performed for TED in case of worsening of the disease: ignore (treatment policy strategy)

The summary measure: difference in means between treatments.

3 Study design

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

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 (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. [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) of proptosis in the fellow eye.

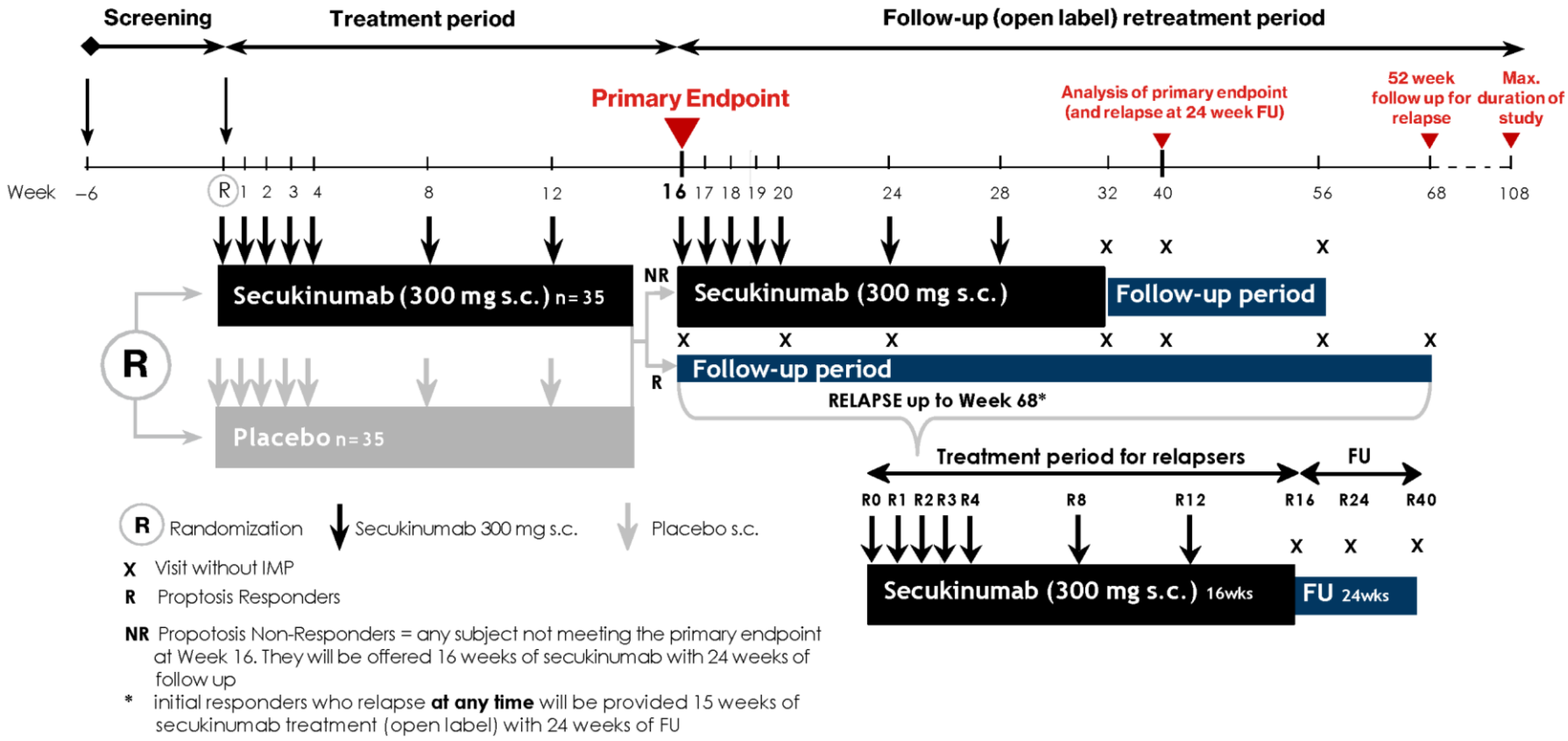
Proptosis non-responder: Patients not achieving response in reduction of proptosis at Week 16 with "response" defined as follows: reduction of ≥ 2 mm from Baseline in the study eye without deterioration (≥ 2 mm increase) of proptosis in the fellow eye.

Proptosis relapser: Patient 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) 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 (please refer to Sections 6.2.3 and 9.1.1).

The maximum duration of the study is 108 weeks: 16 weeks (initial treatment phase) + 52 weeks (follow-up) + 16 weeks (second treatment cycle) + 24 weeks (second follow-up period).

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This study consists of a 16-week double-blind treatment period during which the efficacy and safety of secukinumab 300 mg s.c. for the treatment of patients with moderate to severe TED will be evaluated in a placebo-controlled manner, and a 52-week follow-up period. In addition, it offers a course of open-label secukinumab for participants who fail to respond to treatment at Week 16 (second course for those who received secukinumab initially and first course for those who received placebo initially), and a course of secukinumab for patients who respond at Week 16 but subsequently relapse. Following the course of open-label secukinumab there is a subsequent 24-week follow-up period.

The **randomized design** (including stratification for smoking, a key modifier of TED disease severity and response to immunosuppressive treatment of TED [Eckstein et al 2003]) ensures a comparable and balanced patient profile across treatment arms. The **placebo-controlled, double-blind design** allows the assessment of the efficacy and safety of secukinumab 300 mg in comparison to placebo in an adequate setting.

[redacted] In case of relapse during the follow-up period, patients will be offered the option for re-treatment with open-label secukinumab 300 mg for 16 weeks (including 5 secukinumab injections during the first 5 weeks). This enables collection of data on the efficacy and safety of re-treatment in case of relapse.

Furthermore, the trial offers proptosis non-responders at Week 16 the option of a course of open-label secukinumab 300 mg s.c. (administered as above for relapsers). This will allow exploration of whether an extended treatment period could be beneficial for patients who have not achieved a sufficient response after 16 weeks of treatment. This continued treatment option will be offered to patients from both treatment arms, active as well as placebo. Since a very low rate of response under placebo treatment can be expected, this study design enables placebo treated patients to also receive a course of active treatment within this clinical trial (in case they have not achieved response at Week 16). In addition, if placebo-treated patients achieve a response and relapse (unlikely scenario), they will be offered a course of open label secukinumab.

4.2 Rationale for dose/regimen and duration of treatment

The secukinumab dosing regimen used in this study is in line with the approved dose in PsO, PsA with concomitant PsO or anti-TNF inadequate responders or in radiographic axSpA (AS depending on the clinical response). With a dose level of 300 mg, all available data in PsO and PsA strongly suggest that secukinumab operates at the plateau of the dose-exposure-response curve in these autoimmune diseases, which is one of the reasons to also select this dose level in TED.

Initial loading, i.e., weekly dosing during the first 4 weeks (5 doses) ensures a rapid onset of action which is favorable in the setting of an acute disease such as active TED. Due to its approval in other indications (PsO, PsA, AS and nr-axSpA), an extensive safety database exists for secukinumab 300 mg given every 4 weeks; this 300 mg dosing regimen for secukinumab is associated with a reassuring safety profile as confirmed in multiple clinical trials (up to 5 years) and in the post-marketing setting. A 16-week duration of treatment falls within the range of other immunomodulatory treatment durations in TED (12-24 weeks) including corticosteroids and teprotumumab. European Group on Graves' Orbitopathy (EUGOGO) guidelines include a 12-week duration for corticosteroids (Bartalena et al 2012) and teprotumumab was approved based on a 24-week treatment duration. Notably, there was no further differentiation between teprotumumab and placebo regarding proptosis response between Week 18 and Week 24 (Douglas et al 2020).

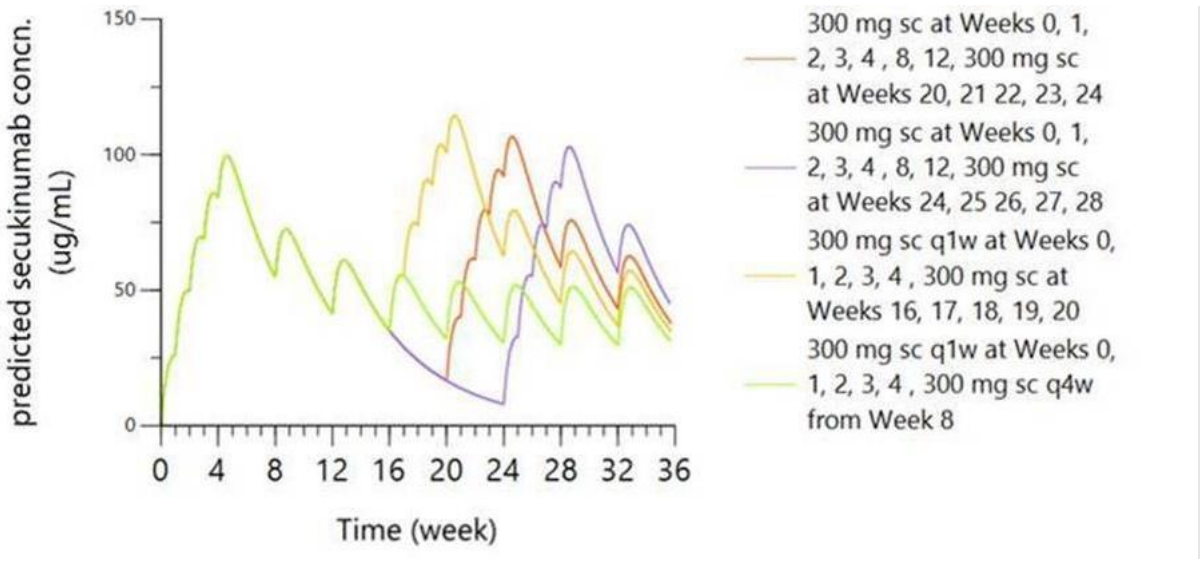
Regarding pharmacokinetic (PK) considerations, IL-17A concentrations in lacrimal fluid (tears) of active TED patients have been reported from 30 pg/mL (Chen 2019) to 386 pg/mL (Ujhelyi et al 2012). The IL-17A concentration in the lesional skin of PsO patients is approximately 10 pg/mL (Bruin et al 2017). The secukinumab trough serum levels using the every 4-week dosing regimen were 38 µg/mL at steady state; 30% of serum levels reach the skin (13 µg/mL). There is no evidence to suggest that secukinumab concentrations in the orbital tissue would differ from that significantly; good penetration of secukinumab into the inflamed and well-vascularized orbital space is anticipated. There will potentially be higher local IL-17A concentrations in TED than in PsO. Even when higher local IL-17A concentrations can be expected in TED than in PsO, secukinumab will still be in highly sufficient molar excess to fully neutralize IL-17A bioactivity using the proposed dosing regimen.

Patients who did not respond to the initial treatment course (secukinumab and placebo treated) at Week 16 will be offered a 16-week course of secukinumab (open-label) at that time with maintenance of the blind to the initial randomized treatment. Patients who are initial responders (secukinumab and placebo treated) at Week 16, and then relapse during follow-up will also be offered a 16-week course of secukinumab (open-label) at that time, while also maintaining the blind to the initial randomized treatment.

The course of open-label secukinumab will be a second course of active treatment for patients initially randomized to secukinumab. It will include a loading similar to the initial treatment course (i.e., weekly dosing during the first 4 weeks, 5 doses). PK modeling was performed to simulate the maximum concentration (Cmax) for patients who have received secukinumab 300 mg during the double-blind treatment phase, considering different starting time points with Week 16 as the earliest possible time point (for proptosis non-responders) (Figure 4-1). This modeling predicts a Cmax of about 120 µg/mL, when loading is initiated at Week 16, and a somewhat lower Cmax if the loading is initiated at a later time point (e.g., Week 20 or Week 24). In case loading starts at Week 16, the predicted Cmax at approximately Week 21 is approximately 20% higher than after loading during initial treatment. No significant impact on patient safety is anticipated as short-term loading doses of higher exposure have been performed with no significant impact on safety (see Investigator's Brochure (IB)).

Patients initially randomized to placebo who receive open-label secukinumab during follow-up will follow the predicted time-concentration profile shown in Figure 4-1 without retreatment.

Figure 4-1 PK modeling of second treatment course including initial loading



4.3 Rationale for choice of control drug (placebo)

Placebo has been selected for the control arm, as it enables the best measure of efficacy of secukinumab in the treatment of moderate to severe TED. Furthermore, placebo will be given for a limited duration of 16 weeks.

Except for teprotumumab (approved by FDA in Jan 2020), which is only available in the United States, there is no approved therapy for patients with active, moderate to severe TED as described in Section 1. Systemic corticosteroids are used in some patients, but they are characterized by sub-optimal efficacy with very limited impact on proptosis, a high relapse rate, marginal impact on long-term outcomes, as well as toxicity concerns.

Other immunomodulatory compounds tested in TED, e.g., teprotumumab, rituximab or tocilizumab, were also tested in comparison to placebo for up to 24 weeks (Stan et al 2015, Perez-Moreiras et al 2018, Douglas et al 2020).

Risks will be minimized by very frequent, careful ophthalmologic monitoring of signs of disease progression. In case of worsening of TED the patient should be discontinued from study drug at the discretion of the investigator (also refer to Section 9.1.1). Furthermore, the risk is minimized by the in- and exclusion criteria of the trial, which ensure that high-risk patients with high disease activity, need for surgery or signs of optic neuropathy are excluded from this study.

4.4 Purpose and timing of primary analysis

The primary analysis will be performed after all patients have completed Week 40 assessments and it will include the primary endpoint (Week 16) and relapse rate data up to 24 weeks following the end of treatment. This will support potential regulatory filing. A final analysis is planned at the EOS once all patients have completed their EOS visit. There may be other analyses between Week 40 and Week 108 to support other regulatory filings.

4.5 Risks and benefits

Secukinumab has demonstrated a positive benefit-risk ratio in the treatment of several chronic inflammatory conditions for which IL17A plays a central role, including plaque-PsO, PsA, AS and nr-axSpA. As IL-17A has been recognized as an important mediator in the immuno-pathogenesis of TED, secukinumab will potentially have beneficial effects for patients with TED by inhibiting IL-17A-driven inflammation which may reduce disease activity, tissue expansion, and fibrosis. As placebo patients who are non-responders at Week 16 have the option to receive secukinumab, they will also have this potential benefit.

The safety data from the completed and ongoing studies across various indications including AE and SAE data, laboratory parameters and immunogenicity data demonstrate a consistent and favorable safety profile. No dose dependency with secukinumab (300 mg vs. 150 mg) has been observed with respect to overall rates of AEs/SAEs in the clinical development program. Details of the risks and benefits are outlined in the current version of the IB.

Furthermore, extensive post-approval real-world evidence has been generated in clinical practice, confirming the favorable safety profile observed in the development program.

Observed risks include infections, in particular, upper respiratory tract infections, neutropenia and hypersensitivity reactions that can be seen with administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easily manageable and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate, and transient and did not lead to treatment discontinuation.

Patients randomized to the placebo arm will not receive active treatment with secukinumab during the first 16 weeks of the trial. However, they will be monitored very closely in order to identify any progression or need for other treatment. If they have not achieved a proptosis response at Week 16, they have the opportunity to receive a course of active secukinumab treatment starting at Week 16.

In case of worsening of the disease and need for other treatment or therapeutic interventions, e.g., orbital decompression, investigators and patients can stop study treatment at any time and apply other treatments as needed.

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

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

Taking into account the individual risks, the expected risk profile of secukinumab from a mechanism of action perspective in patients with TED is anticipated to be similar to that of the approved indications. Novartis is not aware of any scientific evidence that would indicate potential differences in the safety profile of secukinumab between patients with TED and patients with PsO, PsA, AS or nr-axSpA. Patients with TED are usually on treatment with

anti-thyroid medication and therefore at a potentially higher risk for developing neutropenia, which will be carefully monitored by regular blood tests throughout the study.

The bothersome symptoms of active, moderate to severe TED, the significant impact on patient's quality of life, the potential long-term functional impairment and the very limited availability of effective and safe treatment options for these patients lead to a very high degree of unmet medical need in the treatment of this indication. The well-established, consistent and favorable safety profile of secukinumab and the potential of secukinumab to reduce disease activity, improve symptom severity and improve long-term functional outcome in patients with TED, suggest that participation in this trial offers a well justifiable benefit-risk profile.

5 Study population

The study population comprises male or female patients with active, moderate to severe TED with a CAS of ≥ 4 in the more severely affected (study) eye. The "study eye" will be defined as the more severely affected eye at the Baseline Visit. Both "study eye" and "fellow eye" will be assessed for efficacy. Approximately 70 patients are planned to be randomized. No replacement patients are planned.

5.1 Inclusion criteria

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

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed.
2. Male or non-pregnant, non-lactating female patients ≥ 18 years of age.
3. Clinical diagnosis of active, moderate to severe TED (**not** sight-threatening) in the study eye at Baseline associated with two or more of the following:
   - Lid retraction ≥ 2 mm.
   - Moderate or severe soft tissue involvement.
   - Exophthalmos ≥ 3 mm above normal
   - Inconstant or constant diplopia.
4. Onset of TED symptoms fewer than 12 months prior to Baseline.
5. Clinical activity score (CAS) ≥ 4 (on a 7-point scale, with a score of ≥ 3 indicating active TED) in the more severely affected (study) eye at Screening and Baseline. (Proptosis is the primary qualifier for selection of the study eye. In case both eyes show a similar degree of proptosis, other inflammatory signs and symptoms (CAS) should be taken into account by the investigator for the selection of the study eye).
6. Peripheral euthyroidism or mild hypo-/hyperthyroidism defined as fT3 and fT4 < 30% above/below normal limits at Screening. Every effort should be made to correct the mild hypo-/hyperthyroidism promptly and to strictly maintain the euthyroid state until the end of this study.
   Note: Central lab retests will be allowed during the Screening Period (day -42 to -1) if fT3 and fT4 values are outside the above-mentioned cut-off criteria.

7. Orbital MRI assessment available confirming the diagnosis of TED for patients initially presenting with hypo- or euthyroidism (without treatment for hyperthyroidism) before or at the time of TED diagnosis (to rule-out other potential causes of the orbital signs and symptoms).

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study:

1. Improvement in CAS of ≥ 2 points and/or improvement in proptosis of ≥ 2 mm in the study eye between Screening and Baseline.
2. Signs of sight-threatening TED defined by optic neuropathy or severe corneal injury.
3. Patients, in the opinion of the investigator, requiring immediate or urgent medical treatment with glucocorticoids for TED.
4. Patients requiring immediate surgical ophthalmological intervention or planning corrective surgery/irradiation during the course of the study.
5. Decreased best corrected visual acuity (BCVA) as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect within the last 6 months.
6. Any other ophthalmic and/or orbital disease or other condition that might interfere with the assessment of TED.
7. Previous orbital radiotherapy.
8. Previous ophthalmological/orbital surgery for TED (e.g., orbital decompression).
9. Previous use of biological agents for the treatment of TED.
10. Previous use of systemic, non-biological, immunomodulatory agents for the treatment of TED (e.g., mycophenolate or cyclosporine).
11. Previous exposure to secukinumab or other biologic drugs directly targeting IL-17A or the IL-17 receptor (e.g., ixekizumab, brodalumab).
12. Previous treatment with rituximab, tocilizumab or teprotumumab.
13. Previous use of systemic corticosteroids for the treatment of TED, except for oral corticosteroids with a cumulative dose equivalent to < 1 g oral prednisone/prednisolone if the corticosteroid was discontinued at least 4 weeks prior to Baseline.
14. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
15. Use of other investigational drugs within 5 half-lives of enrollment or within 30 days, whichever is longer.
16. Previous or ongoing use of prohibited treatments (see Section 6.2.2). Respective washout periods detailed in this section must be adhered to.
17. History of hypersensitivity to any of the study drug constituents.
18. Pregnant or nursing (lactating) women.
19. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study or longer if required by locally-approved prescribing information (e.g., 20 weeks in the European Union). Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For countries where applicable, the use of spermicidal foam/gel/film/cream/vaginal suppository will be allowed.
- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%); for example, hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

20. Past medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to Screening except for hepatitis C successfully treated and cured.
21. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis.
22. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-PLUS test (QFT) at Screening. Patients with a positive or indeterminate QFT test may participate in the study if full tuberculosis work up (according to local practice/guidelines) was completed within 12 weeks prior to randomization and establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local guidelines prior to randomization.
23. Significant medical problems, including but not limited to:
    - Congestive heart failure (New York Heart Association status of class III or IV).
    - Severely reduced kidney function (estimated glomerular filtration rate (eGFR) $\leq$ 29 mL/min/1.73 m^2).
    - Uncontrolled diabetes (Type I or Type II) defined as HbAlc $\geq$ 10% at Screening.

24. Total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1500/µl or hemoglobin < 8.5 g/dl at Screening.
25. History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as serum glutamic oxaloacetic transaminase (SGOT) (aspartate aminotransferase (AST)), serum glutamic pyruvic transaminase (SGPT) (alanine aminotransferase (ALT)), alkaline phosphatase and serum bilirubin. The investigator should be guided by the following criteria:
    - SGOT (AST) and SGPT (ALT) may not exceed 3 × the upper limit of normal (ULN). A single parameter elevated up to and including 3 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to randomization, to rule-out laboratory error.
    - Alkaline phosphatase may not exceed 2 × ULN. An elevation up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to randomization, to rule-out laboratory error.
    - Total bilirubin may not exceed 2 × ULN. If the total bilirubin concentration is increased above 2 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
26. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma *in situ* of the cervix; or non-invasive malignant colon polyps that have been removed).
27. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal), which in the opinion of the Investigator significantly immunocompromise the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.
28. Diagnosis of inflammatory bowel disease (past or present).
29. Current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the patient unsuitable for the trial or puts the patient at increased risk.
30. Any medical or psychiatric condition, which in the investigator's opinion would preclude the patient from adhering to the protocol or completing the study per protocol.
31. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.
32. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
33. Ongoing participation (including safety follow-up period) in other interventional studies.

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

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Study treatment	Pharmaceutical dose form	Route and frequency of administration	Supply type	Sponsor (global or local)
Baseline to Week 16 (Double-blind)				
Secukinumab 300 mg	2 × 150 mg PFS	s.c. at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12.	Double-blind supply; PFS	Sponsor (local)
Placebo	2 x 0 mg PFS	s.c. at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12.	Double-blind supply; PFS	Sponsor (local)
Week 16 to end of study (EOS) (Open-label)				
Secukinumab 300 mg	2 x 150 mg PFS	Non-responders at Week 16: s.c. at Week 16, Week 17, Week 18, Week 19, Week 20, Week 24 and Week 28. Responders at Week 16 who relapse thereafter: s.c. at time of relapse, then 1, 2, 3, 4, 8 and 12 weeks from time of relapse.	Open-label supply; PFS	Sponsor (local)

PFS = prefilled syringe, q4w = every 4 weeks, s.c. = subcutaneous

6.1.2 Additional study treatments

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

6.1.3 Treatment arms

The maximum duration of the study is 108 weeks: 16 weeks (initial treatment phase) + 52 weeks (follow-up) + 16 weeks (second treatment phase) + 24 weeks (second follow-up period) as indicated in Figure 3-1.

Double-blind treatment period (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, Week 2, Week 3, Week 4, Week 8, Week 12
- Arm 2: placebo s.c. at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Patients will be stratified according to smoking status (up to 20% 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 non-responders at Week 16 (as defined in Section 3) 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 to [redacted] safety.
- Proptosis relapsers (as defined in Section 3) from Week 16 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 since time of relapse. Thereafter, patients will be followed up for a further 24 weeks (i.e., 40 weeks after start of retreatment) to assess [redacted] safety.

Definitions of responder, non-responder and relapser

Please refer to Section 3 (Study design).

6.1.4 Treatment duration

Patients will be treated with double-blind secukinumab or placebo for the first 16 weeks of the study (last administration at Week 12). Patients who are proptosis non-responders at Week 16 or those who are proptosis responders at Week 16 but who relapse thereafter (relapsers) will be given the option of retreatment with open-label secukinumab for a further 16 weeks.

6.2 Other treatments

6.2.1 Concomitant therapy

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If the patient is already

enrolled, Novartis should be contacted to determine if the patient should continue participation in the study.

6.2.2 Prohibited medication and procedures

Use of any treatments (medication and procedures) displayed in Table 6-2 that could confound the efficacy and safety of the study treatment are NOT allowed during the study, starting at Baseline (Day 1) and after, for any indication; wash-out periods for these treatments are indicated in the table. If the use of these treatments is required, then the patient should **NOT** be randomized into the study.

The Investigator should instruct the patient to notify the study site about any new treatments he/she takes after the start of study treatment. All prohibited medications and significant non-drug therapies administered after the patient starts study treatment must be listed on the CRF.

If a prohibited treatment listed in Table 6-2 is used during the study, the patient should discontinue use of the prohibited treatment if he/she wishes to continue study treatment.

If during study treatment a patient uses a treatment for TED or a procedure is performed for TED, other than secukinumab, in case of worsening of the disease, the investigator should discontinue the patient from study treatment and the patient will be classified as a non-responder.

At the discretion of the Investigator, if the patient's use during the study of a prohibited treatment listed in Table 6-2 presents undue safety risk for the patient, the patient should be discontinued from study treatment as per Section 9.1.1.

In case of use of prohibited medication that cannot be stopped during any follow-up period, the patient's study discontinuation should be considered after discussion with the sponsor.

Live vaccinations should not be given until 12 weeks after last study treatment administration. If the patient receives a live virus vaccination during a course of study treatment, the patient must discontinue study treatment.

Table 6-2 Prohibited medication / treatments/ procedures

Prohibited treatments	Wash-out period (before first study drug administration)
Orbital radiotherapy	No prior use allowed
Surgery for the treatment of TED	No prior use allowed
Biological agents targeting IL-17 or the IL-17 receptor (e.g., secukinumab ixekizumab, brodalumab)	No prior use allowed
Biological agents targeting IL-23/p19 (e.g., guselkumab, risankizumab, tildrakizumab)	No prior use allowed
Ustekinumab	No prior use allowed
Rituximab, tocilizumab, teprotumumab	No prior use allowed

Prohibited treatments	Wash-out period (before first study drug administration)
Biological and other systemic immunomodulating agents targeting TNF-alpha (e.g., adalimumab, infliximab, etanercept)	12 weeks
Systemic, biological agents for the treatment of TED	No prior use allowed
Any cell-depleting therapies including but not limited to anti-CD20 or other investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	No prior use allowed
Biological immunomodulating agents other than above	24 weeks
Live virus vaccinations (including nasal-spray flu vaccine)	6 weeks
Non-biological, systemic immunomodulating agents (e.g., methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, hydroxychloroquine)	12 weeks
Selenium and biotin	3 weeks prior to Screening visit
Systemic corticosteroids for treatment of TED	No prior use allowed except for the following: oral corticosteroids with a cumulative dose equivalent < 1 g oral prednisone/prednisolone if the corticosteroid was discontinued at least 4 weeks prior to Baseline
Systemic corticosteroids for treatment of other conditions than TED	6 weeks prior to Screening visit (topical steroids for dermatological conditions and inhaled corticosteroids are allowed)
Corticosteroid eye drops	4 weeks
Treatment for latent tuberculosis	Must be initiated prior to randomization (see exclusion criterion No. 21 [Section 5.1])
Any other investigational treatment	30 days or 5 half-lives (whichever is longer)

6.2.3 Rescue medication

No rescue medication will be provided within this trial.

Patients may receive other treatment or procedures for TED at the discretion of the investigator in case of worsening of the disease. Investigators should confirm that the new treatment is for TED due to worsening of the disease, and they must immediately discontinue patients from study treatment in this case. For follow-up after study treatment discontinuation, please refer to Section 3 (Study design).

6.3 Patient numbering

6.3.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is enrolled for Screening and is retained for the patient throughout his/her participation in the trial. A new Patient No. will be assigned at every subsequent enrollment if the patient is re-screened. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient's participation is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the patient is assigned to the next sequential Patient No. available.

6.3.2 Treatment assignment, randomization

At Baseline (Randomization Visit/Day 1) all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified according to smoking status since smoking has a well-known impact on treatment efficacy in TED.

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

6.4 Treatment blinding

Patients, investigator staff and persons performing the assessments will remain blind to the identity of the treatment assigned at Baseline from the time of randomization until final database lock, using the following methods:

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

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

[redacted]

Unblinding of the original assigned treatment will occur in the case of patient emergencies and at the conclusion of the study.

The clinical trial team will be blinded to the identity of the treatment assigned at Baseline from the time of randomization until certain members conducting the analysis will be unblinded after the Week 40 database lock (DBL). However, designated clinical trial team members including all members who are in contact with the clinical sites will remain blinded to the original treatment assignment until the final DBL and analysis. Details will be specified in the Blinding Charter. Investigators, site personnel and participants will remain blinded until the end of the study.

6.5 Dose escalation and dose modification

Study treatment dose adjustments are not permitted. Study treatment interruption should be avoided with the following exception:

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

6.5.1 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record CRF. Compliance to the planned administration schedule is expected to be high since the administration of study treatment will be done in the presence of the Investigator or study personnel. Compliance will also be assessed by means of site and patient-specific drug accountability by Novartis study personnel during the site monitoring visits using medication pack numbers and Drug Label Form information.

[redacted]

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will

automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- Protocol number
- Name *(if available)*
- Patient number

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1).

A unique medication number is printed on the study medication label.

For the double-blind period, investigator staff will select the study treatment to dispense to the patient as per the treatment assigned to the patient by contacting the IRT and obtaining the medication numbers.

For the open-label period, investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication numbers.

The study medication has a 2-part label (base label plus tear-off label). Immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label (tear-off label) from the packaging and affix it to the source document.

In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visits to the study site, study drug may be shipped or provided directly to patients for home administration if needed. When site visits are not possible, regular phone calls/virtual contacts or visits of site staff to the patient´s home, depending on local regulations and capabilities (according to visit schedule or more frequently if needed, and weekly when patient is receiving weekly dosing) will occur between the site and the patient for instructional purposes, for safety monitoring and review of the patient´s ophthalmological and general health status until the patient can again visit the site. This is necessary to ensure that there are no safety concerns to the patient requiring treatment interruption or discontinuation. If in the opinion of the investigator the patient requires an in-person assessment, arrangements will be made for the patient to be evaluated at the site, or if this is not feasible, by a local ophthalmologist or in an emergency healthcare setting. In consultation with the investigator, selected ophthalmological assessments (e.g., visual acuity, intraocular pressure, color vision) can also be done by a local optometrist to enable continuous monitoring of the patient´s ophthalmological status if on-site visits or visits to a local ophthalmologist are not feasible. Assessment results must be reported to and discussed with the investigator as soon as possible in this case.

Delivery of the Investigational Medicinal Product (IMP) directly to a patient's home is at the discretion of the investigator and would be permitted only during the duration of the healthcare disruption. The patients will be supplied with material to document the home administration and to allow accountability of the study medication. At the site level, the agreement with/approval of the investigator should be obtained to implement home delivery.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secure location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the IB.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment (in case home administration became necessary, i.e., in case of a major healthcare disruption).

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

6.7.2 Instruction for prescribing and taking study treatment

Secukinumab solution for s.c. injection or placebo solution will be provided in PFS as described in Section 6.1.1.

Each patient will require 1 box (containing 2 × PFS) for each treatment visit throughout the study, i.e.,

- Two secukinumab 150 mg PFS **OR** two secukinumab placebo 150 mg PFS during the double-blind period.
- Two secukinumab 150 mg PFS during the open-label period.

Patients will be assigned to treatment as described in Section 6.1.3.

All study treatment kits assigned by the IRT will be recorded in the IRT system.

Administration

Administration of all doses of study treatment at the study site should be performed after the study assessments for the specific visit, including blood sampling and QoL questionnaire, have been completed.

The first study treatment administration will occur at the Baseline Visit, after all study scheduled assessments for this visit have been performed (and inclusion/exclusion criteria confirmed) and only after the scheduled blood samples have been drawn.

Prior to administration, the boxes containing the PFS with study treatment solution should be allowed to come to room temperature unopened. Used PFS should be disposed immediately after use in a sharps container **OR** according to local regulations.

The study treatment solution must be injected s.c. in intact areas of the skin. If possible throughout the trial, the study treatment should be administered to one of the following body regions, rotating the injection site from visit to visit: right thigh, left thigh, right stomach, left stomach, upper outer arm (when assisted by site personnel).

All dates and times of injections during the study must be recorded on the appropriate CRF.

In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visits to the study site, home administration of the study drug is permitted as described above (Section 6.7). Home administration can be performed by the patient, a trained caregiver, or study personnel. Study participants or caregivers will be trained adequately on how to perform administration of the study treatment, if not already trained. If the patient or caregiver is not trained for drug administration and cannot visit the site to undergo training, the site can consider providing suitable virtual training and oversight. A joint decision together with the patient or caregiver should be made as to whether this constitutes sufficient training and oversight.

7 Informed consent procedures

Eligible patients may only be included in the study after providing IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1 and Table 8-2) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 and Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the study discontinuation visit will be performed. This study discontinuation visit should include all assessments of the Week 16 (if discontinued during double-blind treatment), NR32 (for non-responders), R16 (for relapsers) or Week 68 (for patients who discontinued during the follow-up period) visit. See also Section 9.1.1.

At this study discontinuation visit, dispensed investigational product should be reconciled, and the AEs and concomitant medications recorded on the CRF.

In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visitsto the study site, regular phone calls/virtual contacts or visits of site staff to the patient´s home, depending on local regulations and capabilities, will occur (according to the visit schedule or weekly if during the weekly dosing period) for instructional purposes, for safety monitoring and review of the patient´s ophthalmological and general health status until the patient can again visit the site. This is necessary to ensure that there are no safety concerns to the patient requiring treatment interruption or discontinuation. If in the opinion of the investigator the patient requires an in-person assessment, arrangements will be made for the patient to be evaluated at the site, or if this is not feasible, by a local ophthalmologist or in an emergency healthcare setting. In consultation with the investigator, selected ophthalmological assessments (e.g., visual acuity, intraocular pressure, color vision) can also be done by a local optometrist to enable continuous monitoring of the patient´s ophthalmological status if on-site visits or visits to a local ophthalmologist are not feasible. Assessment results have to be reported to and discussed with the investigator as soon as possible in this case.

Events qualifying for being reported in the case report form (e.g., AEs, etc.) should be entered as appropriate.

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 not feasible, should be attempted**.** Patients should be reminded to be fasting prior to visits with laboratory assessments.

Table 8-1 Assessment schedule (double-blind treatment period and follow-up for responders at Week 16)

Period	Screening Period	Treatment Period								Post-Treatment Follow-Up[2]						
Visit Name	**Screening (Week -6 to Baseline)**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 56**	**Week 68**	**USV[3]**
Days	**-42 to -1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**393**	**477**	
Informed consent	X															
Demography	X															
Inclusion/exclusion criteria	X	X														
Washout evaluation/instruction	S	S														
Relevant medical history	X	(X)														
Smoking history/status	X	X														
TED medical history	X	(X)														
Physical examination	S	S					S		S		S		S		S	(S)
Ophthalmologic assessment[1]	X	X		X		X	X	X	X	X	X	X	X	X	X	(X)
Height	X															
Weight	X	X							X							
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
12-Lead ECG	S															
Hematology and blood chemistry (fasting)	X	X				X	X	X	X	X	X					(X)
Urinalysis (local analysis)[4]	S	S							S		S					(S)

Period	Screening Period	Treatment Period								Post-Treatment Follow-Up[2]						
Visit Name	**Screening (Week -6 to Baseline)**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 56**	**Week 68**	**USV[3]**
Days	**-42 to -1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**393**	**477**	
Thyroid laboratory test (fasting)	X	X				X	X	X	X	X	X	X	X	X	X	(X)
QuantiFERON TB-PLUS test	X															
Serum pregnancy test	X															
Urine pregnancy test (local analysis)		S				S	S	S	S	S	S	S	S		S	(S)
Adverse events (including injections site reactions)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																
Responder/NR-assessment									X							
Prior/concomitant medications/non-drug therapy	Update as necessary															
[redacted]																
CAS	X	X		X		X	X	X	X	X	X	X	X	X	X	(X)
Proptosis measurement	X	X		X		X	X	X	X	X	X	X	X	X	X	(X)
Diplopia grading[6]	X	X		X		X	X	X	X	X	X	X	X	X	X	(X)
GO-QoL		X		X		X	X	X	X	X	X	X	X	X	X	
Contact Interactive Response Technology (IRT)	X	X	X	X	X	X	X	X	X							

Period	Screening Period	Treatment Period								Post-Treatment Follow-Up[2]						
Visit Name	**Screening (Week -6 to Baseline)**	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 56**	**Week 68**	**USV[3]**
Days	**-42 to -1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**393**	**477**	
Randomization		X														
Study drug administration		X	X	X	X	X	X	X								
[redacted]																

X = assessment to be recorded in the clinical database or received electronically from a vendor.
S = source data.
1 = Ophthalmic examination (please refer to Section 8.3.4).
2 = For responders only. Non-responders and patients who relapse during follow-up, will receive a second treatment course (see next table).
3 = Unscheduled visits (USV) might be required e.g., if patients observe symptoms between scheduled visits or for safety reasons. The safety assessments listed herein may be performed at the discretion of the investigator as needed to resolve the reason for the unscheduled visit. (S)AE assessment and concomitant medications are mandatory for all unscheduled visits.
4 = Kits for urinalysis will be provided by central lab and test is performed locally.
[redacted]
6 = Gorman score/subjective diplopia score (Bahn et al 1987).
[redacted]
( ) = Parentheses denote assessments that are on a per need basis at investigator´s discretion.

Table 8-2 Assessment schedule (re-treatment for non-responders and relapsers)

Period	**Second Course Treatment Period**								**Post-Treatment Follow-Up**		
Visit name non-responder	**Week NR16[4]**	**Week NR17**	**Week NR18**	**Week NR19**	**Week NR20**	**Week NR24**	**Week NR28**	**Week NR32**	**Week NR40**	**Week NR56**	**USV[2]**
Days	**113**	**120**	**127**	**134**	**141**	**169**	**197**	**225**	**281**	**393**	
Visit name relapsers§	**Week R0[5]**	**Week R1**	**Week R2**	**Week R3**	**Week R4**	**Week R8**	**Week R12**	**Week R16**	**Week R24**	**Week R40**	**USV[2]**
Days since relapse	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**169**	**281**	
Physical examination	S					S		S	S		(S)
Ophthalmologic assessment[1]	X		X		X	X	X	X	X	X	(X)
Weight	X							X			
Vital signs	X	X	X	X	X	X	X	X	X	X	(X)
Hematology and blood chemistry (fasting)	X				X	X	X	X	X		(X)
Urinalysis (local analysis)[3]	S							S	S		(S)
Thyroid laboratory assessments (fasting)	X				X	X	X	X	X	X	(X)
Urine pregnancy test (local analysis)	S				S	S	S	S	S	S	(S)
Adverse events (including injections site reactions)	X	X	X	X	X	X	X	X	X	X	X
[redacted]											
Responder/NR-assessment								X			
Prior/concomitant medications/non-drug therapy	Update as necessary										
[redacted]											
CAS	X		X		X	X	X	X	X	X	(X)

Period	**Second Course Treatment Period**								**Post-Treatment Follow-Up**		
Visit name non-responder	**Week NR16[4]**	**Week NR17**	**Week NR18**	**Week NR19**	**Week NR20**	**Week NR24**	**Week NR28**	**Week NR32**	**Week NR40**	**Week NR56**	**USV[2]**
Days	**113**	**120**	**127**	**134**	**141**	**169**	**197**	**225**	**281**	**393**	
Visit name relapsers§	**Week R0[5]**	**Week R1**	**Week R2**	**Week R3**	**Week R4**	**Week R8**	**Week R12**	**Week R16**	**Week R24**	**Week R40**	**USV[2]**
Days since relapse	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**169**	**281**	
Proptosis measurement	X		X		X	X	X	X	X	X	(X)
Diplopia grading[6]	X		X		X	X	X	X	X	X	(X)
GO-QoL	X		X		X	X	X	X	X	X	
Contact Interactive Response Technology (IRT)	X	X	X	X	X	X	X	X			
Study drug administration*	X	X	X	X	X	X	X				
[redacted]											

* = Patients who are non-responders at Week 16 or patients who relapse during follow-up receive 16 weeks of treatment with open-label secukinumab.
§ = Relapse can occur at any time during the 52-week follow-up period (i.e., from Week 16 onward to Week 68).
X = assessment to be recorded in the clinical database or received electronically from a vendor. S = source data.
1 = Ophthalmic examination (please refer to Section 8.3.4).
2 = Unscheduled visits (USV) might be required e.g., if patients observe symptoms between scheduled visits or for safety reasons. The safety assessments listed herein may be performed at the discretion of the investigator as needed to resolve the reason for the unscheduled visit. (S)AE assessment and concomitant medications are mandatory for all unscheduled visits.
3 = Kits for urinalysis will be provided by central lab and test is performed locally.
4 = Only applicable for assessments that have not been performed at the W16 Visit in non-responders.
5 = Only applicable for assessments that have not been performed at the Visit at which relapse was diagnosed.
6 = Gorman score/subjective diplopia score (Bahn et al 1987).
( ) = Parentheses denote assessments that are on a per need basis at investigator´s discretion.

8.1 Screening

Patient's eligibility for the study will be assessed during the Screening period (Day -42 to -1) and at the Baseline Visit (see Table 8-1).

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

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

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

8.1.1 Information to be collected on screening failures

Patients who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a Screen Failure. All reasons for a Screen Failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are Screen Failures, unless the patient experienced a SAE during the Screening Phase (see Section 10.1.3 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the Screen Fail that the patient was not randomized.

Patients who are randomized and fail to start treatment will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF.

Patients randomized in error (= mis-randomized subjects) are defined as those subjects who 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.

8.2 Patient demographics/other baseline characteristics

Baseline assessments will occur during the Screening Visit or the Baseline Visit depending on the assessment as indicated in Table 8-1.

Patient demographics and Baseline characteristics to be collected for all patients include: year of birth, age, sex, race, ethnicity, height (cm), weight (kg). Patient race and ethnicity data are collected and analyzed to identify any variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

8.2.1 Smoking history

The current and/or previous use of tobacco products will be recorded, as well as the estimated number of pack-years based on the approximate consumption per year. Non-smokers will be

advised not to start smoking during the study. 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.

8.2.2 Tuberculosis screening

A central laboratory immunological test (QuantiFERON TB-Plus) must be performed at Screening to screen the patient population for latent tuberculosis infection. The results must be known prior to randomization to determine the patient's eligibility for the study.

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

- The patient has no evidence of active tuberculosis.
- If presence of latent tuberculosis is established then treatment must have been initiated and maintained according to local guidelines prior to randomization.

The QuantiFERON TB-Plus test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

8.2.3 Relevant medical history/ current medical history

Relevant medical history and current medical conditions, not including TED, prior to signing the ICF will be recorded in the Medical History eCRF page. Whenever possible, diagnoses and not symptoms will be recorded.

8.2.4 Prior and concomitant medications

Concomitant medications and prior medications taken over the 6 months preceding study enrollment for reasons other than thyroid disease and TED will be captured at the Screening Visit, and updated as necessary in the relevant eCRF.

8.2.5 TED and thyroid medical and treatment history

Disease history will be collected at Screening. The information to be collected and entered in the TED History eCRF page and Prior TED Therapies eCRF page will include the following:

- Date of onset of TED symptoms.
- Date of first diagnosis of TED.
- Underlying thyroid condition (Graves' disease, Hashimoto's thyroiditis, other).
- Previous treatments for TED (including but not limited to previous use of biologic therapies) and the reason for discontinuation of each therapy.

8.2.6 Serum pregnancy test

A serum pregnancy test will be performed for females of childbearing potential at Screening.

8.2.7 Other baseline characteristics

Other Baseline characteristics will be collected as described in Section 8.3, Section 8.4 and Section 8.5.

8.3 Efficacy

Efficacy assessments will be performed for both eyes at each assessment time point. The most severely affected eye will be defined as the "study eye" at the Baseline Visit. If there is a discrepancy between CAS and proptosis in determining the study eye, this will be adjudicated always to the eye with the most significant proptosis. In case both eyes show a similar degree of proptosis, other inflammatory signs and symptoms (CAS) should be taken into account by the investigator for the selection of the study eye. If both eyes are affected equally, the Investigator will choose the "study eye". Both eyes will be assessed for efficacy but the study eye will be used to assess the primary, secondary [redacted] outcome measures.

In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site study visits, selected efficacy assessments (if feasible for the individual assessments) can alternatively be done via phone calls/virtual contacts or visits of site staff to the patient´s home, depending on local regulations and capabilities. 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 not feasible, should be attempted.

8.3.1 Clinical activity score according to EUGOGO

TED activity will be assessed using the CAS at the frequency indicated in the study schedule (Table 8-1 and Table 8-2) based on the following signs and symptoms in accordance with the European Group on Graves' Orbitopathy (EUGOGO) guideline (Mourits et al 1997, Bartalena et al 2016):

- Symptoms
  - Spontaneous retrobulbar pain
  - Pain on attempted upward or downward gaze
- Signs
  - Redness of eyelids
  - Redness of conjunctiva
  - Swelling of caruncle or plica
  - Swelling of eyelids
  - Swelling of conjunctiva (chemosis)

For each item present, 1 point is given. The sum of these points is the CAS score (Mourits et al 1997), i.e., minimum score of 0 and maximum score of 7.

- Inactive TED = CAS < 3.
- Active TED = CAS ≥ 3.

8.3.2 Proptosis

Proptosis measurements will be performed (ideally by the same observer) at the frequency indicated in the study schedule (Table 8-1 and Table 8-2). The same Hertel instrument, and the same outer intercanthal distance, should be used for each measurement. Instructions for the measurement of proptosis are included in ophthalmological manual (proptosis [exophthalmometry] assessment).

8.3.3 Diplopia grading

Diplopia will be graded according to the Gorman score/subjective diplopia score (Bahn et al 1987). This assessment, which is also called "Bahn-Gorman Score" comprises 4 different grades:

- 0 = No diplopia
- 1 = Intermittent diplopia (i.e., diplopia in primary position of gaze when tired or when first awakening)
- 2 = Inconstant diplopia
- 3 = Constant diplopia

A change of one grade will be considered to be clinically relevant.

8.3.4 Ophthalmological assessments

Ophthalmological assessments will be performed as indicated in a separate ophthalmological manual. These examinations should include subjective symptoms (e.g., epiphora, photophobia), Worth test, ocular motility (measured in degrees, by means of the Light Reflex Method [Dolman et al 2012]), best corrected visual acuity (Snellen), visual field tests, pupil examination, swinging flashlight test, color vision assessment (Ishihara color plates), lid retraction, intraocular pressure (Goldman), fluorescein staining of the cornea, slit lamp examination, spectral domain-optical coherence tomography (SD-OCT) assessment of the macula and papilla and optic nerve assessment (only nonmydriatic). If significant abnormalities are noted compared to previous visits, including a loss of two lines or more of vision, development of pupil abnormalities including afference pupillary defect, rise in intraocular pressure, development of corneal infiltrates, or other abnormalities not here specified but of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.

8.3.5 Disease severity assessments

Disease severity will be assess according to EUGOGO guidelines (Bartalena et al 2016).

Severity	Parameters
Mild TED	Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have one or more of the following: minor lid retraction (< 2 mm), mild soft-tissue involvement, exophthalmos < 3 mm above normal, no or intermittent diplopia and corneal exposure responsive to lubricants.
Moderate to severe TED	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have 2 or more of the following: lid retraction ≥ 2 mm, moderate or severe soft-tissue involvement, or exophthalmos ≥ 3 mm above normal, inconstant or constant diplopia.
Sight-threatening TED	Patients with DON and/or corneal breakdown

To assess disease severity, the following parameters will be examined (refer to ophthalmological manual):

Parameter	Assessments
Lid retraction	Distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed and with distant fixation
Soft-tissue involvement	Eyelid swelling, redness of eyelids (erythema), conjunctival redness or conjunctival edema/swelling (chemosis)
Exophthalmos	Measured in mm using the same Hertel exophthalmometer and same outer intercanthal distance for an individual patient.
Diplopia	Subjective diplopia score
Corneal exposure	Normal/staining/erosion/ulceration
Optic nerve involvement	• Best corrected visual acuity • Color vision • Visual fields • Optic disc (OCT assessment) • Relative afferent pupillary defect (absent/present, assessed by swinging flashlight test)

8.3.6 Thyroid eye disease quality of life

Please refer to Section 8.5.1.

8.3.7 Appropriateness of efficacy assessments

The efficacy assessments selected are considered appropriate for this study in patients with moderate to severe TED.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. For details on AE collection and reporting, refer to AE section (Section 10).

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse measurements. After the patient has been sitting for 5

Assessment	Specification
	minutes, with back supported and both feet placed on the floor, SBP and DBP will be measured 3 times using an automated validated device with an appropriately sized cuff. The repeat sitting measurements will be made at 1 to 2 minute intervals and the mean of the 3 measurements will be used. The results of all measurements, including the mean measurement, should be recorded in the source data. If possible, assessments should be performed by the same study site staff member and at the same arm throughout the study. Normal blood pressure will be defined as SBP of 90 to < 120 mmHg, and diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure findings will be hypertension (SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg) or hypotension (SBP of < 90 mmHg and/or a DBP of < 60 mmHg). A blood pressure indicative of prehypertension (SBP of 120 to < 140 mmHg and/or DBP of 80 to < 90 mmHg) will not be regarded as notable (Whelton et al 2017). A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rate will be a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia). Whether action needs to be taken to address notable vital signs will be decided by the Investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visits to the study site, regular phone calls, virtual contacts or visits of site staff to the patient´s home, depending on local regulations and capabilities, will occur (according to the visit schedule or weekly if during the weekly induction phase) for safety monitoring and review of the patient´s ophthalmological and general health status until the patient can again visit the site. This is necessary to ensure that there are no safety concerns to the patient requiring treatment interruption or discontinuation. If in the opinion of the investigator the patient requires an in-person assessment, arrangements will be made for the patient to be evaluated at the site, or if this is not feasible, by a local ophthalmologist or in an emergency healthcare setting. In consultation with the investigator, selected ophthalmological assessments (e.g., visual acuity, intraocular pressure, color vision) can also be done by a local optometrist to enable continuous monitoring of the patient´s ophthalmological status if on-site visits or visits to a local ophthalmologist are not feasible. Assessment results have to be reported to and discussed with the investigator as soon as possible in this case.

Events qualifying for being reported in the case report form (e.g., AEs) should be entered as appropriate.

If patients cannot visit the site to have urine pregnancy tests done, urine pregnancy test kits may be shipped or provided directly to the patient (e.g., together with the study drug). After appropriate instruction, patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients do the pregnancy test first and only if the test result is negative proceed with the administration of the study drug.

Depending on local regulations and capabilities, study site staff may visit the patient at home to draw blood/urine samples if needed.

8.4.1 Laboratory evaluations

Clinically notable laboratory findings are defined in Appendix 1. Please refer to Table 8-1 and Table 8-2 for the timing of laboratory evaluations.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

Test category	Test name
Hematology	Hematocrit, Hemoglobin, Platelets, Red Blood Cells (RBCs), White Blood Cells (WBCs), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline Phosphatase, Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Gamma-glutamyl Transferase (GGT), Lactate Dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Glycated Hemoglobin (HbA1c) will be assessed from fasting blood samples.
Urinalysis	The central laboratory will provide dipsticks to the sites for local analysis of urine. Dipstick analysis will measure specific gravity, protein, glucose and blood. Microscopy and white blood cell count and red blood cell count sediments will be assessed in case of an abnormal dipstick test. Only samples with abnormal dipstick will be assessed by the central laboratory. Study sites should record the results in the source documentation.
[redacted]	
Pregnancy test	Please refer to Section 8.4.2.
Fertility test	A follicle stimulating hormone (FSH) test will be performed if required for fertility testing in the absence of other records of fertility (see Section 8.4.2)

8.4.2 Pregnancy and assessments of fertility

Pregnancy testing

Secukinumab must not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see Exclusion Criteria definitions, Section 5.2).

A serum β-human chorionic gonadotropin (hCG) test will be performed in all women of childbearing potential at Screening. All pre-menopausal women who are not surgically sterile at Screening will have local urine pregnancy tests performed as indicated in Table 8-1 and Table 8-2. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial. Additional pregnancy testing might be performed if requested per local requirements. Refer to Section 10.1.4 for details on reporting of pregnancy.

Assessments of fertility

Refer to Section 5.2 for criteria to determine women that are not of childbearing potential.

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

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

In the absence of the above medical documentation, FSH testing is required of any female patient who states that they are of non-childbearing potential regardless of reported reproductive/menopausal status at Screening/Baseline.

8.4.3 Other safety evaluations

A standard 12-lead electrocardiogram (ECG) will be performed as indicated in Table 8-1 and will be reviewed locally. Clinically relevant abnormalities should be recorded on the relevant medical history/current medical conditions/AE eCRF page for the Screening ECG.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population as well as for secukinumab clinical studies.

8.5 Additional assessments

8.5.1 Thyroid eye disease quality of life

Quality of life will be evaluated with the use of the GO-QoL questionnaire, comprising 2 subscales assessed separately or in combination (Terwee et al 1998). These 2 subscales are as follows:

1. The consequences of double vision (diplopia) and decreased visual acuity on visual functioning, and

2. The psychological consequences of a changed appearance.

Scores on each sub-scale as well as the score on the overall GO-QoL scale have a range of 0 to 100 points. A change of 8 points is considered to be clinically relevant.

Guidelines for administering GO-QoL questionnaire

The patient must be given the GO-QoL questionnaire at the scheduled visit before any clinical assessments are conducted. A patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

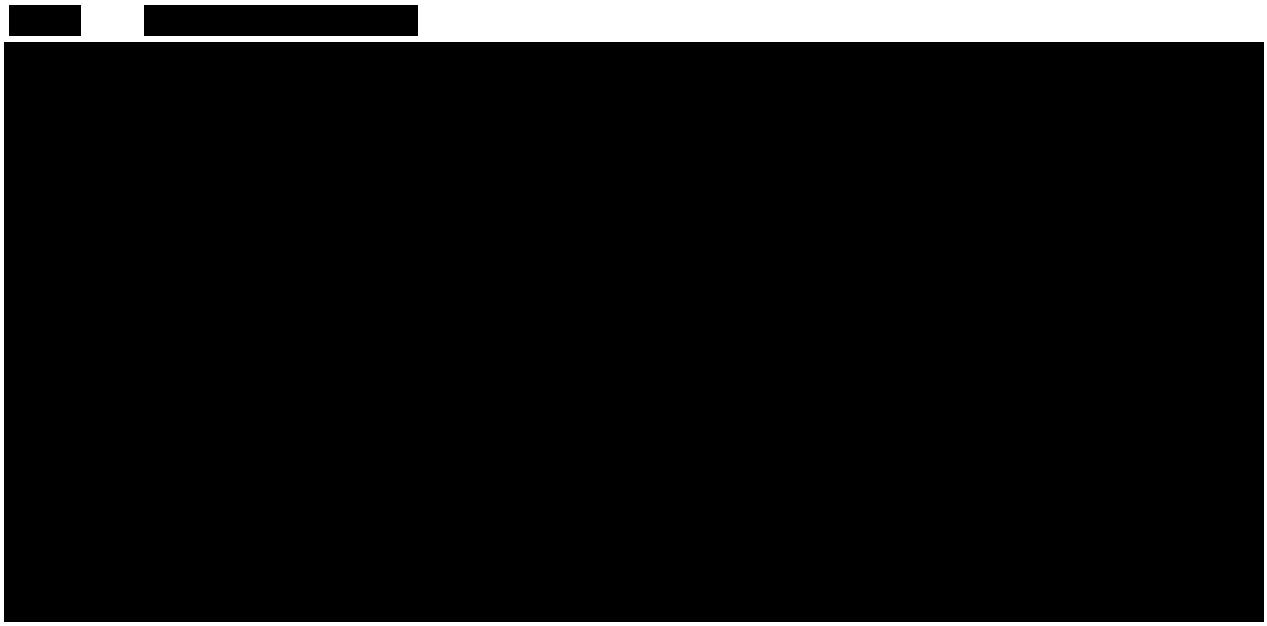
The GO-QoL questionnaire should be completed in the language most familiar to the patient.

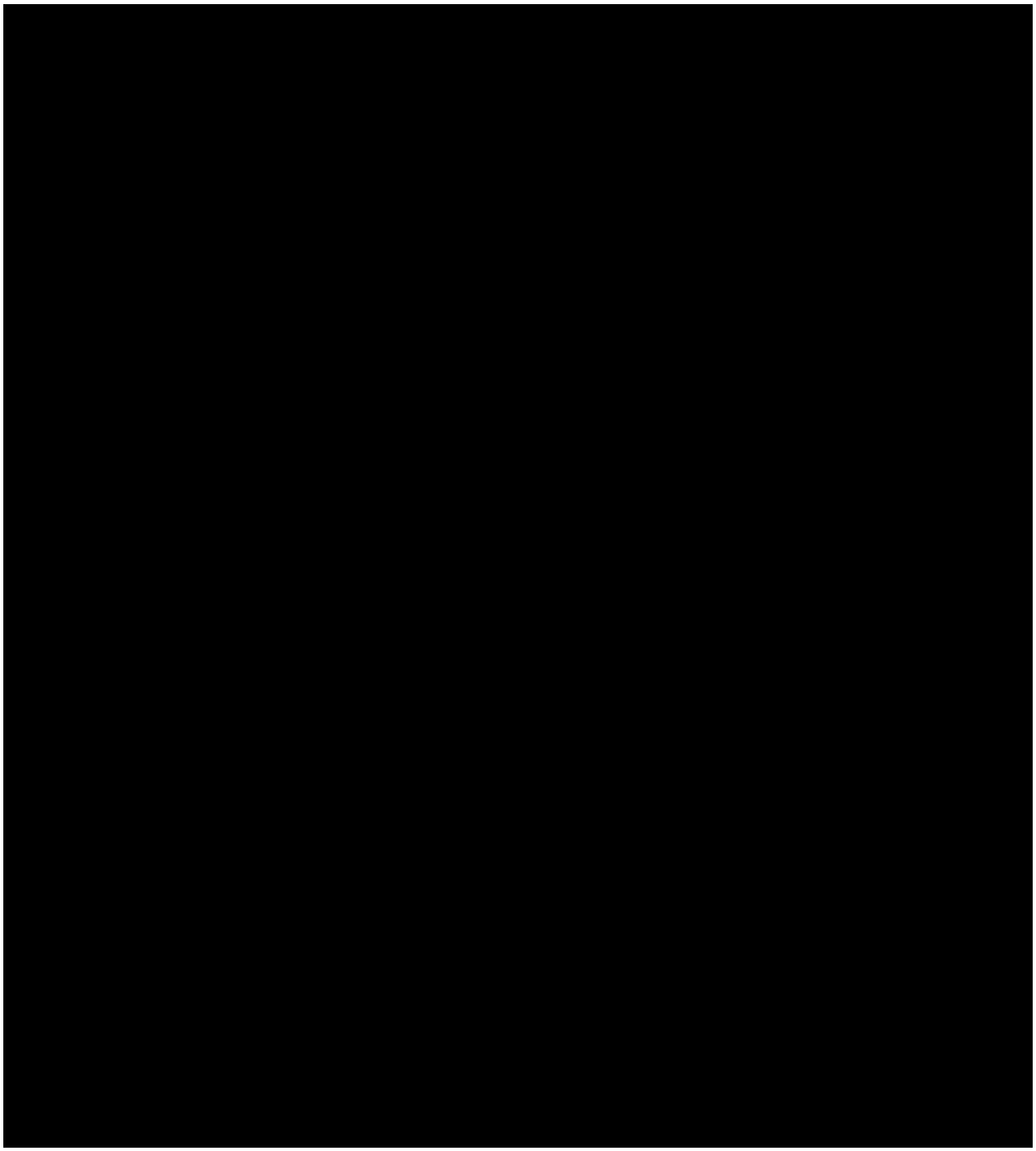
If self-administered, the patient should be given sufficient space and time to complete the questionnaire.

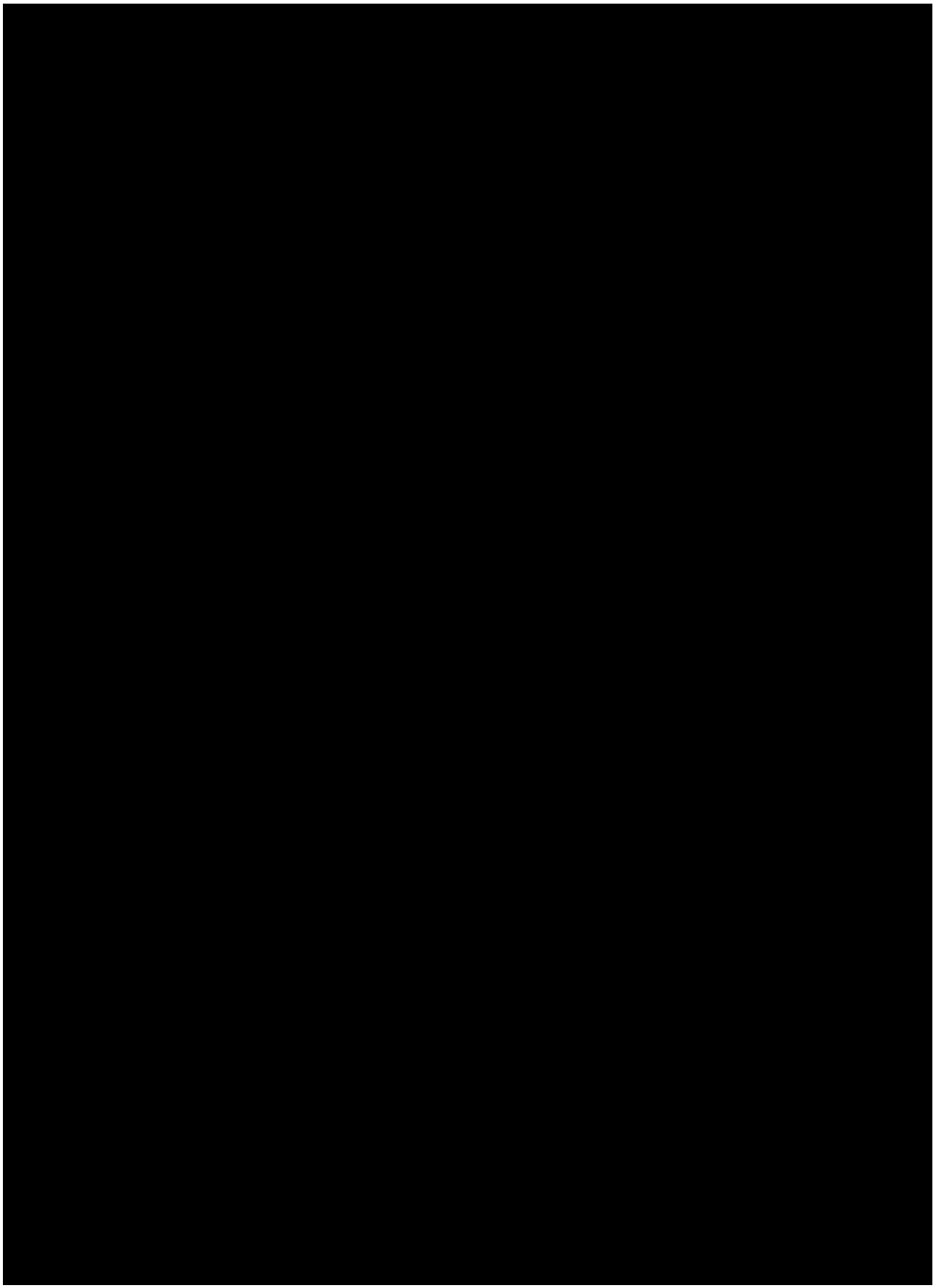
The site personnel should check the GO-QoL for completeness and ask the patient to complete any missing responses. The questionnaire will be completed on paper. This will be considered the source file.

Completed measure(s) (including when using paper questionnaire measures and any unsolicited comments written by the patient) must be reviewed and assessed by the investigator for responses, which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 of the study protocol.

In the event of a major healthcare disruption (e.g., a pandemic or epidemic) that limits or prevents on-site visits to the study site the GO-QoL might alternatively be done remotely from the patient´s home (e.g., online), depending on local regulations and technical capabilities.







9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

The investigator closely monitors the disease activity of a patient throughout the entire study and must discontinue study treatment or study participation for a given patient if he/she believes that continuation would negatively impact the patient's well-being.

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

Study treatment must be discontinued under the following circumstances:

- Subject decision.
- If any of the following (evidence of disease progression) occurs in the study eye or fellow (contralateral) eye:
    - Compressive optic neuropathy that in the opinion of the investigator requires urgent surgical intervention or medical treatment with glucocorticoids
    - Severe corneal injury that requires surgical treatment
    - Severe/major loss of vision defined as a decrease of best-corrected visual acuity to below 0.1 (Snellen equivalent of 20/200)
    - Other abnormalities not here specified but that the investigator determines would require study treatment discontinuation
- Emergence of the following AEs:
    - Any severe or SAE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable concomitant medication.

  - Onset of lymphoproliferative disease or any malignancy, except for treated basal cell carcinoma, treated actinic keratoses, treated *in situ* carcinoma of the cervix or non--invasive malignant colon polyps which are being or have been removed.
  - Life-threatening infection.
  - Severe hypersensitivity reaction or anaphylactic reaction.
  - Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the patient at a safety risk for continuation in the study (a general guidance on clinically notable laboratory values is provided in Appendix 1).
  - Pregnancy.
- Use of any biologic immunomodulating agent except secukinumab.
- Other treatment or procedure for TED in case of worsening of the disease.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Use of prohibited treatment as per recommendations in the prohibited treatment section if the treatment with prohibited medication increases the patient's safety risk and if it cannot be discontinued.
- Emergency unblinding

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

In addition to the study treatment discontinuation criteria above, which apply throughout the entire study, the following criterion applies from week 16 onwards for discontinuation of study participation of a patient:
Any deterioration compared to baseline values that the investigator considers to be clinically relevant in this individual case will result in study discontinuation of the patient. The evaluation should take into account the overall course of the disease of the individual case (e.g., individual fluctuations of ocular parameters).

Patients may decide to discontinue their participation in the study for any reason at any time.

Premature discontinuation of study treatment

Patients who prematurely discontinue study treatment during the double-blind treatment period (Weeks 0 - 16) or during a course of open-label secukinumab administered during the follow-up period (at or after Week 16), for any reason other than withdrawal of informed consent should **not** be considered as discontinued from the study. **Where possible, they should return for the study visits indicated** in the Assessment Schedule during treatment. These include up to Week 16 (if discontinued during double-blind treatment), up to NR32 (for non-responders), and up to R16 (for relapsers). In case patients are not willing to continue attending further study visits, they should attend an End of Treatment (EOT) visit 4 weeks after the last dose of study drug. This EOT visit includes all assessments of the Week 16 (if discontinued during double-blind treatment), NR32 (for non-responders) or R16 (for relapsers) visit.

Additionally, a follow-up visit (EOS) should be done 12 weeks after last study drug administration, including all assessments done at: Week 24 (if discontinued during double-blind treatment), Week NR40 (for non-responders) or Week R24 (for relapsers).

Premature discontinuation of study

Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the study discontinuation visit will be performed. This study discontinuation visit should include all assessments of the Week 16 (if discontinued during double-blind treatment), NR32 (for non-responders), R16 (for relapsers) or Week 68 (for patients who discontinued during the follow-up period) visit.

Additionally, all randomized and/or treated patients should have a follow-up (EOS) visit conducted 12 weeks after last administration of study treatment, if not yet completed (or at least a safety follow-up call or contact, if a visit cannot be performed). This EOS visit includes all assessments of the Week 24 (if discontinued during the double-blind treatment period or the follow-up for responders), Week NR40 (for non-responders) or Week R24 (for relapsers) visit. The information collected is recorded in the eCRF. Documentation of attempts to contact the patient should be recorded in the source documentation.

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

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

After study treatment discontinuation or study discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- AEs/SAEs

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

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

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

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

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

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

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their study completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g., each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

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

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
   - Mild: usually transient in nature and generally not interfering with normal activities.
   - Moderate: sufficiently discomforting to interfere with normal activities.
   - Severe: prevents normal activities.
2. Its relationship to the study treatment (suspected: yes or no). If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be ‘not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/withdrawn

6. Its outcome (i.e., recovery status or whether it was fatal).

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment in case of early study discontinuation, preferably a follow-up visit or contact 12 weeks after last study treatment should be performed.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- They induce clinical signs or symptoms
- They are considered clinically significant
- They require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

10.1.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- Fatal
- Life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
- Is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective if a clinical event has occurred (see Section 10.1.5).

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

Serious adverse events occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported to the Competent Authorities and relevant Ethics Committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

SAE reporting will be done according to the assessment schedule throughout treatment and follow-up periods.

In case of early study discontinuation, any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial patient becomes pregnant, the study treatment should be stopped, and the trial patient must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy.

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

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness (Table 10-1).

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug and/or concomitant medication (e.g., thyrostatic treatment) and/or hyperthyroidism related liver enzyme elevation, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following 2 categories of abnormalities / AEs have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base Liver CRF pages

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personnel at the trial site as summarized below (please see Appendix 2 for detailed information).

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event, which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist consultancies, based on the investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

10.2.2 Renal safety monitoring

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 27,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests resulting in clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen or urea, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

10.2.3 Data monitoring committee

Not applicable.

10.2.4 Adjudication committee

Not applicable.

11 Data collection and database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1 and Table 8-2) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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

11.2 Database management and quality control

Novartis personnel (or designated contract research organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator

site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, Screen Failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the patient and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria,

documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

The data will be analyzed by Novartis and/or a designated CRO.

The primary endpoint analysis will include the primary endpoint (Week 16) and results of retreatment for proptosis non-responders, after all patients have completed the Week 40 visit assessment. This will support potential regulatory filing as described in Section 4.4. A final analysis is planned at the EOS once all patients have completed their EOS visit. There may be analyses in addition to Week 40 and Week 108 timepoints to support regulatory filings.

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

12.1 Analysis sets

The Randomized Set consists of all randomized participants. Unless otherwise specified, mis-randomized participants (mis-randomized in IRT) will be excluded from the randomized set. Mis-randomized participants are defined as those participants who 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 participants are treated as screen failures.

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned. Patients will be analyzed according to the treatment they have been assigned to.

The Safety Set includes all patients who received at least one dose of study treatment/reference treatment. Patients will be analyzed according to the study treatment received.

12.2 Patient demographics and other baseline characteristics

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

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

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

12.3 Treatments

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

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

12.4 Analysis of the primary endpoints/estimands

During scientific advice sessions, the FDA and the EMA expressed different preferences regarding the primary and secondary endpoints and their ordering. Therefore, this study will have 2 different analysis strategies and corresponding endpoint definitions, Plan A is intended for the EMA submission and Plan B is intended for the submission to FDA. The plan used for other health authorities will be based on local decisions.

Plan A (EU)

The primary objective of this study is to demonstrate the effect of secukinumab 300 mg compared to placebo on the overall responder rate at Week 16.

The primary endpoint is the proportion of patients achieving overall response at Week 16 defined as follows: ≥ 2 point reduction in 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 (contralateral) eye.

Plan B (FDA)

The primary objective is to demonstrate the effect of secukinumab 300 mg compared to placebo on the responder rate in ≥ 2 mm reduction of proptosis at Week 16.

The primary endpoint is the 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.

12.4.1 Definition of primary endpoints/estimands

For the definition of primary and secondary estimands, see Section 2.1 and Section 2.2.

12.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis to be rejected is that there is no difference in marginal response rates for patients with secukinumab vs. patients with placebo after 16 weeks.

Let pj denote the probability of a response at 16 weeks for treatment group j, j=0, 1 where

- 0 corresponds to placebo
- 1 corresponds to secukinumab

The following hypotheses will be tested:

H_0: $p_1 = p_0$ versus H_A: $p_1 \neq p_0$

The primary analysis will be performed comparing treatments with respect to the primary endpoint in a logistic regression model with treatment group and stratum (i.e., smoking status) as factors and Baseline proptosis as covariate. Difference in marginal response proportions between treatments and its 95% confidence interval (CI) will be imputed using the marginal standardization method, details will be provided in the SAP. The primary analysis will be based on the FAS and will be performed when all patients have completed the Week 16 assessment.

Testing strategy

The following hypotheses will be included in the testing strategy, and type-I-errors will be set such that a family-wise-type-I-error of $\alpha = 0.05$ is kept.

Plan A

Primary objective:

H_1 Secukinumab 300 mg is not different to placebo regimen with respect to the proportion of patients achieving overall response (as defined above) at Week 16.

Key secondary objectives:

H_2 Secukinumab 300 mg is not different to placebo regimen with respect to the proportion of patients achieving a CAS response defined as a ≥ 2-point reduction at Week 16 without corresponding deterioration in CAS (≥ 2-point increase) in the fellow eye.

H_3 Secukinumab 300 mg is not different to placebo regimen with respect to the proportion of patients achieving a proptosis response defined as a ≥ 2 mm reduction in proptosis at Week 16 without corresponding deterioration in proptosis (≥ 2 mm increase) in the fellow eye.

H_4 Secukinumab 300 mg is not different to placebo regimen with respect to the mean change from baseline in CAS at Week 16.

The family-wise error will be set to $\alpha = 0.05$ (2-sided), which will be controlled via the proposed fixed testing sequence. The hypothesis for the composite primary objective will be tested first and in case of rejection, H_2 and H_3 will be tested simultaneously. This can be done without any multiplicity adjustment, as H_2 and H_3 are the hypotheses for the single components

contained in the primary composite and rejection of H_1 would necessitate the rejection of at least one of the component hypotheses H_2 or H_3. Then, based on the rejection of H_2 and H_3, the final test will be performed for H_4. Further secondary endpoints will be tested outside of the confirmatory framework without adjustments for multiple testing.

Plan B

Primary objective:

H_1 Secukinumab 300 mg is not different to placebo regimen with respect to the proportion of patients achieving a proptosis response defined as a ≥ 2 mm reduction in proptosis at Week 16 without corresponding deterioration in proptosis (≥ 2 mm increase) in the fellow eye.

Key secondary objectives:

H_2 Secukinumab 300 mg is not different to placebo regimen with respect to the proportion of patients achieving a CAS response defined as a ≥ 2-point reduction at Week 16 without corresponding deterioration in CAS (≥ 2 points increase) in the fellow eye.

H_3 Secukinumab 300 mg is not different to placebo regimen with respect to the proportion of patients achieving overall response (as defined above) at Week 16.

H_4 Secukinumab 300 mg is not different to placebo regimen with respect to the mean change from baseline in CAS at Week 16.

The family-wise error will be set to $\alpha = 0.05$ (2-sided), which will be controlled via the proposed fixed testing sequence. Further secondary endpoints will be tested outside of the confirmatory framework without adjustments for multiple testing.

12.4.3 Handling of remaining intercurrent events of primary estimand

Not applicable, all intercurrent events and their handling are defined above.

12.4.4 Handling of missing values not related to intercurrent event

The primary endpoint should in principle be available for all patients who do not discontinue the trial. However, if for any reason the response status is unknown for such a patient, he/she will be counted as a non-responder.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Treatment groups will be compared using a Mantel-Haenszel-Test.

12.4.6 Supplementary analysis

12.4.7 The primary analysis will be conducted separately within the two strata.Supportive analyses

An additional Bayesian analysis may be conducted. Posterior distributions of the treatment effect will be derived as a guidance for internal decision making on further development in this indication. Details will be specified in a separate analysis plan.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy endpoints

Plan A

The 2 components of the primary endpoint, the **CAS response** and the **proptosis response** will be analyzed separately using the same methodology as for the primary endpoint.

Plan B

The **CAS response** and the **overall response** will be analyzed using the same methodology as for the primary endpoint.

The **mean change from baseline in CAS**, **the mean change from baseline in proptosis** and the **mean change from baseline in GO-QoL** score will be analyzed using a mixed model for repeated measures (MMRM) with factors treatment group and stratum and with baseline as a covariate. Least-square mean differences with corresponding confidence intervals and p-values will be calculated for each visit time point as estimates for the treatment effect.

The proportion of patients achieving **response in diplopia and the proportion of patients with an improvement in disease severity at Week 16** will be analyzed analogous to the primary endpoint.

12.5.2 Safety endpoints

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

Safety summaries (tables, figures) include only data from the on-treatment period and follow-up period with the exception of Baseline data that 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 AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse events

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

The number and percentage of patients with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on PT) will be summarized in the following ways:

- By treatment, primary SOC and PT.
- By treatment, primary SOC, PT and maximum severity.

Separate summaries will be provided for study treatment related AEs, death, SAEs, other significant AEs leading to discontinuation.

The number (and proportion) of patients with adverse events of special interest (AESIs) will be summarized by treatment.

A patient with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

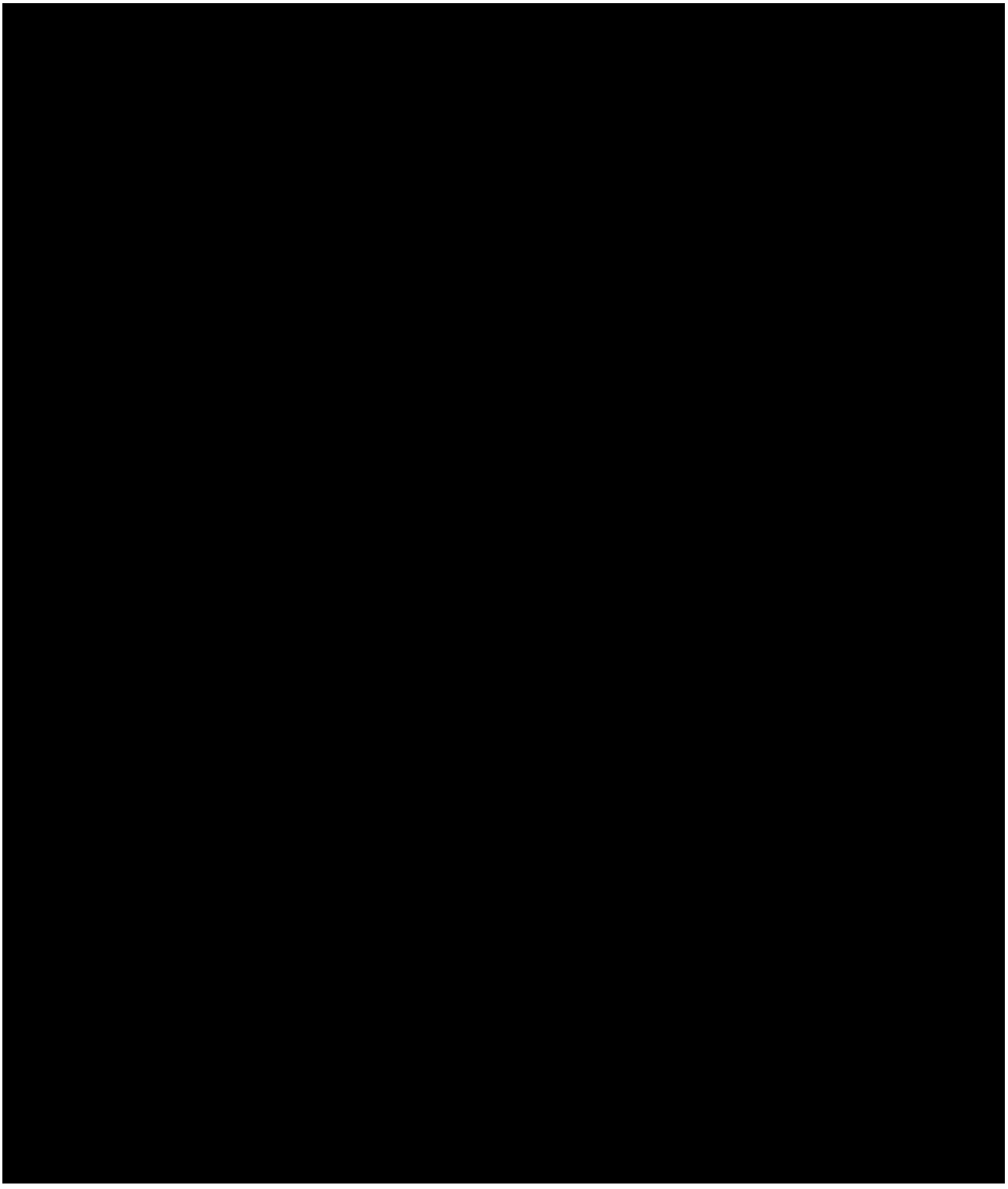
Vital signs

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

Clinical laboratory evaluations

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

[redacted]



12.7 Interim analyses

Please refer to Section 4.4.

12.8 Sample size calculation

For Plan A (EMA submission), the primary endpoint is the proportion of patients achieving overall response at Week 16 defined as follows: ≥ 2 point reduction in 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.

For Plan B (FDA submission), the primary endpoint is the 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.

The sample size calculation is given for the primary endpoint of the EMA strategy Plan A that takes into account both CAS and proptosis response rates. For the FDA strategy Plan B, the deliberations given for the secondary endpoint below apply, which in effect follow the same principles as the primary endpoint.

12.8.1 Primary endpoint

In the Phase 3 teprotumumab study (Douglas et al 2020) for which data are available on active and placebo arms, the percentage of patients achieving a reduction of 2 mm or more in proptosis and a reduction of 2 points or more in CAS in the study eye at Week 24 was 78% for patients receiving teprotumumab and 7.1% for patients receiving placebo ($p < 0.001$). In the Phase 2 clinical trial of teprotumumab (Smith et al 2017), the corresponding responder rates at Week 24 were 69% (teprotumumab) vs. 20% (placebo) ($p < 0.001$).

For the current study, we are hypothesizing response rates of 60% for secukinumab vs. 20% for placebo. A response rate of 60% is considered clinically meaningful given the medical need for effective treatment with a therapy of active, moderate to severe TED that does not carry the toxicity risks of current treatment alternatives, e.g., high dose i.v. corticosteroids. With this response rate and the expected safety profile of secukinumab to be similar to that already established, the response will fall in line with a favorable benefit-risk assessment.

Under these assumptions, 35 patients per treatment arm (70 patients in total) are required to achieve a power of 90% to demonstrate superiority at a significance level of 0.05 using the 2-group continuity corrected Chi-squared test of equal proportions.

In case of deviations in the group proportions/percentages for the primary endpoint and keeping the number of patients per group at 35 and the significance level constant, the following table includes the differing power scenarios for the planned study. They show a robust statistical basis for this trial in terms of power.

Placebo response	Secukinumab response	Power
0.175	0.60	0.94
0.20	0.60	0.90
0.225	0.60	0.85

12.8.2 Secondary endpoints

For the key secondary endpoints included in the fixed testing sequence described above, treatment effects in about the same order of magnitude as for the primary endpoint are expected; therefore, the power for these endpoints should also be similar and should be adequate.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion *(*defined as last patient last visit*)* and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

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

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study patients.

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

14.1 Protocol amendments

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

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in Section 8.4.

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the Investigator/qualified site staff whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the patient. For additional information please refer to the laboratory manual.

Liver function and related variables

ALT (SGPT):	> 3 x upper limit of normal (ULN)
AST (SGOT):	> 3 x ULN
Total bilirubin:	> 2 x ULN
Alkaline phosphatase:	> 2 x ULN

Renal function and electrolyte variables

Creatinine (serum):	> 1.5 x ULN

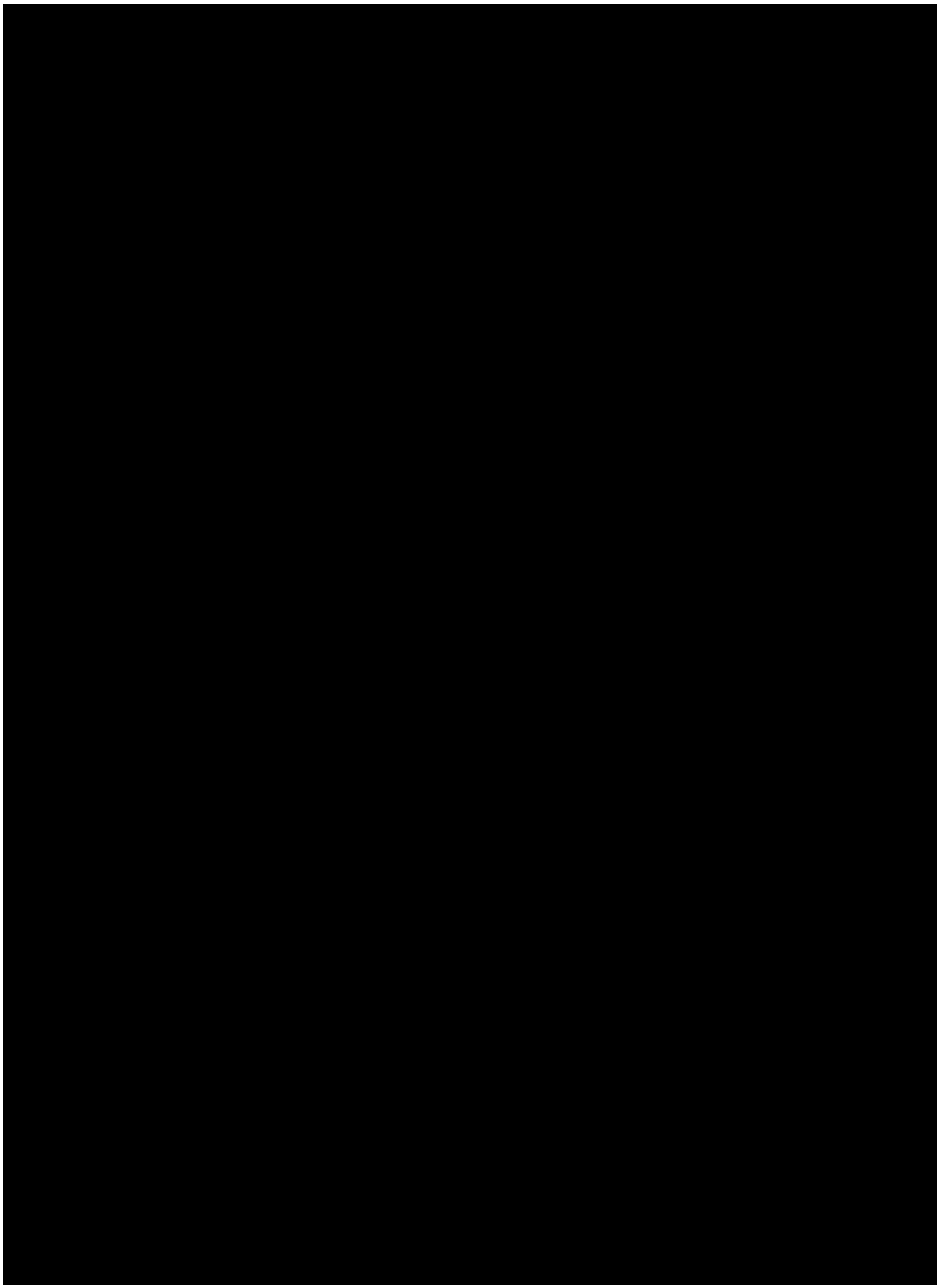
Hematology variables

Hemoglobin:	≥ 20 g/dL decrease from Baseline
Platelet count:	< lower limit of normal (LLN)
White blood cell count:	< 0.8 x LLN
Neutrophils:	< 0.9 x LLN
Eosinophils:	> 1.1 x ULN
Lymphocytes:	> 1.1 x ULN

Urinalysis variable

Protein urine dipstick:	++* (* ++ is ≥ 100 mg/dL)

[redacted]



16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-3 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
Liver events	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
ALT=alanine aminotransferase, ALP=alkaline phosphatase, AST=aspartate aminotransferase, INR=international normalized ratio, TBL=total bilirubin, UNL=upper normal limit

Table 16-4 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, pt/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

Criteria	Actions required	Follow-up monitoring

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Alb=albumin, AESI=adverse event of special interest, ALP=alkaline phosphatase, CRF=case report form, INR=international normalized ratio, γGT=gamma glutamyl transferase, LFT=liver function test, pt=prothrombin time, TBL=total bilirubin, ULN= upper limit of normal

16.3 Appendix 3: GO-QoL assessment

GO-Quality Of Life Questionnaire ☐ initial ☐ follow-up Date

The following questions deal specifically with your thyroid eye disease. Please focus on the past week while answering these questions.

During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?

Tick the box that matches your answer. The boxes correspond with the answers above them.
Please tick only one box for each question.

		Yes seriously limited	Yes a little limited	No not at all limited
1)	Bicycling (never learned to ride a bike☐)	☐	☐	☐
2)	Driving (no driver's licence ☐)	☐	☐	☐
3)	Moving around the house	☐	☐	☐
4)	Walking outdoors	☐	☐	☐
5)	Reading	☐	☐	☐
6)	Watching TV	☐	☐	☐
7)	Hobby or pastime, i.e.	☐	☐	☐

		Yes severely hindered	Yes a little hindered	No not at all hindered	
8)	During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	☐	☐	☐	Score

The following questions deal with your thyroid eye disease <u>in general</u>

		Yes, very much so	Yes a little	No not at all	
9)	Do you feel that you appearance has changed because of your thyroid eye disease?	☐	☐	☐	
10)	Do you feel that you are stared at in the streets because of thyroid eye disease	☐	☐	☐	
11)	Do you feel that people react unpleasantly because of your thyroid eye disease?	☐	☐	☐	
12)	Do you feel that your thyroid eye disease has an influence on your self-confidence?	☐	☐	☐	
13)	Do you feel socially isolated because of your thyroid eye disease	☐	☐	☐	
14)	Do you feel that your thyroid eye disease has an influence on making friends?	☐	☐	☐	
15)	Do you feel that you appear less often on photos than before you had thyroid eye disease?	☐	☐	☐	
16)	Do you try mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐	Score