Official Title: A Phase III, Randomized, Double-Masked, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Satralizumab in Participants with Moderate-to-Severe Thyroid Eye Disease

NCT Number: NCT05987423

Document Date: Protocol Amendment Version 3: 30-Aug-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PARTICIPANTS WITH MODERATE-TO-SEVERE THYROID EYE DISEASE**
PROTOCOL NUMBER:	GP44467
STUDY NAME	SatraGO-1
VERSION NUMBER:	*3*
TEST PRODUCT:	Satralizumab (RO5333787)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 163819 EU CT Number: 2023-503309-13-00 NCT Number: NCT05987423
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 *4058* Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol	
Version	Date Final
3	See electronic date stamp on final page of this document
2	08 November 2023
1	14 March 2023

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

GP44467 has been amended primarily to update the exclusion criteria relating to previous corticosteroid use, provide clarification regarding the method used to determine the ≥3 mm proptosis requirement, and update Appendix 8 to provide mean (with range) exophthalmometry values for race and gender. Other updates include clarification to the exclusion criteria for prior strabismus surgery and Botulinum toxin injection, addition of an optional ECG assessment during screening, addition of Appendix 9 (order of assessments), change to the number of re-screening opportunities allowed per patient and ICF validity period, update to the complete physical exam requirements, laboratory requirements (central vs. local), and total number of study sites.

Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The study will now allow enrollment of patients who have had previous exposure to corticosteroids ≥ 1g for the treatment of TED or other conditions, if the protocol mandated wash out period of 3 months is met.
    - Specifically, the eligibility criteria now exclude individuals with active TED who have previous use of IV or oral corticosteroids with a cumulative dose equivalent to ≥ 1g of methylprednisolone or equivalent for the treatment of TED or any other condition within 3 months of screening.
- Additional information relating to the ≥3 mm proptosis requirement for study eligibility have been added to the protocol in the inclusion criteria and in Appendix 8.
    - The method used to confirm the ≥3 mm proptosis requirement is at the discretion of investigators, and can be based on patient-specific parameters such as differences in study eye versus non-study eye for unilateral TED, prior exophthalmometry measurement, comparison to old photographs, or referencing the normal values listed in Appendix 8.
    - Appendix 8 (Upper Limit of Normal (ULN) Exophthalmometry Values for Race and Gender) was updated to ‘Normal Exophthalmometry Values (Mean and Range) for Race and Gender’ because mean values are considered to provide a clearer reference point than the ULN values previously provided. Appendix 8 still serves for information purposes only, and ultimately the method used to determine the ≥3 mm proptosis requirement is at the Investigator’s discretion, as described above.

Other updates and clarifications include:

- Update to the exclusion criteria for prior strabismus surgery to clarify that a history of surgery for congenital strabismus is not exclusionary.
- Update the exclusion criteria to clarify that patients with use of Botulinum toxin injection for any condition in either eye, eyelid, or periocular region within 3 months prior to screening are not eligible for the study.

- The prohibited therapies section of the protocol (Section 6.8.2) was updated to clarify that (1) use of Botulinum toxin injection for any condition in either eye, eyelid, or periocular region is not permitted during the study, and (2) Systemic or local steroids for TED or conditions other than TED are not permitted during the study.
- The SOA has been updated to add an optional ECG assessment during screening. The baseline ECG assessment remains mandatory.
- The requirement for a complete blood count and liver test to be performed within 28 days prior to baseline was removed; in patients whose screening window is extended to 42 days, these tests must be performed prior to baseline but remain valid for the whole 42-day screening period.
- Laboratory assessments for masked parameters (i.e. CRP, fibrinogen, and complement [C3, C4, and CH50], and immunoglobulins) will no longer be collected during screening, since they are not required as part of the study eligibility assessment. Table 1 Schedule of Activities has been updated to remove quantitative immunoglobulins from the screening visit. As fibrinogen is part of the hematology panel, and CRP and complement are part of the chemistry panel, removing these specific tests from screening will be handled via the central laboratory. Additional information on how to handle visit scheduling in Part II of the study if the Week 24 visit is performed out of window has been added to protocol Section 4.1.1.2.

  Updated guidance to investigators regarding the genitourinary exam component of the complete physical exam has been added (Schedule of Activities and Section 8.2.1 Safety Assessments - Physical Examinations). Due to the invasive nature of the genitourinary exam and since the safety of the study medication and TED do not directly impact a patient's genitourinary system, the protocol will now allow for flexibility in conducting this specific examination. The genitourinary exam is no longer mandatory and may be completed if clinically indicated per investigator's judgement.
- The protocol was updated to increase the number of screenings allowed per patient. Previously, one re-screening opportunity (for a total of two screenings per individual) was allowed at the investigator's discretion. In the updated protocol (Section 4.1.1, Section 5.4, and Table 1 footnotes), three re-screens are now permitted, for a total of four screenings per individual. Additionally, at re-screening, all visit assessments are required to be performed except TB test and optional ECG if within normal limits.
- Section 4.1.1, Section 5.4, and the Table 1 footnotes were amended to update the ICF validity period to cover screening periods which extend to 42 days (previously the ICF validity period was 28 days). Also, it was clarified that individuals do not need to re-sign the consent form before rescreening unless a new version of the consent form has been implemented at the site.
- The protocol was updated to allow the serum pregnancy test, urine pregnancy test, urinalysis, and tuberculosis tests to be conducted at either the central or local laboratory. (See appendix 2 and the Table 1 footnotes.)

- Section 8.10.1.1 states imaging should be performed no more than 48 hours prior to study treatment administration. This was updated to allow imaging to now be performed no more than 72 hours prior to study treatment administration. This section was also amended to state that if the baseline optional orbital MRI assessment is missed then no subsequent MRI assessments should be conducted. Similarly, in Section 8.10.1.2, it was updated to state that if the baseline optional facial photograph assessment is missed then no subsequent facial photograph assessments should be conducted.
- It was clarified that the early termination (ET) visit should be performed for patients who are discontinuing from the study. A correction was made to the footnote regarding the ET visit in the Schedule of Activities (footnote ‘d’).
- In Section 8.2.2 (Vital Signs), an update was made to remove the requirement for temperature to be measured via oral or axillary methods. Body temperature may now be collected per the site's designated method for temperature collection. The type of thermometer/location of temperature measurement is not deemed to have any impact on patient safety or the data integrity of the trial.
- In Section 5 and Appendix 1, the number of study sites was updated from approximately 50 to approximately 70, to support the worldwide enrollment activities and study timelines.
- The order of key secondary endpoints to be tested hierarchically has been updated in Section 9.2 (Statistical Hypotheses), Section 9.3.3 (Analyses for the European Medicines Agency), and Section 9.3.4 (Analyses for the Japan Pharmaceuticals and Medical Devices Agency). The analysis datasets and accompanying descriptions were also updated in Section 9.1.
- In Section 3 Table 2, the analysis of improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from baseline (Day 1) to Week 48 has been added for responders and non-responders
- Section 5.3.5 Other Activity Restriction is a new section added to the protocol informing participants that blood donation is not permitted while taking study treatment and for at least 12 weeks after treatment discontinuation.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to version 2 of the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PARTICIPANTS WITH MODERATE-TO-SEVERE THYROID EYE DISEASE**
PROTOCOL NUMBER:	GP44467
VERSION NUMBER:	*3*
TEST COMPOUND(S):	Satralizumab (RO5333787)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PARTICIPANTS WITH MODERATE-TO-SEVERE THYROID EYE DISEASE**
REGULATORY AGENCY IDENTIFIERS:	**IND Number: 163819** **EU CT Number: 2023-503309-13-00** **NCT Number: NCT05987423**

STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of subcutaneous satralizumab, a recombinant, humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody, in participants with moderate-to-severe thyroid eye disease (TED). The main treatment for active TED is off-label use of corticosteroids, orbital radiotherapy and immunomodulatory therapy; chronic inactive TED is largely managed by surgical intervention. Teprotumumab, a monoclonal IGF-1R inhibitor, is approved for treatment of TED in the United States *and other countries*; however, it has been associated with several side effects and a high risk of relapse. There remains an unmet need for a disease-modifying therapy, with an improved safety profile and reduced risk of relapse.

OBJECTIVES AND ENDPOINTS

The primary and secondary objectives are listed below. A complete list of objectives, including exploratory objectives is available in Section 3.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of subcutaneous satralizumab compared with placebo at Week 24	• Proportion of participants with active disease achieving ≥ 2mm reduction in proptosis from baseline (Day 1) at Week 24 in the study eye, provided there is no deterioration of proptosis (≥ 2mm increase) in the fellow eye
Secondary Objectives	**Corresponding Endpoints**
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on proptosis response	• Proportion of participants with active and chronic inactive disease achieving ≥ 2 mm reduction in proptosis from baseline (Day 1) at Week 24 in the study eye provided there is no corresponding deterioration in proptosis (≥ 2 mm increase) in the fellow eye
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on change in proptosis	• Change from baseline (Day 1) in proptosis at Week 24 in participants with active disease[b] • Change from baseline (Day 1) in proptosis at Week 24 in participants with active and chronic inactive disease
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on reduction/improvement in diplopia	• Proportion of participants with active disease achieving ≥ 1 grade reduction/improvement in diplopia at Week 24 among participants with baseline diplopia • Proportion of participants with active and chronic inactive disease achieving ≥ 1 grade

	reduction/improvement in diplopia at Week 24 among participants with baseline diplopia
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on improvement in orbital pain	• Proportion of participants with active disease achieving absence of motility-induced pain at Week 24 among participants with motility-induced pain at baseline in the study eye • Proportion of participants with active disease achieving absence of spontaneous pain at Week 24 among participants with spontaneous pain at baseline in the study eye
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on health-related quality of life	• Proportion of participants with a ≥6 point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from baseline at Week 24
• To further assess the efficacy of subcutaneous satralizumab at Week 24	• Proportion of participants with active disease achieving overall response at Week 24, defined as a ≥2-point reduction in CAS, AND a ≥2 mm reduction in proptosis from baseline (Day 1) in the study eye, provided there is no corresponding deterioration in CAS or proptosis (≥2 point/mm increase) in the fellow eye • Proportion of participants with active disease achieving a ≥2-point reduction in CAS in the study eye from baseline (Day 1) to Week 24 • Proportion of participants achieving a CAS value of 0 or 1 in the study eye (indicating no or minimal inflammation, respectively) at Week 24 • Proportion of participants with a ≥10-point improvement in the OSDI overall scores across all levels of baseline severity at Week 24 • Change from baseline (Day 1) in the OSDI Ocular Symptoms, and Vision-related Function subscale scores at Week 24 • Change in Oxford corneal staining scores from baseline (Day 1) at Week 24[a]
• To assess the efficacy of subcutaneous satralizumab at Week 48 in those participants who are proptosis non-responders at Week 24	• Proportion of participants achieving ≥2mm reduction in proptosis at Week 48 in the study eye (provided there is no corresponding deterioration in proptosis [≥2 mm increase] in the fellow eye). • Proportion of participants achieving overall response at Week 48, defined as a ≥2-point reduction in CAS, AND a ≥2 mm reduction in proptosis from baseline (Day 1) in the study eye, provided there is no corresponding deterioration in CAS or proptosis (≥2 point/mm increase) in the fellow eye • Proportion of participants achieving a ≥2-point reduction in CAS in the study eye from baseline (Day 1) to Week 48

	• In the subset of participants with baseline (Day 1) diplopia (>0): Proportion of participants achieving Grade ≥1 reduction/improvement in diplopia at Week 48. • Proportion of participants with a ≥6 point improvement in the Visual Functioning and Appearance subscale scores of the GO-QoL from *Week 24* to Week 48 • *Proportion of participants with a ≥6 point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from baseline (Day 1) to Week 48* • Change in proptosis from baseline (Day 1) to Week 48 • Proportion of participants requiring surgical intervention for TED up to Week 48
• To assess the efficacy of subcutaneous satralizumab at Week 48 in those participants who are proptosis responders at Week 24	• Proportion of participants with worsening of proptosis by ≥2 mm from Week 24 to Week 48 • Proportion of participants with worsening of proptosis by ≥2 mm from baseline (Day 1) to Week 48 • Change in proptosis from Week 24 to 48 • Change in CAS from Week 24 to 48 • Proportion of participants with a ≥6 point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from *Week 24* to Week 48 • *Proportion of participants with a ≥6-point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from baseline (Day 1) to Week 48* • Change in proptosis from baseline (Day 1) to Week 48 • Change in CAS from baseline (Day 1) to Week 48 • Proportion of participants requiring surgical intervention for TED up to Week 48
• To evaluate the safety and tolerability of satralizumab	• Incidence, seriousness, and severity of AEs, with severity determined according to NCI CTCAE V5 • Change from baseline (Day 1) in vital signs, targeted clinical laboratory test results, ECG parameters, and body weight

• To characterize the satralizumab PK profile by evaluating plasma exposure over 24 weeks • To evaluate potential relationships between drug exposure and the efficacy and safety of satralizumab	• Serum concentration of satralizumab at specified timepoints • Estimates of primary PK parameters (e.g., CL/F and V/F) and secondary PK parameters (e.g., AUC) derived using popPK modeling • Relationship between selected covariates and exposure to satralizumab • Relationship between serum concentration or PK parameters for satralizumab and efficacy endpoints, and safety endpoints

AUC = area under the concentration-time curve; CAS = Clinical Activity Score; CL = clearance; GO-QoL = Graves' Ophthalmopathy Quality of Life; OSDI = Ocular Surface Disease Index; V/F = apparent volume of distribution.

[a] Corneal staining will be graded using the Oxford Grading Scheme Chart (a 6-point scale that range from 0 to V; see Section 8.1.2.6 and Appendix 10).

[b] Unless otherwise noted, all ocular efficacy analyses are for the study eye only.

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonisation (ICH) E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

OVERALL DESIGN AND STUDY POPULATION

This Phase III, randomized, double-masked, placebo-controlled, multicenter study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo for the treatment of participants with moderate-to-severe active and chronic inactive thyroid eye disease.

The study includes the following phases:

- Screening period (up to 28 days)
- Placebo-controlled treatment periods: This will be split into two parts:
  - Part I: Weeks 1-24; with study treatment administered until Week 20, and primary endpoint assessed at Week 24
  - Part II: Weeks 24-48, with study treatment administered until Week 44, and an analysis conducted at Week 48.

    The final visit of Part I coincides with the first visit of Part II (Week 24). At this visit, response to treatment will be assessed. Proptosis non-responders from either arm will receive satralizumab treatment in Part II. Proptosis responders from either arm will be re-randomized to satralizumab or placebo in Part II, regardless of their original treatment assignment.
  - Follow-up period: Weeks 48-72. Participants will be assessed every 2 months through telephone calls.

The primary endpoint will be assessed at Week 24, followed by an analysis at Week 48, and a final analysis conducted at Week 72.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Moderate-to-severe thyroid eye disease
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years

Test Compound:	Satralizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 120

STUDY TREATMENT

Satralizumab or placebo will be administered by SC injection. The dose of study treatment will be determined based on participant's body weight. Participants will receive satralizumab according to body weight at [redacted]

In the Part I period:

Participants will receive satralizumab or placebo on Day 1, Week 2, and Week 4 (loading doses) and then Q4W at Weeks 8, 12, 16, and 20 (maintenance doses).

The treatment which participants receive in Part II of the study is determined by their proptosis response at the end of Part I (Week 24 primary endpoint).

In the Part II period:

Participants who are proptosis non-responders at Week 24 will receive satralizumab treatment during Part II (Weeks 24 through Week 44).

Participants who are proptosis responders (defined as ≥ 2mm reduction in proptosis in the study eye provided there is no corresponding deterioration in proptosis (≥ 2mm increase) in the fellow eye) at Week 24 will be re-randomized in a 1:1 ratio to receive SC satralizumab or matching placebo (from Weeks 24 through Week 44), regardless of their original treatment assignment in Part I.

The final in-person visit of the study is at Week 48 (4 weeks after the final dose); subsequent follow up visits will be conducted by telephone every 8 weeks until Week 72.

DURATION OF PARTICIPATION

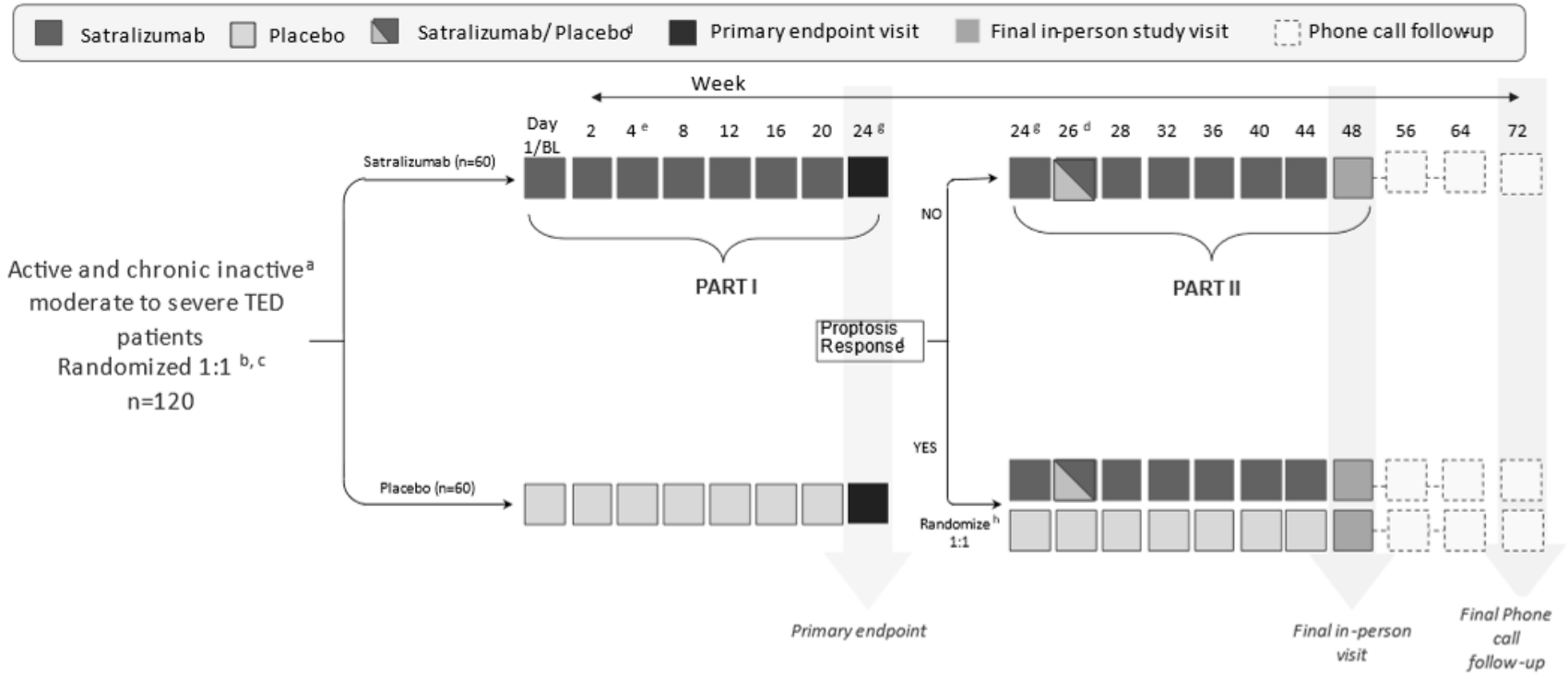
The total duration of study participation for each individual is expected to be approximately 72 weeks.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Data Coordinating Center

1.2 STUDY SCHEMA

Figure 1 Study Schema



BL = baseline; Q4W = every 4 weeks; TED = thyroid eye disease.

[a] [redacted]

[b] Participants randomized 1:1 to receive either satralizumab (body weight-based tiered dosing) or placebo. Dosing on Day 1 and at Weeks 2 and 4, and then at Weeks 8, 12, 16, and 20 (a total of seven doses).

[c] Randomization stratified by current smoking status (current smoker, including the use of e-cigarettes vs. former smoker vs. never smoked) and TED disease activity status (active vs. inactive).

[d] Participants who received placebo during Part I and commence satralizumab in Part II will receive a loading dose of satralizumab at Week 26; participants who received satralizumab in Part I and continue to receive satralizumab in Part II do not require a loading dose and will receive placebo at Week 26.

[e] Rescue intervention *for the study eye* is permitted starting from Week 4 based on protocol-defined criteria as assessed by the investigator. After receiving rescue medication, participants will be discontinued from study drug, but will be encouraged to continue in the study and complete all remaining study visit assessments, with a particular emphasis on the Week 24 and 48 visits.

[f] Based on proptosis response at Week 24 (i.e., the primary endpoint), non-responders will receive satralizumab from Week 24 to Week 44 followed by the final in-person evaluation at Week 48; and responders will be re-randomized to receive placebo or satralizumab with doses starting at Week 24 and continuing through Week 44. After the final non-dosing in-person visit at Week 48, participants will have telephone follow-up every 2 months for 6 months (i.e., at Weeks 56, 64, and 72). Note that participants that discontinue the study drug in Part I but choose to stay in the trial for Part II will not be re-randomized and will not receive any further study treatment (satralizumab/placebo).

[g] Week 24 will be the final visit for Part I and the first visit for Part II.

[h] At re-randomization at Week 24, the original randomization stratification factors measured at baseline (smoking status and TED disease activity status) will be used.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Weeks	*Screening*[a]	**Part I**								**Part II**							**Follow-up** [b]	**ET Visit** [d]
	–4	**Day 1/ (BL Visit)**	**2**	**4**	**8**	**12**	**16**	**20**	**24**[c]	**26**	**28**	**32**	**36**	**40**	**44**	**48 (Final in-person Visit)**	**56, 64, 72 (Phone)**	
Day(s) (Window)	–28 to –1	1	15 (±3)	29 (±3)	57 (±7)	85 (±7)	113 (±7)	141 (±7)	169 (±7)	183 (±3)	197 (±3)	225 (±7)	253 (±7)	281 (±7)	309 (±7)	337 (±7)	393, 449, 505 (±7)	(±7)
Main Written informed consent [e]	x																	
Optional informed consent (RBR, orbital MRI, and/or facial photographs) [e]	x																	
Review of inclusion/ exclusion criteria [f]	x	x																
Demographic data	x																	
Medical and surgical history (including tobacco history) and baseline disease conditions [g]	x	x																
Height		x																
Body Weight [h]	x	x			x		x		x			x		x		x		x
Complete Physical examination [i]	x	x							x							x		x
Limited Physical Examination [j]			x	x	x	x	x	x		x	x	x	x	x	x			

Table 1 Schedule of Activities (cont.)

Weeks	*Screening*[a]	Part I								Part II							Follow-up [b]	ET Visit [d]
	–4	Day 1/ (BL Visit)	2	4	8	12	16	20	24[c]	26	28	32	36	40	44	48 (Final in-person Visit)	56, 64, 72 (Phone)	
Day(s) (Window)	–28 to –1	1	15 (±3)	29 (±3)	57 (±7)	85 (±7)	113 (±7)	141 (±7)	169 (±7)	183 (±3)	197 (±3)	225 (±7)	253 (±7)	281 (±7)	309 (±7)	337 (±7)	393, 449, 505 (±7)	(±7)
Vital signs [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
12-Lead ECGs[l]	*x*	x				x			x				x			x		x
Hematology [m, n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Chemistry [m, o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Pregnancy test [p]	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x
Urinalysis [q]	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x
Tuberculosis screening [r]	x																	
HIV test	x																	
Hepatitis B and C Test [s]	x																	
Hepatitis B viral DNA (if required) [s]	x					x			x				x			x		x
Thyroid functioning test (TSH, FT3, FT4) [t]	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x
Quantitative immunoglobulins		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Adverse events [u]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1 Schedule of Activities (cont.)

Weeks	*Screening*[a]	Part I								Part II							Follow-up [b]	ET Visit [d]
	–4	Day 1/ (BL Visit)	2	4	8	12	16	20	24[c]	26	28	32	36	40	44	48 (Final in-person Visit)	56, 64, 72 (Phone)	
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Concurrent ocular procedures *w*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual Acuity *y*, x	x	x		x		x		x	x		x		x		x	x		x
Slit-lamp exam *y*, x	x	x		x		x		x	x		x		x		x	x		x
Pupillary exam *y*, x	x	x		x		x		x	x		x		x		x	x		x
Indirect ophthalmoscopy *y*, *x*	x	x							x							x		x
Eyelid measurement *x*	x	x				x			x				x			x		x
Iris pigmentation		x																
Intraocular pressure *x*	x	x		x		x		x	x		x		x		x	x		x
Proptosis x, y, *z*	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x
Diplopia x, *y*	x	x		x		x		x	x		x		x		x	x		x
Motility restriction x, *y*	x	x		x		x		x	x		x		x		x	x		x
CAS assessment x, *y*	x	x		x		x		x	x		x		x		x	x		x
Clinical Measures of Severity *aa*, *x*	x	x		x		x		x	x		x		x		x	x		x
Corneal staining *bb*, *x*	x	x		x		x		x	x		x		x		x	x		x
GO-QoL Questionnaire *cc*, *x*		x				x			x				x			x		x

Table 1 Schedule of Activities (cont.)

Weeks	*Screening*[a]	Part I								Part II							Follow-up [b]	ET Visit [d]
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OSDI Questionnaire *dd, x*		x				x			x				x			x		x
Optional Orbital MRI *ee*		x							x							x		x
Optional facial photographs *ff*		x							x							x		x
Study drug administration *gg*		x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Serum PK sample		x	x	x	x	x			x	x	x	x	x			x		x
Biomarker sample (PD)		x	x	x	x	x			x	x	x	x	x			x		x
Biomarker sample (exploratory)	x	x	x	x	x	x			x	x	x	x	x			x		x
Thyroid-related autoantibodies		x		x	x	x			x		x	x	x			x		x
Optional Blood sample (RBR) *hh*		x																
ADA Sample		x	x	x	x	x			x	x	x	x	x			x		x

Ab = antibody; ADA = anti-drug antibodies; VA = visual acuity; BL = baseline; CRP = C-reactive protein; CAS = clinical activity score; eCRF = electronic Case Report Form; ET = early termination; GGT = gamma-glutamyl transferase; GO-QOL = Graves' Ophthalmopathy Quality of Life; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; IL-6 = interleukin 6; LDL = low-density lipoprotein; LDH = lactate dehydrogenase; OSDI = ocular surface disease index; PD = pharmacodynamic; PK = pharmacokinetic; RBR = research biosample repository; TB = tuberculosis; TED = thyroid eye disease.

Table 1 Schedule of Activities (cont.)

Notes: All laboratory assessments are to be conducted by the central laboratory apart from the urine pregnancy test, urinalysis, and TB test, *which may be performed at the central or local laboratory as outlined in Table A2-1).* All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those performed at screening, self–administered PROs, the optional orbital MRI, and optional facial photography. All clinical laboratory, PK, PD, biomarker, and ADA samples should be obtained pre-dose at indicated visits.

Notes: All laboratory assessments are to be conducted by the central laboratory apart from the urine pregnancy test, urinalysis, and TB test, which may be performed at the central or local laboratory as outlined in Table A2-1). All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those performed at screening, self-administered PROs, the optional orbital MRI, and optional facial photography. All clinical laboratory, PK, PD, biomarker, and ADA samples should be obtained pre-dose at indicated visits.

[a] The screening period is up to 28 days. The screening period may be extended in exceptional circumstances but cannot exceed 42 *days.* Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for *three re*-screening *opportunities* (for a total of *four* screenings per individual) at the investigator's discretion.

[b] The patient will be contacted at Weeks 56, 64 and 72 for a telephone follow up visit, to review adverse events, concomitant treatments, and any treatments or surgery received for TED.

[c] Week 24 will be the final visit for Part I and the first visit for Part II. *Every effort should be made to ensure the Week 24 visit occurs within the ±7-day visit window. If the patient performs the Week 24 visit out-of-window, please refer to Section 4.1.1.2 for how to schedule subsequent visits.*

[d] An ET visit will be performed for participants who permanently discontinue from *the study. In those who discontinue from the study, the* ET visit should *ideally occur* within 4 weeks after the *patient's last study treatment.* At this visit, a complete set of assessments will be conducted. If the ET coincides with a scheduled visit, the ET visit should be completed instead of the scheduled visit.

[e] Informed consent must be documented before any study-specific screening procedure is performed, and *does not have* to *be re-signed unless a new version* of *the* consent *form has been implemented at the site.* The Informed Consent Forms for optional orbital MRIs, facial photographs, and for the optional collection and/or storage of samples for RBR can be signed either at the screening or on Day 1 visit prior to the MRI, facial photograph, or sample collection.

[f] *Ensure the participant eligibility is confirmed for the study prior to randomization.*

[g] Medical history, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cardiovascular, cerebrovascular, infectious diseases and ophthalmic), surgeries, reproductive status, smoking history, use of alcohol and drugs of abuse will be recorded at screening. In addition, disease-specific medical history will be collected, including thyroid dysfunction medical history, relevant prior surgeries, procedures, and treatments.

[h] Baseline body weight (as measured on Day 1) will be used to determine the initial weight-based dosing for participants in the study. Participants with body weight [redacted]kg will receive [redacted]mg, participants with [redacted]kg will receive [redacted]mg, and participants [redacted]kg will receive [redacted] mg. The dose may be adjusted if the participant's body weight changes as per guidance in Table 6.

Table 1 Schedule of Activities (cont.)

[i] Perform a complete physical examination at screening and other specified visits that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. *A genitourinary examination will be completed if clinically indicated per investigators judgement.* Any abnormality identified at baseline (Day 1) *must* be recorded on the General Medical History and Baseline Conditions eCRF. Record changes from baseline in patient notes. Record new or worsened clinically significant abnormalities as adverse events on the Adverse Event eCRF.

[j] During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record changes from baseline (from Day 1) in patient notes. Record new or worsened clinically significant abnormalities as adverse events on the Adverse Event eCRF.

[k] Vital signs include measurement of body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position. Vital signs will be taken while the participant is in a seated position after resting for 5 minutes. Vital signs are measured just before dosing and 15 (±5) minutes and 60 (±5) minutes after dosing for the first five doses in Part I, and the first five doses in Part II, in case of study drug injection reaction. After the 5th dose (in Part I or Part II), vital signs should be measured only before study drug administration.

[l] ECG should be performed prior to blood draws. *ECGs are mandatory at baseline, but an optional ECG may be performed during screening to allow additional time to evaluate any findings.*

[m] Frequent monitoring of safety laboratory parameters is required due to the systemic administration of satralizumab and requirement to monitor and manage identified and potential risks associated with the drug; this includes monitoring criteria for treatment interruption or discontinuation (such as elevated ALT and AST, and decreased neutrophil or platelet levels), as described in Appendix 4.

[n] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), quantitative platelet count, fibrinogen and INR. *Note that fibrinogen will not be assessed during screening.*

[o] Chemistry includes albumin, total protein, total bilirubin, ALP, AST, ALT, GGT, LDH, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ferritin, BUN, creatinine, sodium, Cl, K, Ca, P, complements (CH50, C3, C4), lipase, CRP, and serum CK. *Note that CRP and complement will not be assessed during screening*

[p] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests *(urine beta-hCG [sensitivity of at least 25 mU/mL])* will be performed pre-dose at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed *(Appendix 2). All serum and urine pregnancy tests may be performed centrally or locally.*

[q] Samples for clinical laboratory tests should be collected pre-dose on dosing days. Dipstick urinalysis should be performed. If abnormalities are detected, a complete urinalysis is to be performed as deemed necessary. Refer to Appendix 2.

[r] A TB test (e.g., tuberculin test and/or Quantiferon® test) should be conducted according to local guidance (see Appendix 7). If the potential participant is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment. Additional tests for the diagnosis of latent and active TB should be done as per the local guidance and standard of care (in individuals with a positive TB test and in individuals who have a potential risk for TB infection/reactivation). In patients who test

Table 1 Schedule of Activities (cont.)

positive for latent TB and undergo anti-TB treatment per protocol, TB re-testing is not required as part of the re-screening process if the original TB test was conducted within 12 weeks prior to baseline.

[s] HBsAg, HBcAb, HBsAb, HCVAb. All participants must have negative HBsAg test result at screening prior to enrollment. Hepatitis B screening: Participants who are HBsAg positive will be excluded from the study. If HBcAb status is positive, hepatitis B viral DNA will be measured. If HBV DNA is detectable, the individual must be excluded. If HBV DNA is undetectable, the individual may be enrolled. In these participants, HBV DNA measurement must be performed regularly at 12 weekly intervals during the study. Hepatitis C screening: If HCVAb is positive, HCV RNA will be measured. If HCV RNA is undetectable ≥ 12 weeks after HCV treatment completion, the patient can be enrolled.

[t] Subjects must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels < 50% above or below the normal limits). Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.

[u] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug (Day 1), all adverse events should be reported until the final visit (Week 72 phone visit), or if applicable, until the early termination visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3).

[v] Record any concomitant ocular and systemic medications (i.e., any prescription medications, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated medications.

[w] Record all concurrent ocular procedures performed on the study or fellow eye.

[x] Ophthalmic examinations and efficacy assessments must be performed prior to dosing.

[y] Both eyes in all participants should be evaluated with the following assessments: eyelid measurement, iris pigmentation, pupillary examination, proptosis, slit-lamp examination, VA, intraocular pressure, indirect ophthalmoscopy, diplopia, motility restriction, clinical measures of severity, corneal staining, and CAS (see Section *8.1, Appendix 9 and Appendix 11)*. The findings should be captured in the eCRFs at all specified study visits.

[z] Investigators should ensure that the same base setting is used for individual participants each time the measurement is obtained.

[aa] Clinical Measures of Severity Assessments are outlined in *Appendix 12*.

[bb] Corneal staining will be graded using the Oxford Grading Scheme Chart (a 6-point scale that range from 0 to V; see Section *8.1.2.6* and Appendix *11*).

[cc] GO-QoL is a self-administered questionnaire (see Section *8.1.3.1 and Appendix A12–1.2)*. Questionnaire can be administered no more than 48 hours prior to study treatment administration.

[dd] OSDI is a questionnaire which will assess corneal/ocular surface symptoms and is designed to be administered by *healthcare* professionals to the participants (see Section *8.1.3.2* and Appendix *A12–1.1*).

[ee] Only at sites with MRI capabilities and for participants who consent to orbital MRI. Imaging should be performed no more than *72* hours prior to study treatment administration.

Table 1 Schedule of Activities (cont.)

[ff] Only at sites where facial photographs are permitted and feasible, and for participants who consent to facial photography. Facial photographs should be performed no more than 48 hours prior to study treatment administration.

[gg] *Study* drug will be administered from baseline to Week 44.

[hh] Not applicable for a site that has not been granted approval for optional RBR. Performed only for participants at participating sites who have provided written informed consent to participate.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, pharmacokinetics and pharmacodynamics of SC satralizumab, a recombinant, humanized anti-interleukin (IL)-6 receptor (IL-6R) monoclonal antibody, in patients with moderate-to-severe active and chronic inactive thyroid eye disease (TED), a complex orbital inflammatory autoimmune disorder. There remains an unmet medical need in patients with active moderate-to-severe TED and in those with chronic inactive TED. In the United States *and a few other countries*, IV teprotumumab is approved for the treatment of TED but it may not be universally successful or available and is associated with disease relapse or substantial side effects (Allen et al. 2021). In the rest of world, IV pulses of corticosteroids (CS) are the mainstay of treatment for active moderate-to-severe TED, but are also associated with disease relapses and substantial side effects (Patel et al. 2019). Additionally, there is no established medical treatment for chronic inactive TED other than surgical intervention.

2.2 BACKGROUND

2.2.1 Background on Thyroid Eye Disease

TED, also referred to as Graves' ophthalmopathy or orbitopathy (GO) or thyroid-associated orbitopathy, is a chronic inflammatory disorder predominantly associated with Graves' disease (Bartley 1994). While 90% of TED is associated with Graves' disease, 5% occurs in hypothyroid state and 5% in euthyroid individuals. The clinical presentation of TED is highly variable in severity, ranging from mild disease which may be self-limiting, to severe sight-threatening disease in 3–7% of cases (Wiersinga and Bartalena 2002; Barrio-Barrio et al. 2015). Moderate-to-severe disease can be associated with permanent visual impairment, as well as morphologic disfiguring changes to the face, related to proptosis, lid lag, and gaze disturbances, all of which impact patient quality of life (Gerding et al. 1997; Kahaly et al. 2002; Wiersinga 2012).

TED is an autoimmune disease and although the underlying pathophysiological mechanism is not completely understood, it is presumed to be mediated through the activation of orbital fibroblasts by autoantibodies directed against thyroid antigens, such as thyrotropin receptor (TSH receptor; TSHR) autoantibodies and insulin-like growth factor-1 receptor autoantibodies (Ezra et al. 2012). Typically, TED has a progressive (active) inflammatory phase, which eventually leads to the emergence of fibrosis and a mixed inflammatory or fibrotic phase followed by a stable (inactive) post-inflammatory phase. In the early, active inflammatory stages of TED, which are reported to typically last from up to 1 year (Bahn 2010) to 3 years (Douglas et al. 2022a), studies have found both focal and diffuse inflammatory infiltration of the orbital tissues. Extraocular and levator muscles, and adipose tissues are infiltrated by mononuclear cells such as CD4+ and CD8+T lymphocytes, B cells and macrophages (Weetman et al. 1989; Gupta and Douglas 2011; Khong et al. 2016). T cells produce inflammatory cytokines such as IL-2

and IL-6, interferon-γ and the tumor necrosis factors, activating the orbital fibroblasts which proliferate and produce collagen and glycosaminoglycans responsible for the tissue expansion seen in TED (Dik et al. 2016). In addition, orbital fibroblasts differentiate into new mature fat cells further increasing orbital tissue volume. In a disease of longer duration, the production of inflammatory mediators expands, as type 2 helper T-cells predominate and produce IL-5 and IL-10. Other inflammatory mediators such as IL-1, IL-6, IL-16, and transforming growth factor β [TGF-β]) are produced with the involvement of macrophages, fibroblasts, and adipocytes in the orbit as well (Bahn 2012).

Historically, the mainstay of treatment for active, moderate-to-severe TED consists of off-label use of oral or IV pulses of CSs (Kahaly et al. 2005; Bartalena et al. 2012). However, up to 40% of patients fail to respond to CS treatment (Terwee et al. 2005; Zang et al. 2011). Many patients experience significant side effects including hyperglycemia, hypertension, gastritis and weight gain, or suffer relapse of disease after the CS treatment stops (Patel et al. 2019). Alternative therapies consist of orbital radiotherapy, and immunomodulatory therapy (rituximab, tocilizumab, and azathioprine) used off-label in clinical practice.

Teprotumumab is currently approved in the United States *and other countries* for the treatment of TED regardless of TED activity or duration. While it provides clinical improvement in some patients, adverse events such as elevated blood glucose, alopecia, nausea, fatigue, hearing impairment, muscle spasm, diarrhea and change in menstrual cycle present a substantial burden. Additionally, relapse rates after cessation of teprotumumab in patients with active TED are quite high with rebound of proptosis and diplopia in approximately 40% and 50%, respectively (Allen et al. 2021; Douglas et al. 2022b). Due to the multiple side effects, limited efficacy to only a subset of patients, and relapse rates associated with the CS therapy as well as with teprotumumab, an unmet medical need remains in patients with moderate-to-severe TED for an alternative treatment option through disease modification accompanied by reduced risk of relapse and with an improved safety profile.

Furthermore, there is limited established medical treatment for chronic inactive TED and surgical intervention remains the mainstay of treating patients who continue to suffer from visual impairment, diplopia or disfiguring proptosis and keratopathy, with patients needing to wait at least 6 months or longer after reaching the inactive phase of their disease before having any reconstructive or rehabilitative procedures (Bartalena et al. 2016). These surgeries are often performed 2 to 6 months apart (Bartalena 2013b; Davies and Burch 2020), suggesting that patients may suffer the physical, psychological, and financial burden of multiple surgeries over a number of years (Ponto et al. 2013). Surgical procedures are often unsuccessful, leaving the patient with residual visual impairments such as diplopia (Barrio-Barrio et al. 2015). Furthermore, up to 11% of patients undergoing orbital decompression require repeat procedures (Zhang-Nunes et al. 2015).

Therefore, a new treatment option with a potentially disease modifying mechanism of action with long-term efficacy and with tolerable side effects administered via a convenient route of administration, is needed to address the needs of the TED patient population.

2.2.2 Background on Satralizumab

Satralizumab is a subcutaneously administered recycling humanized anti-IL-6R monoclonal antibody. Satralizumab shows pharmacological effects of IL-6R blockade at an every 4-week dosing frequency by SC injection, supported by its prolonged half-life compared with a typical IgG antibody, due to its recycling property. The drug achieves its pharmacological effects by binding to the IL-6R, thereby inhibiting IL-6 signaling and the actions of IL-6.

Satralizumab is approved for the treatment of patients with neuromyelitis optica spectrum disorder (NMOSD) who are aquaporin-4 (AQP4) antibody positive. In a limited number of countries, satralizumab was approved for the treatment of patients with NMOSD, irrespective of their AQP4-IgG serostatus.

Detailed information on satralizumab is provided in the Satralizumab Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of SC satralizumab, a recombinant, humanized anti-IL-6R monoclonal antibody to address a significant unmet medical need of patients with moderate-to-severe active and chronic inactive TED, a complex orbital inflammatory autoimmune disorder.

Inflammation mediates the pathogenesis of TED, during the initial active phase as well as the subsequent chronic mixed inflammatory or fibrotic phase, as the disease continues to evolve to the final quiescent stage. Evidence from a number of in vitro and ex vivo experiments support an important role of IL-6 and its receptor in the disease, suggesting the potential of satralizumab as a novel drug for treatment of TED. Patients with active TED have higher levels of serum IL-6R than those with inactive TED (Slowik et al. 2012). IL-6 also increases the expression of TSHR in orbital fibroblast pre-adipocytes (Dik et al. 2016). Polymorphisms in the IL-6 gene are thought to be involved in the predisposition to and development of TED (Anvari et al. 2010). Further, in vitro and ex vivo data have demonstrated a role for IL-6 in TED by showing that IL-6 expression from orbital tissue correlates with orbital tissue expansion (Hiromatsu et al. 2000). IL-6 has the ability to increase TSHR mRNA levels in cultured orbital fibroblasts of patients with TED. In addition, autoantibodies against TSHR increase IL-6 expression in orbital pre-adipocyte fibroblasts and IL-6 secretion by mature adipocytes (Kumar et al. 2010).

There are no clinical data available where satralizumab is used for the treatment of TED; however, clinical trial results from academic investigator led studies and series with systemic administration of anti-IL6R antibody, tocilizumab, support an important role of IL-6 and its receptor in TED (Pérez-Moreiras et al. 2014; Pérez-Moreiras et al. 2018; Sánchez-Bilbao et al. 2020).

Furthermore, there is limited established medical treatment for chronic inactive TED and surgical intervention remains the mainstay of treating patients who continue to suffer from visual impairment, diplopia or disfiguring proptosis and keratopathy, with patients needing to wait at least 6 months or longer after reaching the inactive phase of their disease before having any reconstructive or rehabilitative procedures (Bartalena et al. 2016).

Satralizumab has demonstrated efficacy and safety in its approved indication of NMOSD. In the two Phase III studies in NMOSD, satralizumab every 4 weeks (Q4W) as monotherapy (BN40900) or in combination with immunosuppressive therapies (ISTs) (BN40898) was generally safe and well tolerated by patients with NMOSD.

Satralizumab has not yet been tested in patients with TED. However, it is expected that the safety profile of satralizumab in patients with TED would be consistent with its class effect as an IL-6R inhibitor. All necessary measures will be taken to closely monitor the safety of the participants enrolled in this study.

Taking into account the potential for efficacy in patients with moderate-to-severe TED for whom there is a high unmet medical need, the safety profile for satralizumab, and the risk-mitigation measures for this study, the benefit–risk ratio is expected to be acceptable for satralizumab in the treatment of TED. Refer to Appendix 4 for information on anticipated risks for satralizumab, and risk mitigation measures, including guidelines for managing adverse events associated with satralizumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of satralizumab may be found in the satralizumab Investigator's Brochure.

2.3.1 Assessment Impact of COVID-19 on Benefit–Risk

An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment of this study protocol, including, but not limited to, the patient population under study, study treatment and/or treatment combination being evaluated. Based on that assessment, the safety monitoring, management guidelines, and the risk-mitigation measures provided in the study protocol are considered adequate.

An assessment was conducted to determine whether there is any impact of the COVID-19 vaccines on the benefit-risk assessment of this study protocol.

General information for vaccines as provided in Section 6.8 (Concomitant Therapy) and Appendix 4 (Safety Plan) are also applicable to COVID-19 vaccines. Based on this assessment, no additional risk-mitigation measures related to COVID-19 are proposed at this time. The recommendations and management plan provided in the study protocol are considered adequate.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of satralizumab compared with placebo in participants with moderate-to-severe TED.

Table 2 presents the primary and key secondary objectives for the study expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (ICH 2020). Table 3 presents the remaining objectives and corresponding endpoints.

Table 2 Primary and Key Secondary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
• To evaluate the efficacy of subcutaneous satralizumab compared with placebo at Week 24	• Population: adult participants with TED (active disease for primary hypothesis) as defined by the study inclusion and exclusion criteria. • Variable: proportion of participants achieving ≥2mm reduction in proptosis from baseline (Day 1) at Week 24 in the study eye, provided there is no deterioration of proptosis (≥2mm increase) in the fellow eye • Treatment (as randomized): – Experimental: satralizumab SC [redacted] mg, [redacted] mg, or [redacted] mg (for bodyweight [redacted] respectively), at Day 1, Week 2, and Week 4 (loading doses) and maintenance doses Q4W thereafter until Week 20. Seven doses in total during the 24-week Part I period – Control: placebo SC at Day 1, Week 2, and Week 4 (loading doses), and maintenance doses Q4W thereafter until Week 20. Seven doses in total during the 24-week Part I period • Intercurrent events and handling strategies: – Early discontinuation of study treatment due to AEs or lack of efficacy: treatment policy strategy – Use of any prohibited systemic treatment or prohibited therapy for either eye (study eye or fellow eye): evaluated as non-responder – Administration of rescue treatment: evaluated as non-responder – Orbital or ocular surgery for TED (e.g., orbital decompression, eyelid or strabismus surgery) in either eye (study eye or fellow eye): evaluated as non-responder • Population-level summary: difference in proportions of proptosis responders at Week 24 between the satralizumab and placebo group

Table 2 Primary and Key Secondary Objectives and Corresponding Estimands (cont).

Key Secondary Objectives	Estimand Definition
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on proptosis response	• Population: adult participants with TED (active and chronic inactive disease) as defined by the study inclusion and exclusion criteria • Variable: proportion of participants achieving ≥2 mm reduction in proptosis from baseline (Day 1) at Week 24 in the study eye provided there is no corresponding deterioration in proptosis (≥ 2 mm increase) in the fellow eye • Treatment: as defined above • Intercurrent events and handling strategies: as in primary estimand definition • Population-level summary: difference in proportions of proptosis responders in overall (active and chronic inactive) population at Week 24 between the satralizumab and placebo arm
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on change in proptosis	• Population: adult participants with TED (active disease) as defined by the study inclusion and exclusion criteria • Variable: Change from baseline (Day 1) in proptosis at Week 24 • Treatment: as defined above • Intercurrent events and handling strategies: intercurrent events as defined above. A treatment policy strategy will be applied to all intercurrent events • Population-level summary: least square mean difference between the satralizumab and placebo group
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on change in proptosis	• Population: adult participants with TED (active and chronic inactive disease) as defined by the study inclusion and exclusion criteria • Variable: change from baseline (Day 1) in proptosis at Week 24 • Treatment: as defined above • Intercurrent events and handling strategies: intercurrent events as defined above. A treatment policy strategy will be applied to all intercurrent events • Population-level summary: least square mean difference between the satralizumab and placebo group

Table 2 Primary and Key Secondary Objectives and Corresponding Estimands (cont).

Key Secondary Objectives (cont.)	Estimand Definition
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on reduction/improvement in diplopia	• Population: in subset of active TED participants as defined by the study inclusion and exclusion criteria with baseline (Day 1) diplopia > 0 • Variable: proportion of participants achieving ≥ 1 grade reduction/improvement in diplopia at Week 24 • Treatment: as defined above • Intercurrent events and handling strategies: as in primary estimand definition • Population-level summary: difference in proportions of participants achieving ≥ 1 grade reduction/improvement in diplopia at Week 24 between the satralizumab and placebo group
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on reduction/improvement in diplopia	• Population: in subset of overall (active and chronic inactive) TED participants as defined by the study inclusion and exclusion criteria with baseline (Day 1) diplopia > 0 • Variable: proportion of participants achieving ≥ 1 grade reduction/improvement in diplopia at Week 24 • Treatment: as defined above • Intercurrent events and handling strategies: as in primary estimand definition • Population-level summary: difference in proportions of participants achieving ≥ 1 grade reduction/improvement in diplopia at Week 24 between the satralizumab and placebo group
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on improvement in orbital pain	• Population: in subset of active TED participants as defined by the study inclusion and exclusion criteria with motility-induced pain at baseline (Day 1) in the study eye • Variable: proportion of participants achieving absence of motility-induced pain at Week 24 • Treatment: as defined above • Intercurrent events and handling strategies: as in primary estimand definition • Population-level summary: difference in proportions of participants with absence of motility-induced pain at Week 24 between the satralizumab and placebo group

Table 2 Primary and Key Secondary Objectives and Corresponding Estimands (cont).

Key Secondary Objectives (cont.)	Estimand Definition
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on improvement in orbital pain	• Population: in subset of active TED participants as defined by the study inclusion and exclusion criteria with spontaneous pain at baseline (Day 1) in the study eye • Variable: proportion of participants achieving absence of spontaneous pain at Week 24 • Treatment: as defined above • Intercurrent events and handling strategies: as in primary estimand definition • Population-level summary: difference in proportions of participants with absence of spontaneous pain at Week 24 between the satralizumab and placebo group

AE = adverse event; SC = subcutaneous; Q4W=Every 4 weeks; TED = thyroid eye disease.
Note: Unless otherwise noted, all ocular efficacy analyses are for the study eye only.

Table 3 Other Secondary and Exploratory Objectives and Endpoints

Other Secondary Objectives and Endpoints	
Efficacy Objectives	**Corresponding Endpoints**
• To assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24 based on health-related quality of life	• Proportion of participants with a ≥ 6 point improvement in the Visual Functioning and Appearance subscale scores of the GO-QoL from baseline at Week 24
• To further assess the efficacy of subcutaneous satralizumab at Week 24	• Proportion of participants with active disease achieving overall response at Week 24, defined as a ≥2-point reduction in CAS, AND a ≥2 mm reduction in proptosis from baseline (Day 1) in the study eye, provided there is no corresponding deterioration in CAS or proptosis (≥2 point/mm increase) in the fellow eye • Proportion of participants with active disease achieving a ≥2-point reduction in CAS in the study eye from baseline (Day 1) to Week 24 • Proportion of participants achieving a CAS value of 0 or 1 in the study eye (indicating no or minimal inflammation, respectively) at Week 24 • Proportion of participants with a ≥10-point improvement in the OSDI overall scores across all levels of baseline severity at Week 24 • Change from baseline (Day 1) in the OSDI Ocular Symptoms, and Vision-related Function subscale scores at Week 24 • Change in Oxford corneal staining scores from baseline (Day 1) at Week 24[b]

Table 3 Other Secondary and Exploratory Objectives and Endpoints (cont.)

Efficacy Objectives	Corresponding Endpoints
• To assess the efficacy of subcutaneous satralizumab at Week 48 in those participants who are proptosis *non-* responders at Week 24	• Proportion of participants achieving ≥2mm reduction in proptosis at Week 48 in the study eye (provided there is no corresponding deterioration in proptosis [≥ 2 mm increase] in the fellow eye). • Proportion of participants achieving overall response at Week 48, defined as a ≥ 2-point reduction in CAS, AND a ≥ 2 mm reduction in proptosis from baseline (Day 1) in the study eye, provided there is no corresponding deterioration in CAS or proptosis (≥ 2 point/mm increase) in the fellow eye • Proportion of participants achieving a ≥ 2-point reduction in CAS in the study eye from baseline (Day 1) to Week 48 • In the subset of participants with baseline (Day 1) diplopia (> 0): Proportion of participants achieving Grade ≥ 1 reduction/improvement in diplopia at Week 48. • Proportion of participants with a ≥ 6-point improvement in the Visual Functioning and Appearance subscale scores of the GO-QoL from *Week 24 at* Week 48 • *Proportion of participants with a ≥ 6- point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from baseline (Day 1) to Week 48* • Change in proptosis from baseline (Day 1) to Week 48 • Proportion of participants requiring surgical intervention for TED up to Week 48

Table 3 Other Secondary and Exploratory Objectives and Endpoints (cont.)

Efficacy Objectives	Corresponding Endpoints
• To assess the efficacy of subcutaneous satralizumab at Week 48 in those participants who are proptosis responders at Week 24	• Proportion of participants with worsening of proptosis by ≥2 mm from Week 24 to Week 48 • Proportion of participants with worsening of proptosis by ≥2 mm from baseline (Day 1) to Week 48 • Change in proptosis from Week 24 to 48 • Change in CAS from Week 24 to 48 • Proportion of participants with a ≥6-point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from Week 24 at Week 48 • *Proportion of participants with a ≥6- point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL from baseline (Day 1) to Week 48* • Change in proptosis from baseline (Day 1) to Week 48 • Change in CAS from baseline (Day 1) to Week 48 • Proportion of participants requiring surgical intervention for TED up to Week 48

Table 3 Other Secondary and Exploratory Objectives and Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of satralizumab	• Incidence, seriousness, and severity of AEs, with severity determined according to NCI CTCAE V5 • Change from baseline (Day 1) in vital signs, targeted clinical laboratory test results, ECG parameters, and body weight
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the satralizumab PK profile by evaluating plasma exposure over 24 weeks • To evaluate potential relationships between drug exposure and the efficacy and safety of satralizumab	• Serum concentration of satralizumab at specified timepoints • Estimates of primary PK parameters (e.g., CL/F and V/F) and secondary PK parameters (e.g., AUC) derived using popPK modeling • Relationship between selected covariates and exposure to satralizumab • Relationship between serum concentration or PK parameters for satralizumab and efficacy endpoints, and safety endpoints
Exploratory Objectives and Endpoints	
Efficacy Objectives	**Corresponding Endpoints**
• To further assess the efficacy of subcutaneous satralizumab compared with placebo at Week 24	• Change in CAS from baseline (Day 1) to Week 24 • Proportion of participants requiring orbital decompression surgery or any form of reconstructive surgery from baseline (Day 1) to Week 24 • Change in the motility component on the Clinical Measures of Severity scale (based on EUGOGO consensus) from baseline (Day 1) to Week 24 • Proportion of participants with improvement for each component of the Clinical Measures of Severity scale (based on EUGOGO consensus) from baseline (Day 1) to Week 24 • Proportion of participants at each overall response level at Week 24 (high responders, responders, low responders and non-responders [a]) • Evaluation of each individual component of CAS at Week 24 • In the subset of participants with baseline (Day 1) orbital MR imaging, change in extraocular muscle and fat volume from baseline (Day 1) to Week 24 • Change in VA from baseline at Week 24

Table 3 Other Secondary and Exploratory Objectives and Endpoints (cont.)

Efficacy Objectives	• Corresponding Endpoints
To assess the efficacy of subcutaneous satralizumab compared with placebo in participants with chronic inactive TED at Week 24	• Proportion of participants achieving ≥ 2 mm reduction in proptosis from baseline (Day 1) at Week 24 • Change in proptosis from baseline to Week 24 • Proportion of participants with a ≥ 6-point improvement in the Visual Functioning and Appearance sub-scale scores of the GO-QoL at Week 24 • Proportion of participants achieving ≥ 1 grade reduction/improvement in diplopia at week 24
To further assess the efficacy of subcutaneous satralizumab compared with placebo at Week 48	• Change in CAS from baseline (Day 1) to Week 48 • In the subset of participants with active TED at baseline (Day 1): Time to first achieving CAS value of 0 or 1 in the study eye (indicating no or minimal inflammation, respectively) from baseline (Day 1) to Week 48 • Proportion of participants requiring orbital decompression surgery or any form of reconstructive surgery from baseline (Day 1) at Week 48 • Change in the motility component on the Clinical Measures of Severity scale (based on EUGOGO consensus) from baseline (Day 1) to Week 48 • Proportion of participants with improvement for each component of the Clinical Measures of Severity scale (based on EUGOGO consensus) from baseline (Day 1) to Week 48 • Proportion of participants at each overall response level at Week 48 (high responders, responders, low responders and non-responders [a]) • Evaluation of each individual component of CAS at Week 48 • In the subset of participants with baseline (Day 1) orbital MR imaging, change in extraocular muscle and fat volume from baseline (Day 1) to Week48 • Change in VA from baseline at Week 48 • Proportion of participants with a ≥10-point improvement in the OSDI overall scores across all levels of baseline severity at Week 48 • Change from baseline (Day 1) in the OSDI Ocular Symptoms, and Vision-related Function subscale scores at Week 48 • Change in Oxford corneal staining scores from baseline (Day 1) at Week 48[b]

Table 3 Other Secondary and Exploratory Objectives and Endpoints (cont.)

To further assess the efficacy of subcutaneous satralizumab compared with placebo at Week 72	Proportion of participants requiring medical therapy, orbital decompression surgery or any form of reconstructive surgery for TED from Week 48 through Week 72
Pharmacodynamic Objective	**Corresponding Endpoint**
To evaluate the pharmacodynamics of satralizumab	• Absolute values and change from baseline in serum levels of biomarkers IL-6 and soluble IL-6 receptor
Immunogenicity Objective	**Corresponding Endpoint**
To evaluate the immune response to satralizumab	• Prevalence of ADAs at baseline (Day 1) and incidence of ADAs during the study
To evaluate potential effects of ADAs on efficacy, biomarker, safety, and PK endpoints	• Relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objectives	**Corresponding Endpoints**
To identify and/or evaluate biomarkers that are predictive of response to satralizumab, can provide evidence of satralizumab activity, or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in circulation that may include thyroid receptor auto-antibodies and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; AE = adverse event; AUC = area under the concentration–time curve; CAS = clinical activity score; EUGOGO = European Group on Graves Orbitopathy; GO-QoL = Graves' Ophthalmopathy Quality of Life; CL = clearance; IL-6 = interluekin-6; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; OSDI = ocular surface disease index; PK = pharmacokinetic; popPK = population pharmacokinetics; TED = thyroid eye disease; V/F = apparent volume of distribution.

[a] Participants will be classified into one of four response categories (CAS changes are measured on a 7-item scale) for the exploratory endpoint. Participants that meet criteria for several response categories will be allocated to the highest possible category. The handling of missing values will be discussed in the SAP.

- High responders are participants who had a reduction in both proptosis (≥ 2 mm) and CAS (≥ 2 points) from baseline (Day 1) in the study eye, and no deterioration in the fellow eye (i.e., increase in CAS ≥ 2 points or increase in proptosis ≥ 2 mm).
- Responders are participants who had a reduction in either proptosis (≥2 mm) or (but not "and") CAS (≥ 2 points) from baseline (Day 1) in the study eye (but no worsening in the other respective endpoint (proptosis or CAS as defined above in the study eye, and no deterioration in the fellow eye [as defined above]).
- Low responders are participants who had a reduction in either proptosis (< 2mm) or (but not "and") CAS (< 2 points) from baseline (Day 1) in the study eye (but no worsening in the other respective endpoint (proptosis or CAS as defined above in the study eye, and no deterioration in the fellow eye [as defined above]).
- Non-Responders are participants who did not fit into any of the above categories

[b] The scale in the Oxford grading scheme chart categorizes corneal staining into 6 groups according to severity: 0 = absent; I = minimal; II = mild; III = moderate; IV = marked; and V = severe. The observer will compare the overall appearance of the participant's corneal staining with the reference figure in Appendix *11*. The observer should select the appropriate grade that best represents the state of corneal staining. The staining score will be recorded for the exposed interpalpebral cornea and conjunctiva.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This Phase III, randomized, double-masked, placebo-controlled, multicenter study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo for the treatment of patients with moderate-to-severe active and chronic inactive TED.

The study includes the following phases:

- Screening period (up to 28 days long): During the screening period, individuals' eligibility will be evaluated for study participation. The screening period may be extended in exceptional circumstances but cannot exceed 42 days.
- Placebo-controlled treatment periods: this will be split into two parts:
  - Part I: Weeks 1–24; with study treatment administered until Week 20, and primary endpoint assessed at Week 24
  - Part II: Weeks 24–48, with study treatment administered until Week 44, and an analysis conducted at Week 48.

    The final visit of Part I coincides with the first visit of Part II (Week 24). At this visit, response to treatment will be assessed. Proptosis non-responders from either arm will receive satralizumab treatment in Part II. Proptosis responders from either arm will be re-randomized to satralizumab or placebo in Part II, regardless of their original treatment assignment.
- Follow-up period: Weeks 48–72. Participants will be assessed every 2 months through telephone calls.

The primary endpoint will be assessed at Week 24, followed by an analysis at Week 48, and a final analysis will be conducted at Week 72. Figure 1 presents an overview of the study design. A schedule of activities is provided in Section 1.3.

4.1.1 Overview of Study Design

Approximately 120 participants who meet the study eligibility criteria will be randomized on Day 1 in a 1:1 ratio (stratified by current smoking status [current smoker, including the use of e-cigarettes vs. former smoker vs. never smoked] and TED disease activity status [active vs. inactive]) to receive seven SC doses of either satralizumab (with dosing based on body weight [redacted] or matching placebo in Part I. [redacted]

All participants will be allowed to receive rescue intervention per investigator's discretion from Week 4 through the end of the study per the following criteria:

- Diagnosis of sight-threatening disease for which prompt intervention is indicated in the opinion of the investigator, evidenced by:

- Dysthyroid optic neuropathy, or
- Corneal ulceration (defined as a deep corneal erosion which extends through epithelium and Bowman's membrane into corneal stroma)

Participants who receive rescue intervention between Weeks 4 and 48 will be discontinued from the study drug administration but will be encouraged to remain in the study to follow the protocol-defined schedule of activities, with a particular emphasis on the Week 24 and 48 visits, if possible. This will allow for monitoring of participants as well as collection of end-of-study data.

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for *three re*-screening *opportunities* (for a total of *four* screenings per individual) at the investigator's discretion. At re-screening, a new screening number will be assigned to each individual and all screening visit assessments will be performed *(except for TB test and optional ECG if they were within normal limits at screening).* Individuals *do not need to* re-sign the consent form *before rescreening* unless *a new version of* the consent form *has been implemented at the site*. The investigator will record reasons for screen failure.

Only one eye will be assigned as the study eye at Day1/baseline. If both eyes are considered eligible, the eye with the worse severity, as assessed at baseline by evaluation of proptosis, diplopia, pain and other clinical measures of severity, will be selected as the study eye unless the investigator deems the other eye to be more appropriate for treatment in the study. If both eyes have the same severity of disease, the investigator will choose the most appropriate eye as the study eye.

During the study, efficacy measures are investigator-assessed proptosis (measured using a Hertel exophthalmometer instrument provided by the Sponsor for consistency in measurement), and Clinical Activity Score (CAS; 7-item scale). To ensure consistency in measurement, it is of *utmost* importance to have the same observer evaluating proptosis and CAS for the entire duration of the study, and in particular for the baseline, Week 24 and Week 48 visits. Disease severity will be assessed using clinical measures of severity based on the European Group on Grave's Orbitopathy (EUGOGO) consensus statement (Bartalena et al. 2021). Health-related quality of life will be assessed using the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire. Signs of ocular surface/corneal involvement will be assessed using fluorescein staining of the ocular surface and graded on a slit-lamp biomicroscope using the Oxford Grading Scheme Chart. Symptoms of dry eye affecting the ocular surface and their impact on visual function will be assessed with the Ocular Surface Disease Index (OSDI) questionnaire. In addition, standard ophthalmological examination assessing visual acuity, eyelid position, pupillary reaction and retina will be performed. Safety will be monitored via adverse events, vital signs, laboratory parameters, ECGs, and concomitant medication use. Refer to Section 8.2 for details on the safety assessments. All the efficacy and ophthalmic assessments from baseline (Day 1) through Week 48 (for

the primary, key secondary, secondary, and exploratory endpoint analyses) must be done prior to administration of the *investigational medicinal product* dose at the same visit.

4.1.1.1 Part I Period

During Part I, eligible participants will be randomized to receive either satralizumab [redacted] based on body weight) or matching placebo on Day 1 and at Weeks 2, 4, 8, 12, 16, and 20, with a final visit of the Part I period at Week 24. The treatment which participants receive will be assigned via interactive voice or web-based response system (IxRS).

4.1.1.2 Part II Period

After the 24-week treatment period in Part I, participants will enter a second treatment period called Part II. The treatment which participants receive in Part II of the study will be assigned via IxRS and is determined by their proptosis response at the end of Part I (Week 24 primary endpoint):

- Participants who are proptosis non-responders at Week 24 will receive satralizumab treatment during Part II (Weeks 24–44).
- Participants who are proptosis responders at Week 24 will be re-randomized in a 1:1 ratio (using the original randomization stratification factors measured at baseline (smoking status and TED disease activity status) to receive SC satralizumab (with dosing based on body weight [redacted]) or matching placebo (Weeks 24–44), regardless of their original treatment assignment in Part I.
  - *Note:*
    - *The Week 24 visit must be recorded in IxRS for the re-randomization at Week 24 to occur. If the Week 24 visit is out of window, the subsequent visits in Part II will not align with the visit days listed in Table 1 , since these are based on the Week 24 visit occurring on Day 169 ± 7 days.*
    - *In such cases where the participant's Week 24 visit is delayed, the site should use the IxRS visit window (and not the visit window in Table 1) for scheduling patient's subsequent visits in Part II, since the date of all subsequent visits in Part II would be based on the actual date of the Week 24 visit (Day 1 of Part II).*
- Participants that discontinue the study drug in Part I but choose to stay in the trial for Part II will not be re-randomized and will not receive any further study treatment (satralizumab/placebo). These participants will continue to be followed in the study in order to monitor for safety and collect end of study data; during this time, they will be able to receive standard of care at the investigator's discretion.

During Part II of the study, the participants and the study staff will remain masked to the treatment the participants received during Part I of the study.

Due to the study design, participants who received placebo during Part I and receive satralizumab in Part II will receive a loading dose of satralizumab at Week 26; participants who received satralizumab in Part I and receive satralizumab in Part II do not require a loading dose and will receive placebo at Week 26.

The final visit at Week 48 in Part II (4 weeks after the final dose) is the last in-person visit of the study; subsequent follow up visits will be conducted by telephone (see Section 4.1.1.3).

4.1.1.3 Follow-up Period

After Week 48, participants will enter a 6-month telephone follow-up period. The patient will be contacted every 2 months (i.e., at Weeks 56, 64, and 72) for a telephone follow-up visit, to review adverse events, concomitant treatments, and any treatments or surgery received for TED.

If the patients choose to visit the study site in-person during the 'telephone follow-up period', the same information that would be collected from telephone conversation will be obtained; no other data will be recorded on the eCRF.

Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used. The iDMC will monitor patient safety on an ongoing basis. The iDMC will perform periodic unmasked safety reviews and make recommendations to the Sponsor on trial continuation or modification. The final decisions will rest with the Sponsor.

All summaries and analyses will be prepared by an independent Data Coordinating Center (iDCC) and presented by treatment group for the iDMC's review. Members of the iDMC and iDCC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities. The Sponsor will share unmasked primary endpoint data with the iDMC after readout. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1).

4.1.2 Patient Input into Study Design

Representatives from different organizations within the patient community were interviewed and asked to provide feedback on the following aspects of the study:

- Study design, endpoints, inclusion and exclusion criteria activities, and participant reported outcomes (PROs)
- Recruitment and retention (e.g., inclusivity of underserved patient communities, potential recruitment challenges, possible retention challenges)

This feedback was taken into consideration when developing the protocol.

4.2 RATIONALE FOR STUDY DESIGN

A multicenter, randomized, double-masked, placebo-controlled design was selected to minimize the bias in the evaluation of SC satralizumab as a treatment for patients with moderate-to-severe TED.

To ensure the safety of all participants during the study, several safety assessments have been included (e.g., regular ophthalmic monitoring, adverse event monitoring [ocular and systemic], and laboratory safety tests). See Section 8 for a description of study assessments.

4.2.1 Rationale for Study Population

As mild TED is often self-limiting and can spontaneously improve, the study will enroll patients with moderate-to-severe (active and chronic inactive) disease that will be defined according to the EUGOGO criteria for severity assessment of two or more of the following:

- Lid retraction ≥2 mm,
- Moderate or severe soft tissue involvement,
- Exophthalmos ≥3 mm above normal for race and gender
- Inconstant or constant diplopia

Eligible participants must be adults, aged ≥18 years at baseline (Day 1). Pediatric population will not be enrolled into this study because TED is a rare condition in children and when it does occur, it is mild in severity and self-limiting. In addition, TED in children is largely amendable to restoration of thyroid function and local supportive therapy.

Study participants will be required to be euthyroid or mildly hyperthyroid or hypothyroid at the baseline visit, based on the measurement of normal free thyroid hormone concentrations. This criterion is meant to eliminate a potential bias due to the impact of systemic hyper- or hypo-thyroidism on the satralizumab versus placebo comparison.

The proposed study will include patients with active and chronic inactive TED, [redacted]

[redacted]

4.2.2 Rationale for Control Group

In this study, placebo will be used as the comparator to evaluate the efficacy and safety of SC satralizumab from baseline (Day 1) through Week 24 (Part I); placebo will also be the comparator used in Part II, where proptosis responders at Week 24 will be re-randomized to satralizumab or placebo and treated through Week 44.

Globally, systemic corticosteroids are used as an off-label treatment option in TED, and remain the mainstay of management for active, moderate-to-severe TED because of their rapid anti-inflammatory and immunosuppressive effects in some patients at high doses (Gillespie et al. 2012; Bartalena et al. 2016). Even in the United States *and countries* where teprotumumab has been approved, off-label oral or IV CS therapy continues to be used as the first line therapy (followed by off-label SC or IV tocilizumab or radiation as a second line option at some clinics), due to less tolerability of teprotumumab treatment, and complexities in coordinating care with infusion centers. The treatment response to CSs is not always consistent, as a large proportion of patients (up to 40%) still experience disease progression (Bartalena et al. 2012) or do not respond to CS therapy at all requiring one or more surgical interventions (Zang et al. 2011). CSs may even mediate adipogenesis, possibly contributing to the expansion of orbital fat in TED and worsening the disease (Draman and Ludgate 2016), and long-term side effects associated with high dose CS treatment can include hepatotoxicity, Cushing syndrome, osteoporosis (of particular concern in women), increased risk of serious infections, glaucoma, diabetes mellitus, and other severe consequences. Given the substantial burden from the use of CSs, the Sponsor considers placebo as a comparator for this study. In addition, the route of administration of CSs would limit masking to treatment assignment if used as a comparator in the study. To address any ethical considerations and mitigate any potential risks to study participants, all enrolled participants will be eligible for rescue intervention from Week 4 based on protocol-defined criteria as described in Section 6.1.2.

Furthermore, in patients with chronic inactive TED, there is currently limited established medical treatment. Inactive disease is less amenable to available medical treatments that are used for the active stage. Surgical intervention remains the mainstay of treating patients with chronic inactive TED but is often unsuccessful or has to be repeated in a series of procedures over a long period of time. Therefore, the use of CSs would be less suitable in this population.

This study will be a multicenter, global Phase III study, and as satralizumab is administered subcutaneously, teprotumumab IV infusions would not be an acceptable comparator for multiple reasons, including the different route of delivery and the fact that

teprotumumab is approved *only* in *a few* countries outside of the United States for treatment of TED. Additionally, this study is recruiting patients with both active and chronic inactive TED, and the most robust data available with teprotumumab in TED are in patients with active disease; there is currently more limited evidence on teprotumumab's effectiveness in the population with chronic inactive TED. Even in patients with active TED, approximately 40% of teprotumumab treated patients who initially responded do experience disease relapse as their disease transitions from active to the chronic inactive phase. Serious and frequent adverse events, some occurring in up to approximately 25% patients treated with teprotumumab, such as hearing impairment, elevated blood glucose levels, alopecia, nausea, muscle spasm, diarrhea and changes in menstruation further limit the use for only a subset of patients who accept these risks. An additional challenge with teprotumumab is that its long-term safety profile has not yet been established (Highland et al. 2021; Yu et al. 2021; Belinsky et al. 2022; Chow and Silkiss 2022; Sears et al. 2022; Ding et al. 2022). Teprotumumab route of delivery would also present with masking related challenges limiting its consideration as a comparator. Overall, the limited efficacy data, the relapse rates, the current safety profile associated with teprotumumab, make this agent unsuitable for use as a comparator because it is not well established as a standard of care, and many questions including its long-term efficacy and safety profile remain unanswered.

Despite treatment with the currently available options, patients with TED do not fully recover, continue to suffer and ultimately have to undergo surgery or a series of surgical procedures to correct the signs and symptoms of TED. Due to the limitations of currently available treatments in TED, placebo is considered as the appropriate comparator in this study (in Part I and re-randomized participants in Part II) to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of SC satralizumab. To ensure patient's safety, all study participants will be eligible for rescue intervention from Week 4 based on protocol-defined criteria as described in Section 6.1.2.

4.2.3 Rationale for Primary Endpoint Selection

The primary objective of the proposed Phase III study is to evaluate the efficacy of satralizumab compared with placebo, and the proposed primary efficacy endpoint is proptosis response defined as the proportion of participants achieving a $\geq$2mm reduction in proptosis from baseline (Day 1) at Week 24 in the study eye (i.e., the eye with greater proptosis) provided there is no corresponding deterioration in proptosis ($\geq$2mm increase) in the fellow eye. The changes in PR over time to support the primary endpoint variable will be measured with a Hertel exophthalmometer instrument provided by the Sponsor. To ensure consistency in measurement, it is of *utmost* importance to have the same observer evaluating proptosis for the entire duration of the study, and in particular for the baseline, Week 24 and Week 48 visits.

Some of the clinical symptoms and signs of TED can be explained mechanically by the discrepancy between the increased volume of the orbital tissues and the fixed volume of

the bony orbit. The expanded orbital tissues displace the globe forward and impede venous outflow from the orbit. These changes, combined with the local production of cytokines and other mediators of inflammation, result in pain, proptosis, periorbital edema, conjunctival injection, and chemosis among other signs and symptoms.

One published, randomized, double-masked, placebo-controlled trial that investigated the efficacy of anti-IL-6R monoclonal antibody (tocilizumab) in patients with active, moderate-to-severe CS-resistant TED demonstrated a reduction in proptosis at Week 16 in 93% of patients compared with 47% on placebo (Pérez-Moreiras et al. 2018). Efficacy was also demonstrated with a change in CAS of at least 2 points from baseline to Week 16, which was achieved in 93% of patients receiving tocilizumab versus 59% receiving placebo. Another study, which was prospective, interventional, and non-randomized investigated the use of tocilizumab 8 mg/kg IV Q4W for the treatment of CS-refractory, active (CAS $\geq$ 4) TED in 18 patients. Results demonstrated a reduction in proptosis in 72% of patients, with 83% experiencing improvement in extraocular motility, and resolution of diplopia in 54% of patients. All patients had a significant progressive CAS improvement (mean CAS score reduction 5.89 [$\pm$ 1.4] points, $p < 0.00027$). The improvement in the CAS was stable in all cases up to 27 months, with a minimum follow-up period of 9 months (Pérez-Moreiras et al. 2014).

The disruption of the inflammatory cascade with the corresponding decrease in adipogenesis and extracellular matrix formation mediated by anti-IL-6R blockade with satralizumab is expected to result in improvement of proptosis and CAS signs and symptoms. Unlike CS IV pulses and teprotumumab IV treatment options, which are given over a short-term, leading to a significant rate of TED relapse, continued satralizumab SC dosing is expected to provide an improved benefit–risk profile with improved control of inflammation over the longer term, potentially reducing the need for surgical interventions or secondary treatments.

Based on the heterogeneity of the study population that includes patients with active and chronic inactive TED, the Sponsor proposes PR as the appropriate primary efficacy endpoint in the Phase III study. While the CAS endpoint considers multiple clinical parameters including inflammation driven symptoms, PR is based solely on the change in proptosis. Because the degree of inflammation is decreased in chronic inactive TED, the use of CAS as opposed to PR would result in a more heterogeneous response, thus less representative of the treatment effect relevant to the need in this population.

Furthermore, PR has been consistently used as a primary efficacy endpoint in other clinical trials that investigated the efficacy and safety of treatments in patients with moderate-to-severe TED in active, chronic inactive, as well as mixed population studies.

Overall, the Sponsor considers PR as the currently best assessment to reliably assess efficacy in the target patient population composed of patients with active and chronic inactive TED.

4.2.4 Rationale for Biomarker Assessments

The study will assess whether biomarkers can aid in characterizing the mechanism of action of satralizumab in TED, provide evidence of pharmacodynamic activity of satralizumab in TED, or increase the knowledge and understanding of TED disease biology. Exploratory biomarker samples will be used for research purposes to identify pathway and/or disease biomarkers including but not limited to those reflective of inflammation. PD biomarker samples will be collected for the assessment of target engagement (e.g., IL-6 and soluble IL-6R [sIL-6R]) in response to satralizumab treatment.

4.2.5 Rationale for Rescue Therapy

Participants in both treatment groups will be allowed to receive rescue intervention *for the study eye* at any time from Week 4 through the end of the study, per the following protocol pre-specified rescue criteria:

- Diagnosis of sight-threatening disease for which prompt intervention is indicated in the opinion of the investigator, evidenced by:
  - Dysthyroid optic neuropathy, OR
  - Corneal ulceration (defined as a deep corneal erosion which extends through epithelium and Bowman's membrane into corneal stroma)

The rescue administration criteria are proposed to guarantee the participant's safety and to avoid any delay in appropriate management of sight-threatening disease. In addition, any participant that demonstrates worsening of disease (sight-threatening disease) between screening and baseline will not be enrolled into the study, and will be eligible to receive standard of care.

The choice of rescue intervention will be at the discretion of the investigator according to her or his best medical judgment and could include systemic, local or topical pharmacological approach, radiotherapy, and/or surgical management. Based on their best medical judgment, investigators can place participants on standard-of-care treatment at any time and discontinue them from the study drug if he or she determines that the condition has been deteriorating and the participant's health is at risk.

The date, time, name, dose and route of rescue medication, or type of surgical or radiotherapy procedure will be recorded in the participant's medical chart and in the study electronic Case Report Form (eCRF). The number, time from study start and type of rescue interventions administered in each study arm will be collected as an exploratory endpoint.

Participants who receive rescue intervention between Weeks 4 and 48 will be discontinued from the study drug administration but will be encouraged to remain in the study and to follow the protocol-defined schedule of activities with emphasis on the Week 24 and 48 visits. Participants who receive rescue treatment but do not remain in

the study, should be encouraged by the investigators and study site staff to return to the clinic for an early termination visit, ideally approximately 4 weeks after the final dose for collection of safety and other assessments.

Discontinuation from study treatment will be registered in IxRS and in the eCRF. Rescue intervention is considered as an intercurrent event, and the statistical handling is described in Section 3.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

A weight-tiered dosing approach will be used in this study for the investigation of the safety and efficacy of satralizumab for the treatment of TED as shown in Table 4.

Table 4 Dosing Regimen for Investigation in the Phase III Study of Satralizumab for the Treatment of TED

Bodyweight at Baseline (Day 1)	Dose, Route and Regimen
[redacted]	[redacted]

[redacted] TED = thyroid eye disease.

[redacted]

[redacted]



[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all parts of the study, including the Part I (Day 1–Week 24), Part II (Weeks 24–48) and follow-up period (Weeks 48–72) as shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for statistical analysis or safety follow-up (Weeks 48–72) is received from the last participant, whichever occurs later. The end of the study is expected to occur approximately 72 weeks after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 72 weeks.

5. STUDY POPULATION

Approximately 120 adult (≥ 18 years) male and female patients with moderate-to-severe active and chronic inactive TED will be enrolled in this study at up to *approximately 70* study sites globally.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Age ≥ 18 years at the time of signing Informed Consent Form
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for at least 3 months after the final dose of satralizumab.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. A male condom and a female condom should not be used together because of risk of failure due to friction.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Inclusion Criteria for Individuals with Moderate-to-Severe Active TED

- Clinical diagnosis of active TED with CAS ≥ 3 (on the 7-item scale) at screening and baseline (Day 1) in the study eye.

  Note: Participants presenting with hypo- or euthyroidism (without treatment for hyperthyroidism) at the time of TED diagnosis *must* be carefully confirmed through available tests and imaging methods.

- Diagnosis of active moderate-to-severe TED; with proptosis (exophthalmos) $\geq 3mm$ above normal for race and gender in the study eye.

  Additionally, participants *must* have one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, and/or inconstant or constant diplopia.

  Note: The method used to determine the 3 mm minimum proptosis level is at the investigator's discretion and can be based on patient-specific parameters such as differences in study eye versus non-study eye for unilateral TED, prior exophthalmometry measurement, or prior photograph, or referencing normal ranges listed in Appendix 8. It is important to note that Appendix 8 is for informational purposes only

- Onset of active TED symptoms in the study eye (as determined by participant medical records) ≤ 12 months prior to baseline (Day 1).

- Euthyroid with the baseline disease under control, or have mild hypo- or hyperthyroidism (defined as free T3 and free T4 $\leq 50\%$ above/below normal limits at screening). Euthyroid patients that were previously treated with radioactive iodine therapy or surgery (thyroidectomy) for Graves' disease are eligible to be enrolled after a minimum of 4-weeks post-surgical intervention (thyroidectomy) or after at least a 3-month period following radioactive iodine therapy when thyroid function is expected to be normalized.

  Note: Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state until the end of this study.

Inclusion Criteria for Individuals with Chronic Inactive TED

- Clinical diagnosis of stable, chronic (inactive) TED, as determined by participant medical records indicating CAS < 3 (on a 7-item scale) in both eyes for at least 6 months prior to screening, or all of the following:
  - No progression in proptosis for at least 6 months prior to screening
  - If participant has a history of diplopia due to TED, no progression in diplopia for at least 6 months prior to screening
  - No new inflammatory TED symptoms for at least 6 months prior to screening.
- CAS < 3 (on a 7-item scale) in both eyes at screening and baseline (Day 1) visits
- Initial TED diagnosis > 12 months but < 10 years prior to screening
- History and presence at screening and baseline of chronic TED as estimated by treating physician with proptosis (exophthalmos) ≥ 3 mm above normal for race and gender in the study eye *(see Appendix 8)*. Additionally, participants *must* have one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, and/or inconstant or constant diplopia.

  Note:

  - *The method used to determine the 3 mm minimum proptosis level is at the investigator's discretion and can be based on patient-specific parameters such as differences in study eye versus non-study eye for unilateral TED, prior exophthalmometry measurement, or prior photograph, or referencing normal ranges listed in Appendix 8. It is important to note that Appendix 8 is for informational purposes only*
  - Participants presenting with hypo- or euthyroidism (without treatment for hyperthyroidism) at the time of TED diagnosis *must* be carefully confirmed through available tests and imaging methods.
- Euthyroid with the background disease under control, or have mild hypo- or hyperthyroidism (defined as free T3 and free T4 ≤ 50% above/below normal limits at screening). Euthyroid patients that were previously treated with radioactive iodine therapy or surgery (thyroidectomy) for Graves' disease are eligible to be enrolled after a minimum of 4-weeks post-surgical intervention (thyroidectomy) or after at least a 3-month period following radioactive iodine therapy when thyroid function is expected to be normalized.

  Note: Every effort should be made to correct the mild hypo-/hyperthyroidism promptly and to maintain the euthyroid state until the end of this study.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline Visit (Day 1)
- Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline Visit (Day 1)

- Decreased visual acuity (VA) due to dysthyroid optic neuropathy as defined by a decrease in vision of two lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months *prior to screening*
- Requiring immediate or urgent medical treatment in the judgment of the investigator
- Identified pre-existing ophthalmic disease that, in the judgment of the investigator, would preclude study participation or complicate interpretation of study results, including corneal decompensation unresponsive to medical management and including ophthalmic diseases that will likely require prohibited therapy during the study (e.g., uveitis, idiopathic orbital inflammatory disease)
- Requiring immediate surgical ophthalmological intervention or planning corrective surgery or irradiation during the course of the study, in the judgment of the investigator
- Requiring radioiodine therapy for normalization of thyroid function *during* the course of the study
- Sight-threatening TED characterized by dysthyroid optic neuropathy and/or corneal ulceration (defined as a deep corneal erosion which extends through epithelium and Bowman's membrane into corneal stroma)
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within *3 months* after the final dose of satralizumab.

  Female participants of childbearing potential must have a negative serum pregnancy test result at screening and negative urine dipstick pregnancy test prior to initiation of study treatment.
- Any surgical procedure within 4 weeks prior to baseline (Day 1)

  Minor surgeries defined as procedures requiring only local anesthesia or conscious sedation and are done on an ambulatory or outpatient basis (e.g., toenail surgery, mole surgical excision, tooth extraction) are allowed.
- Plans to have surgical procedure (except minor surgeries) during the study
- Active or presence of recurrent bacterial, viral, fungal, mycobacterial infection, or other infection (excluding fungal infection of nail beds or dental caries) at baseline (Day 1)
- Infection requiring hospitalization or treatment with IV anti-infective agents within 4 weeks prior to baseline (Day 1)
- Evidence of progressive multifocal leukoencephalopathy
- Congenital or acquired immunodeficiency, including HIV infection
- Positive hepatitis B (HBV) test at screening (defined as either of the following):
  - Positive hepatitis B surface antigen (HBsAg)
  - Positive total hepatitis B core antibody (total HBcAb) confirmed by a positive viral DNA polymerase chain reaction test

- Positive hepatitis C (HCV) test at screening (defined as positive HCV antibody and detectable HCV RNA)

  Participants with positive HCV antibody and undetectable HCV RNA 12 weeks after HCV treatment completion are eligible to participate in the study.
- Evidence of latent or active tuberculosis (TB), excluding participants receiving chemoprophylaxis for latent TB infection
  - If a participant is positive for latent TB, then the participant must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration
- Receipt of live or live attenuated vaccine within 6 weeks prior to baseline (Day 1)
- History of diverticulitis or concurrent severe gastrointestinal (GI) disorders (such as symptomatic diverticulosis) that, in the investigator's opinion, may lead to increased risk of complications such as GI perforation
- *Blood* donation (one unit or more), plasma donation or platelet donation within 90 days prior to screening
- History of malignancy within the last 5 years prior to baseline (Day 1), including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured)
- History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions)
- History of drug or alcohol abuse within 1 year prior to baseline (Day 1)
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes an individual's safe participation in and completion of the study
- Presence of any of the following laboratory abnormalities at screening:
  - WBC $< 3.0 \times 10^3/\mu L$
  - ANC $< 2.0 \times 10^3/\mu L$
  - Absolute lymphocyte count $< 0.5 \times 10^3/\mu L$
  - Platelet count $< 10 \times 10^4/\mu L$
  - AST or ALT $> 1.5 \times$ upper limit of normal (ULN)

    If a laboratory retest is conducted, the last retest value before baseline (Day- 1) must meet study eligibility criteria. *Refer to Appendix 2 Table A2-1*

Exclusion Criteria for All Individuals with TED, Both Active and Inactive:

- Non-functioning non-study eye, defined as no physical presence of the non-study eye/globe (anophthalmia) or a phthisical non-study eye.
- Previous orbital radiotherapy in the study eye
- Previous unilateral or bilateral orbital decompression surgery

- Previous exposure to biologic drugs directly targeting IL-6 or IL-6 receptor (including, but not limited to, tocilizumab)
- Use of any investigational agent for any condition within 60 days prior to screening or anticipated use during the course of the trial.
- Prior strabismus surgery in either eye *except history of surgery for congenital strabismus*
- Botulinum toxin injection (or other chemodenervative agents) for *any condition* in either eye*,* eyelid *or periocular region* within 3 months prior to screening.

Exclusion Criteria for Individuals with Active TED Only:

- Any previous use of systemic, non-biologic, non-steroidal immunosuppressive agents for the treatment of TED (e.g., methotrexate, mycophenolate or cyclosporine)
- Previous treatment with any other systemically administered immunomodulatory biological agents, including but not limited to rituximab, teprotumumab, secukinumab, batoclimab at any time prior to screening
- Any prior CS use (IV or oral) with a cumulative dose equivalent to $\geq$1 g of methylprednisolone or equivalent for the treatment of *any condition within 3 months prior to screening.*
- *Any prior CS use (*IV or oral) with a cumulative dose of $<$1 g methylprednisolone or equivalent for the treatment of *any condition* is allowed if discontinued at least *1 month* prior to screening.
- *Any prior CS use (periocular, IVT [intravitreal] injections or via ocular implants) for any condition within 1 month prior to screening in either eye*
  - Previous CS eyedrop use is allowed if discontinued at least 7 days prior to screening.
  - Topical CSs for dermatological conditions are allowed at any time prior to, or during the study

Exclusion Criteria for Individuals with Inactive TED Only:

- Use of systemic, non-biologic, non-steroidal immunosuppressive agents for TED within 3 months prior to screening
- Treatment with any systemically administered immunomodulatory biological agent for TED within 6 months prior to screening.
- Use of any CSs (periocular, IV, oral, IVT injections, or implants) for any indication within 3 weeks prior to screening.
  - Previous CS eyedrop use within 28 days prior to screening.
  - Topical CSs for dermatological conditions are allowed at any time prior to or during the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine or alcohol restrictions. There is no restriction to smoking, (or tobacco consumption including e-cigarette).

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.3.5 *Other Activity Restriction*

Participants should avoid donating blood while taking study treatment and for at least 12 weeks after treatment discontinuation.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for *three* re-screening opportunity (for a total of *four* screenings per individual) at the investigator's discretion. At re-screening, a new screening number will be assigned to each patient and all screening visits assessments will be performed. Individuals *do not need to* re-sign the consent form *before* re-screening unless *a new version of* the consent form *has been implemented at the site*. The investigator will maintain a screening log to record details of all participants screened and record reasons for screening failure, as applicable (see Section 8). Of note, screened individuals that do not meet the eligibility criteria anymore at baseline will be considered screen failed.

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal products (IMP) for this study are satralizumab (RO5333787) and placebo for satralizumab.

IMP will be supplied by the Sponsor as prefilled syringe (PFS) assembled with a plunger rod and needle safety device (NSD) filled with [redacted] mL of solution for SC injection, corresponding to [redacted]mg satralizumab. Satralizumab placebo PFS is identical in composition to satralizumab PFS, but does not contain the satralizumab active ingredient and will be identical in appearance and packaging to satralizumab.

For the [redacted] and [redacted]mg doses, a separate dose of [redacted] mg will be prepared using the 'empty vial method'. In this method, the [redacted]mg PFS containing [redacted] mL of solution will be

transferred into an empty vial, and [redacted] will be withdrawn into the application syringe. For more details, refer to the pharmacy manual.

Rescue therapies are considered auxiliary medicinal products (AxMPs). Appendix 14 identifies all IMPs and AxMPs for this study (for use in the European Economic Area).

6.1 STUDY TREATMENT ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Satralizumab	Placebo
Use	Experimental	Placebo comparator
Type of medicinal product	IMP	IMP
Drug form	Liquid	Liquid
Unit dose strength (s)	[redacted] mg/mL	Not applicable
Dosage level (s)	[redacted], and [redacted] mg[a]	Not applicable
Formulation (s)	Refer to pharmacy manual	Not applicable
Packaging	[redacted]-mL prefilled syringe	[redacted]-mL prefilled syringe
Route of administration	SC injection	SC injection
Source	Sponsor	Sponsor

IMP = investigational medicinal product.

[a] For the [redacted] mg and [redacted] mg doses, a [redacted] mg dose will be prepared from the [redacted] mg syringe using the 'empty vial method.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of medication error, along with any associated adverse events, should be reported as described in Appendix A3–8.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.1.1 Satralizumab and Placebo

Satralizumab or placebo will be administered by SC injection in the abdominal or femoral region by the investigator or designated person after all other study-related procedures have been performed at a site visit.

In the Part I period, participants will receive satralizumab or placebo at Day 1 and Weeks 2 and 4 (loading doses) and then Q4W at Weeks 8, 12, 16 and 20 (maintenance

doses) (seven doses in total, see Section 1.3). The dose of study treatment will be determined based on participant's body weight. Participants will receive one or two injection (s) of satralizumab according to body weight at [redacted] The initial dose of study treatment will be determined as described for Part I of the study and will be based on the body weight at baseline (Day 1). The dose may be adjusted based on changes in body weight during the study according to the guidance set out in Table 6.

The treatment which participants receive in Part II of the study is determined by their proptosis response at the end of Part I (Week 24 primary endpoint):

- Participants who are proptosis non-responders at Week 24 will receive SC satralizumab treatment during Part II (Weeks 24–44).
- Participants who are proptosis responders at Week 24 will be re-randomized in a 1:1 ratio (using the original randomization stratification factors measured at baseline (smoking status and TED disease activity status) to receive SC satralizumab or matching placebo (Weeks 24–44), regardless of their original treatment assignment in Part I.
- Participants that discontinue the study drug in Part I but choose to stay in the trial for Part II will not be re-randomized and will not receive any further study treatment (satralizumab/placebo). These participants will continue to be followed in the study in order to monitor for safety and collect end of study data; during this time, they will be able to receive standard of care at the investigator's discretion.

To maintain masking to treatment assignment from Part I based on the study design, participants who received placebo during Part I and receive satralizumab in Part II will receive a loading dose of satralizumab at Week 26; participants who received satralizumab in Part I and receive satralizumab in Part II do not require a loading dose and will receive placebo at Week 26.

Study drug will be administered within a ±3-day window at Weeks 2 and 4 for Part I, and Weeks 26 and 28 for Part II; and within a ±7-day window for all other dosing visits. The minimal dosing interval should be 8 days for loading doses and 14 days for maintenance doses.

For the first five doses of study drug in Part I and Part II of the study, all participants should be observed for the signs and symptoms of hypersensitivity reactions at the study site for at least 1 hour after administration of study treatment.

Guidelines for medical management of injection reactions are provided in Appendix A3–7, *Appendix 13*

Table 6 describes recommendations that apply for enrolled participants who change weight during the study such that they would fall into a different dosing band.

Table 6 Dosing Guidance for Participants Who Lose or Gain Body Weight during the Study



6.1.1.1 Missed Doses

If there is a delay in dosing such that the minimum allowable interval between doses cannot be maintained within the acceptable dosing windows defined (i.e., minimum dosing interval should be 8 days for loading dose and 14 days for maintenance dose), or dosing cannot be completed prior to the date of the next planned dose, then the dose is considered to have been missed. For any missed study dose, there will be no make-up study drug injection. Study drug should be administered at the next scheduled visit *within the acceptable window* and the Schedule of Activities (SOA) should continue to be followed as described in Section 1.3 *and 4.1.1*provided there are no safety-related reasons for further interruption or discontinuation of study treatment (see Section 7.1). If a patient misses more than two consecutive visits due to an adverse event, investigators may consult with the Medical Monitor/Sponsor for advice or clarification of any protocol-specific criteria regarding study drug continuation, but the decision whether it is appropriate and safe for the patient to continue on study drug will be determined by the investigator.

Participants with active infection during the study should be promptly evaluated and treated appropriately. Study drug injection should not be administered until the infection has been resolved for serious or Grade $\geq$3 infections or controlled for non-serious and Grade $<$3 infections (see Appendix A4–1.1).

If a participant cannot attend the site for a scheduled visit, every effort should be made to collect all the missing data. Additionally, the site staff should follow-up with participants around the time of the scheduled visit by telephone to collect any information on safety and/or TED worsening the participant might experience.

6.1.2 Rescue Intervention

Rescue intervention *for the study eye* is permitted at any time starting from Week 4 through the end of the study, per the following criteria based on investigator's assessment:

- Diagnosis of sight-threatening disease for which prompt intervention is indicated in the opinion of the investigator, usually evidenced by the following:
  - Dysthyroid optic neuropathy, or
  - Corneal ulceration defined as a deep corneal erosion which extends through epithelium and Bowman's membrane into corneal stroma

The choice of rescue intervention is at the discretion of the investigator according to her or his best medical judgment and could include systemic, local or topical pharmacological approach, radiotherapy, and/or surgical management. If needed, investigators may discuss a decision to administer a rescue treatment with the Medical Monitor. Based on their best medical judgment, investigators can place participants on standard of care treatment at any time if the investigator determines that the condition has been deteriorating and participant's health is at risk.

Participants who receive rescue intervention will not be replaced and will not be allowed to restart study drug treatment. Participants who receive rescue intervention between Weeks 4 and 48 will be discontinued from the study drug administration but will be encouraged to remain in the study and to follow the protocol-defined schedule of activities with emphasis on the Week 24 and 48 visits. Participants who receive rescue treatment but do not remain in the study~~,~~ should be encouraged by the investigators and study site staff to return to the clinic for an early termination visit, ideally approximately 4 weeks after the final dose for collection of the safety and other assessments.

The date and time of rescue medication administration, as well as the name, dose, dosing regimen and route of administration of the rescue medication, must be recorded in the participant's medical chart and on the Concomitant Medications eCRF. If surgery or radiotherapy was performed as rescue therapy, date, time, and type of intervention must be recorded in the participant's medical chart and on the Concurrent Ocular Procedure eCRF.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor to confirm the shipment condition and content. Any damaged shipments will be replaced. Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or Satralizumab Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND MASKING

6.3.1 Treatment Assignment

This is a randomized, double-masked study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

After participant eligibility requirements are confirmed, site personnel will contact the IxRS at the Day 1 visit for assignment of a participant identification number (a separate number from the screening number). Participants will be randomized on the same day study treatment is to be initiated (i.e., Day 1 visit).

Participants will be randomized in a 1:1 ratio (stratified by smoking status [current smoker, including the use of e-cigarettes vs. former smoker vs. never smoked] and TED disease activity status [active vs. inactive]) to receive seven SC doses of either satralizumab (with dosing based on body weight; see Table 4) or matching placebo on Day 1, at Weeks 2, and 4 (loading doses); then Q4W at Weeks 8, 12, 16, and 20 (maintenance doses), with a final visit at Week 24.

The treatment which participants receive in Part II of the study is then determined by their proptosis response at the end of Part I (Week 24 primary endpoint):

- Participants who are proptosis non-responders at Week 24 will receive SC satralizumab during Part II (Weeks 24–44).
- Participants who are proptosis responders at Week 24 will be re-randomized in a 1:1 ratio (using the original randomization stratification factors measured at baseline (smoking status and TED disease activity status) to receive SC satralizumab or matching placebo (Weeks 24–44), regardless of their original treatment assignment in Part I.
- Participants that discontinue the study drug in Part I but choose to stay in the trial for Part II will not be re-randomized and will not receive any further study treatment (satralizumab/placebo). These participants will continue to be followed in the study in order to monitor for safety and collect end of study data; during this time, they will be able to receive standard of care at the investigator's discretion.

The final visit at Week 48 in Part II (4 weeks after the final dose) is the last onsite visit of the study. After Week 48, follow-up visits will be conducted every 8 weeks over telephone until Week 72 to review adverse events, concomitant treatments, and any treatments or surgery received for TED. During Part II of the study, the participants and the study staff will remain masked to the treatment the participants received during Part I of the study.

All participants will be allowed to receive rescue intervention per investigator's discretion from Week 4 through the end of the study per rescue criteria (Section 6.1.2).

After randomization and at each study treatment visit, IxRS will assign the appropriate study treatment kit to be used.

6.3.2 Masking

Study site personnel and participants will be masked to treatment assignment during the study. The Sponsor and its agents will also be masked to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfill their job roles during a clinical trial. These roles include the unmasking group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

Selected laboratory parameters that may lead to unmasking of the treatment assignment, such as C-reactive protein (CRP), fibrinogen, satralizumab pharmacokinetics, IL-6, sIL-6R, ADAs, immunoglobulins, and complement levels (C3, C4, and CH50), will be masked to the site and Sponsor.

While PK and immunogenicity samples must be collected from participants assigned to the comparator arm to maintain the masking of treatment assignment, PK and ADA assay results for such participants are generally not needed for the safe conduct or

proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unmasked to participant treatment assignments to identify appropriate samples for analysis. PK samples from participants assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all participants. Postbaseline immunogenicity samples from participants assigned to the comparator arm will not be analyzed for ADAs except by request.

If unmasking is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the $IxRS\ will$ inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.

The investigator should document and provide an explanation for any non-emergency unmasking. If the Medical Monitor agrees to participant unmasking, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to a drug listed in Section 8.3.4. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain masked to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.5 DOSE MODIFICATION

Modification of the satralizumab dose for management of drug-related toxicities is not permitted.

In the event that an enrolled patient gains or loses weight during the study such that they would fall into a different dosing band, the recommendations as shown in Table 6 will apply.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMP satralizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP satralizumab after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP satralizumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g. is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for Thyroid eye disease
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for Thyroid eye disease
- Provision of the Roche IMP is not permitted under the laws and regulations of country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until resolved.
- Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
- Report the overdose, along with any associated adverse events, as described in Appendix 3.

6.8 CONCOMITANT THERAPY

Any medication (including over-the-counter or prescription medicines, nutritional supplements, homeopathic and/or herbal remedies or vaccine) used by a participant in addition to protocol–mandated treatment from 28 days prior to initiation of study treatment to the final study visit (Week 72 visit, or early discontinuation visit) must be recorded on the Concomitant Medications eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

At the discretion of the investigator, participants may start or continue to receive all medication and standard treatments administered for other conditions, except for therapies listed under the exclusion criteria and prohibited medications Section 6.8.2.

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.2.

Use of the following concomitant therapies is permitted as described below:

- Anti-thyroid medications such as methimazole, carbimazole and propylthiouracil
- Thyroid replacement therapy such as levothyroxine
- Local supportive measures for TED including simple analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory therapies), and ocular lubricants
- Medications/supplements for conditions other than TED
- Oral selenium
- Oral contraceptives (see Section 5.1)

6.8.2 Prohibited Therapy

At the discretion of the investigator, participants may continue to receive medications and standard treatments administered for other conditions. However, the use of the following therapies or medications and treatments are prohibited as during the study:

- *Systemic (oral or IV)* and/or *local (periocular, intravitreal, or via ocular implant)* steroids for *any condition*
- High dose oral biotin (>70 mcg per day)
- Systemic immunosuppressive agents such as methotrexate, cyclosporine, azathioprine, mycophenolate, cyclophosphamide, and etanercept
- Systemic biologic agents such as tocilizumab, teprotumumab, rituximab, adalimumab and infliximab
- Orbital irradiation for TED in the study eye
- Radioiodine therapy for Graves' disease
- Ocular or orbital surgery for TED in either eye
- Other investigational or experimental therapies
- Botulinum toxin injection (or other chemodenervative agents) for *any condition* in either eye*,* eyelid *or periocular region*

If necessary, participants may be discontinued from satralizumab treatment and/or the study to receive any prohibited therapy. Participants who discontinue satralizumab due to receipt of prohibited therapy should be encouraged to follow the protocol-defined schedule of activities with emphasis on the Week 24 and 48 visits as outlined in the schedule of activities (see Section 1.3). Participants who do not remain in the study, should be encouraged to return for an early termination (ET) visit, ideally approximately 4 weeks after the final dose for collection of the safety and other assessments.

6.8.3 Immunizations and Vaccinations

It is recommended for all participants to keep up to date with all immunizations according to local immunization guidelines prior to randomization in the study.

- The use of any live or live-attenuated vaccines is not allowed within 6 weeks prior to randomization and during the entire duration of the study.
- Vaccines (including COVID-19 vaccines) other than live or live attenuated are permitted during the study. Intervals between investigational medicinal product (IMP) and vaccines (other than live or live attenuated) are recommended to follow the local label of Enspryng and local immunization guidelines.
- Vaccines may be less effective in immunocompromised patients, however, the effect of satralizumab upon the efficacy of vaccinations is currently unknown. It is recommended that vaccines should be given in accordance with the approved/authorized vaccine label and official local immunization guidance.

Refer to the Satralizumab Investigator's Brochure for further details regarding vaccinations. Please contact the Medical Monitor for any questions on vaccinations in patients participating in this study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant should be encouraged to remain in the study and follow the protocol-defined schedule of activities, with a particular emphasis on the Week 24 and 48 visits. Refer to the schedule of activities (see Section 1.3) for data to be collected. Participants who do not remain in the study, should be encouraged to return for an early termination (ET) visit, ideally approximately 4 weeks after the final dose for collection of the safety and other assessments.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Participants who received rescue treatment
- Use of a prohibited therapy (see Section 6.8.2)|
- Symptomatic deterioration attributed to disease progression|
- Confirmed disease progression (progression to sight-threatening disease) in either eye per investigator assessment according to EUGOGO guidelines on clinical measure of severity

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue from study treatment prematurely will not be replaced and will not be able to restart study treatment. However, these participants should be encouraged to continue their study participation and undergo as many scheduled visits as possible with emphasis on Week 24 and Week 48 visits.

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests as outlined in Appendix A3–7.7, or if the investigator believes that it is in the best interest of the participant to discontinue.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known

mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count, ECG) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, chronic and ongoing conditions (e.g., trauma, cardiovascular, cerebrovascular, infectious diseases and ophthalmic), surgeries, reproductive status, smoking history and use of alcohol and drugs of abuse will be recorded at screening. Any medication and/or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant from 28 days prior to initiation of study treatment will be recorded. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded, per local regulations. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and laboratory test values are acceptable.

8.1 EFFICACY ASSESSMENTS

8.1.1 Standard Ocular Assessments

Ocular assessments will be performed for both eyes, unless otherwise indicated, at specified timepoints according to the schedule of activities in Section 1.3. *Refer to Appendix 9 for the order of key assessment information.* The following assessments must be performed:

- Visual Acuity assessed on Snellen visual acuity chart (perform prior to dilating eyes).
  - VA is to be obtained using patient's habitual distance correction (glasses or contact lenses) or pinhole. Refer to the VA procedure manual for details.
  - Visual acuity examiner certification will be obtained from a third party vendor. The VA examination room must also be certified before any VA examinations are performed. Refer to the VA procedure manual for additional details regarding the visual acuity procedure and the certification process.
- Eyelid measurement of both eyes including margin reflex distance (MRD) 1, MRD2, *vertical* interpalpebral fissure distance, lagophthalmos, and superior and inferior scleral show (perform prior to dosing)
- Iris pigmentation assessment (light and dark grading)
  - The iris pigmentation is to be documented as light or dark for each eye per slit lamp examination as below:
    1. Dark - Most iris area has the appearance of brown shades;
    2. Light - Most iris area has non-brown shades (blue, grey, green, patches of brown, or hazel less than 50% area)
- Intraocular pressure measurement
- Slit-lamp examination

  Undilated anterior segment evaluation will include corneal staining with fluorescein using the standardize Oxford grading system (see Appendix 11) and anterior chamber assessment including anterior chamber cell and anterior chamber flare (see Appendix 15 for guidance on grading scales).
- Dilated binocular indirect high-magnification ophthalmoscopy or dilated examination of posterior segment on a slit-lamp with a high-power lens.

  This will include detailed posterior segment evaluation with focus on determining presence/absence of optic neuropathy and choroidal folds.

  In addition, evaluation of the vitreous including vitreous cells, vitreous haze, and vitreous hemorrhage will be performed (see Appendix 15 for guidance on the grading scales).

8.1.2 Ocular Assessments Specific to Thyroid Eye Disease

8.1.2.1 Proptosis (Exophthalmos)

Proptosis assessments will be performed on the study eye first, followed by the fellow eye. All assessments will be performed using Sponsor-provided Hertel exophthalmometer to maintain consistency in measurement. To ensure consistency in measurement, it is of *utmost* importance to have the same observer evaluating proptosis for the entire duration of the study, and in particular for the baseline, Week 24 and Week 48 visits. In addition, the same base setting must be used on each occasion. Proptosis observer certification will be obtained from a third-party vendor, and the proptosis observer must be certified before any proptosis assessments are performed. Refer to the proptosis manual for instructions on the measurement of proptosis and the certification process.

Proptosis will be measured at screening and baseline (Day 1), and then at 4-week intervals till the final in-person visit (48 weeks). Individuals who have a $\geq$2 mm decrease in proptosis from screening to baseline in the study eye are not eligible for randomization.

8.1.2.2 Diplopia

Diplopia grade will be assessed with the use of the Gorman subjective diplopia score (range: 0–3 points), which includes: no diplopia (absent, scored as 0), diplopia in the primary position of gaze when the patient is tired or awakening (intermittent, scored as 1), diplopia at extremes of gaze (inconstant, scored as 2), and continuous diplopia in the primary or reading position (constant, scored as 3). Measurements will be recorded on the Clinical Measures of Severity eCRF under diplopia (Bartalena et al. 2008).

8.1.2.3 Motility Restriction

Motility restriction is assessed by estimating the degrees of restriction in eye movements. It will be assessed at the same timepoints as the Clinical Measures of Severity.

Monocular excursions in horizontal and vertical directions of gaze are recorded using the light reflex test (Dolman et al. 2012).

Motility restriction assessments will be performed on the study eye first, followed by the fellow eye. The clinician will shine a pen light in line with the eye being examined in ambient room light and observe the participant's eye along the light's axis. The participant will be asked to look in the four cardinal directions and the position of the light reflex is viewed on the surface of the cornea. If the light touches the limbus, the eye is assessed to be turned 45 degrees; if half way between the limbus and pupil edge, the eye is assessed at 30 degrees; and if it is at the pupil edge, it is assessed at 15 degrees. Intermediate ductions are judged by estimating the light position between these points to the nearest 5 degrees.

The monocular ductions of each eye (degrees) will be recorded for adduction, abduction, supraduction and infraduction.

8.1.2.4 Clinical Activity Score

The CAS will be completed at screening, baseline (Day 1) and Weeks 4, 12, 20, and 24 during the Part 1 period, and at Weeks 28, 36, 44 and 48 during the Part II period using the 7-item EUGOGO amended CAS (Wiersinga et al. 2006).

The CAS must be ≥3 points at screening and baseline in the study eye for enrollment of patients with active TED. The CAS must be <3 points in both eyes at screening and baseline for enrollment of patients with chronic inactive TED. Individuals whose CAS score decreases 2 or more points in the study eye between screening and baseline are not eligible to enroll in the study. Of note, study eye will be assigned by investigators at baseline (Day 1).

Table 7 Clinical Activity Score Assessment

Item[a]	Description
1.	Spontaneous orbital pain.
2.	Gaze evoked orbital pain.
3.	Eyelid swelling that is considered to be due to TED.
4.	Eyelid erythema.
5.	Conjunctival redness that is considered to be due to TED (ignore “equivocal” redness).
6.	Chemosis.
7.	Swelling of caruncle or plica.

TED = thyroid eye disease.

[a] Each item is scored (1 = present; 0 = absent) and scores for each item are summed for total score. *For mild eyelid swelling and mild conjunctival redness on the clinical measures of severity scale, the CAS score must be recorded as absent (negative) in accordance with the EUGOGO Clinical Evaluation Atlas (EUGOGO 2001).*

To promote consistency in data collection, it is *of utmost importance to have* the same observer conduct each CAS evaluation for the full duration of the study in particular for the baseline, Week 24 and 48 visits.

8.1.2.5 Clinical Measures of Severity

The severity of the disease will be evaluated using the EUGOGO guidelines (Bartalena et al. 2008; see *Appendix 10*). The following items will be assessed at screening, baseline (Day 1) and Weeks 4, 12, 20, and 24 during the Part I period, and Weeks 28, 36, 44, and 48 during the Part II period. To ensure consistency in measurement, it is of *utmost* importance to have the same observer evaluating each

severity measure which relates to the primary or key secondary endpoints (i.e. proptosis, and the components which are part of CAS e.g., chemosis/conjunctival edema, inflammation/swelling of the caruncle or plica etc.) for the full duration of the study, and in particular for the baseline, Week 24 and Week 48 visits.

Note: For mild eyelid swelling and mild conjunctival redness on the clinical measures of severity scale, the CAS score must be recorded as absent (negative) in accordance with the EUGOGO Clinical Evaluation Atlas (EUGOGO 2021).

EUGOGO (Bartalena et al. 2021) recommends the following classification of patients with TED:

- Mild TED: Patients usually present with one or more of the following characteristics: lid retraction <2 mm, mild soft tissue involvement, exophthalmos <3 mm over the normal for the race or gender, transient or no diplopia and corneal exposure responsive to lubricants.
- Moderate-to-severe TED: Patients usually present two or more of the following characteristics: eyelid retraction ≥ 2 mm, moderate to severe soft tissue involvement, exophthalmos ≥ 3 mm more than normal for their race or gender, and intermittent or constant diplopia.
- TED that is sight-threatening or severe: Patients usually present with optical neuropathy and/or cornea deterioration.

Color Vision Test

Refer to the color vision procedure manual for additional details regarding the color vision testing.

8.1.2.6 Corneal Staining

After instillation of 2% sodium fluorescein in the *eyes*, fluorescein staining of the cornea will be observed using the cobalt blue filter on the slit-lamp biomicroscope. Corneal staining will be graded using the Oxford Grading Scheme Chart (a 6-point scale that ranges from Grade 0 to V, Appendix 11), with each investigator using the same set of image provided by the Sponsor as a guide at baseline (Day 1) and Weeks 4, 12, 20, and 24 during the Part I period, and Weeks 28, 36, 44, and 48 during the Part II period (see Section 1.3). Staining assessment will be based on the intensity of fluorescein staining, ranging from Grade 0 to V for each panel (Grade 0–I: normal; Grade II–III: mild to moderate; Grade IV–V: severe).

8.1.3 Clinical Outcome Assessments

PRO and clinician-reported outcome (ClinRO) instruments will be completed to assess the treatment benefit of satralizumab. In addition, PRO instruments will enable the capture of each participant's direct experience with satralizumab. PRO data will be collected through use of the GO-QoL. ClinRO data will be collected through the use of OSDI.

8.1.3.1 Graves' Ophthalmopathy Quality of Life Questionnaire

The GO-QoL questionnaire (Terwee et al. 1998) will be completed at baseline, Weeks 12 and 24 during the Part I period, and at Weeks 36 and 48 during the Part II period.

The GO-QoL is a 16-item self-administered questionnaire divided into two sub-scales and used to assess the perceived effects of TED by the participants on their: 1) Visual Functioning; and 2) Appearance. Questionnaires can be administered no more than 48 hours prior to study treatment administration. The English version of the questionnaire is included in Appendix 12.

8.1.3.2 Ocular Surface Disease Index

The OSDI instrument is a validated dry eye questionnaire, designed to be administered by *healthcare* professionals to participants. This instrument will assess cornea and ocular surface symptoms for each participant. The OSDI questionnaire (Schiffman et al. 2000) will be completed at baseline (Day 1), Weeks 12 and 24 during the Part I period, and at Weeks 36 and 48 during the Part II period. The OSDI questionnaire consists of three main sections concerning ocular symptoms, visual function, and environmental factors. The OSDI score is a composite measure built on 12 questions, with totals ranging from 0 to 100, and higher scores representing a worse disease index. The English version of the questionnaire is included in Appendix *12*.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

Physical examinations at specified visits in the Schedule of Activities (Table 1) will be performed by investigators. A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. *A genitourinary examination will be completed if clinically indicated per investigators judgement.*

A limited physical examination will include, at a minimum, assessments of the skin (including injection sites), respiratory system, cardiovascular system, and abdomen (liver and spleen). Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes and in the appropriate eCRF.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed while the participant is in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television and cell phones).

Vital signs are measured predose dosing and 15 (±5) minutes and 60 (±5) minutes postdose for the first five dosing visits in Parts I and II, *to monitor for potential* injection reactions. After the fifth dose in Parts I and II (i.e., at Weeks 16 and 20 in Part I, and at Weeks 40 and 44 in Part II), vital signs should be measured only prior to study drug administration.

All vital signs will be recorded on the eCRF.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF)/QT interval.

Single 12-lead ECG recordings will be obtained at specified timepoints (see Table 1) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine or semi-supine position for at least 10 minutes, and the patient should remain in a supine or semi-supine position during recording. The same positioning should be maintained for each patient throughout the study. ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental

distractions (e.g., television, radio, conversation), should be avoided during the preECG resting period and during ECG recording.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, and QTcF based on machine readings of ECG tracings should be recorded on the appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular timepoint the mean QTcF is $>$500 ms or $>$60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency. Clinical laboratory tests conducted by a central laboratory must be conducted in accordance with the laboratory manual.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report (CSR).

Assessment of CRP, fibrinogen, and complement (C3, C4, and CH50) will be performed in a masked manner and results will not be available to site and Sponsor until the

Week 48 analysis. The iDMC will perform periodic unmasked safety reviews, which will include the laboratory parameters that are masked to the Sponsor and site.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study drug (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until the final visit (Week 72) at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs or ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Satralizumab	Satralizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 12 weeks after the final dose of satralizumab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest and Selected Adverse Events

8.3.8.1 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)

- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.8.2 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Infections
- Injection reaction, adverse events considered to be injection reactions that occur during or within 24 hours after study drug administration and are judged to be related to the study drug injection.

8.3.9 Medical Device Complaints

In this study, PFS with NSD is considered a medical device. The investigator must report all medical device complaints and any associated adverse events to the Sponsor, as described in Appendix 6.

8.3.10 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor(s). An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Serum samples will be collected for measurement of concentrations of satralizumab as specified in the schedule of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of satralizumab. Samples collected for analyses of satralizumab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples, unless consent for this was included in an Informed Consent Form. Participant confidentiality will be maintained. At visits during which serum samples for the determination of satralizumab concentration will be taken, one sample of sufficient volume can be used.

PK samples will be destroyed no later than 5 years after the final CSR has been completed to allow for assay development and validation (if needed).

Information on unmasking of personnel responsible for performing PK assays is provided in Section 6.3.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Genetic biomarker assessments will not be performed on mandatory biomarker samples in this study.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Serum samples for determining PD biomarkers, which may include, but are not limited to, IL-6 and sIL-6R
- Blood samples (if available) for exploratory research on biomarkers, which may include, but are not limited to thyroid-related autoantibodies

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.

Screening serum, blood, and plasma samples, including those collected from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedules outlined in Section 1.3 (see Table 1). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10), biomarker samples will be destroyed no later than 15 years after the final CSR has been completed.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to satralizumab will be evaluated in serum samples collected from all participants according to the schedule of activities (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to satralizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to satralizumab and/or further characterize the immunogenicity of satralizumab.

The detection and characterization of antibodies to satralizumab will be performed through use of a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for satralizumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) after the final CSR has been completed at a facility selected by the Sponsor to enable further analysis of immunogenicity of satralizumab.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Optional Imaging

Collection and submission of optional imaging is contingent upon review and approval of the imaging portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for imaging, this section of the protocol will not be applicable at that site.

The central reading center (CRC) will provide sites with the CRC manual and training materials for imaging. Before any study images are obtained, site personnel, test images, and equipment will be certified and validated by the CRC as specified in the CRC manual. All images will be obtained by trained site personnel at the study sites and forwarded to the CRC for independent analysis and/or storage, and will be later transferred to Roche.

8.10.1.1 Optional Orbital Magnetic Resonance Imaging

Optional orbital magnetic resonance imaging will be collected for participants who consent to optional MRI imaging and at sites that have this imaging capability.

Orbital images will be obtained and may be used to assess, including, but not limited to, changes in extraocular muscle, fat volume, proptosis, inflammation, and fibrosis as well as provide information for future education, training, and publication. Imaging will be performed per schedule of activities (Section 1.3). The imaging should be performed no more than *72* hours prior to study treatment administration.

Note: *If a patient misses the scheduled baseline/Day 1 orbital MRI, they will not be eligible for any subsequent orbital MRI assessments.* After randomization, if a patient misses *the Week 24* visit when orbital imaging are scheduled (see Section 1.3) or the images are not taken at the *Week 24* visit (e.g., due to broken equipment), they should be obtained at the next scheduled visit the patient attends.

8.10.1.2 Optional Facial Photography

Optional facial photographs will be collected for participants who consent to optional facial photographs at sites where facial photographs are permitted and feasible.

Facial photographs will be obtained and may be used to assess, including, but not limited to, changes in periorbital inflammation, facial soft tissue, and proptosis as well as provide information for future education, training, and publication. Facial photographs will be performed per SOA *and must be done prior to eye dilation* (Section 1.3) and it should be performed no more than 48 hours prior to study treatment administration.

Note: *If a patient misses the scheduled baseline/Day 1 facial photograph, they will not be eligible for any subsequent photograph assessments.* After randomization, if a patient misses *the Week 24* visit when facial photographs are scheduled (see Section 1.3) or the photos are not taken at the *Week 24* visit (e.g., due to broken equipment), they should be obtained at the next scheduled visit the patient attends.

8.10.1.3 Other Assessments

Additional non-protocol clinical assessments or imaging procedures may be performed as part of standard of care by the investigator at the physician's discretion at the scheduled or unscheduled safety visits (e.g., visual field, color vision tests with color plates or red desaturation, computer tomography), but these do not need to be

submitted to the CRC. The Sponsor will not reimburse the site for these non-protocol clinical assessments or imaging procedures beyond the reimbursable per protocol.

8.10.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.2.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, and peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.3 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.2) will not be applicable at that site.

8.10.4 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to drug, diseases, or drug safety:

- Blood sample collected at baseline (Day 1)
- Leftover blood, serum and plasma, samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.5 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide

any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.6 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.7 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the

site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address: global.rcr-withdrawal@roche.com.

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.8 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

The primary analysis will be performed when all participants have either completed the study through Week 24 or have discontinued from the study prior to Week 24, whichever comes later. An update analysis will be performed when all participants have either completed the study through Week 48 or have discontinued from the study prior to Week 48; whichever comes later.

The final analysis database lock will be performed when all participants have either completed the study through Week 72 (last participant last visit) or have discontinued early from the study, whichever comes later.

Details on the analyses will be provided in the Statistical Analysis Plan.

9.1 ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 8.

Table 8 Participant Analysis Sets

Participant Analysis Set	Description
Part I FAS	*Include all participants randomized on Study Day 1; participants will be included in the analyses according to the treatment they were assigned to at baseline (Study Day 1)*
Part II FAS	*Include participants who entered Part II and were re-randomized on the week 24 visit; participants will be included in the analyses according to the treatment they were assigned to at the week 24 visit (re-randomization). Non-responders are not included*
Part I SAS	*Include all participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received..*
Part II SAS	*Include all participants who entered Part II and were exposed to study treatment (in any part of the trials); participants will be analyzed according to the different possible treatment combinations they actually received in Part I and II. No distinction between responders and non-responders is made*

FAS=full analysis set; SAS=safety analysis set.

9.2 STATISTICAL HYPOTHESES

The primary efficacy endpoint is *proptosis response*, defined as the proportion of participants achieving a≥2mm reduction in proptosis from baseline (Day 1) to Week 24 in the study eye, provided there is no corresponding deterioration of proptosis (≥2 mm increase) in fellow eye in the *Part I FAS (*active FAS.*population).* The following hypothesis will be tested:

- Superiority of satralizumab Q4W versus placebo in PR in the *Part I FAS (*active *population)*

The null and alternative hypothesis for the superiority test are as follows:

- The null hypothesis (H_0) is: $P_{satralizumab} - P_{placebo} = 0$
- The alternative hypothesis (H_a) is: $P_{satralizumab} - P_{placebo} \neq 0$

where $P_{satralizumab}$ and $P_{placebo}$ are the expected PR for the Satralizumab arm and placebo arm, respectively.

If the observed rate is higher in the treatment arm and the two-sided p-value<0.05, the test is considered positive and satralizumab is considered superior to placebo.

A fixed-sequencing test approach will be used to control the overall type I error rate for the hypothesis testing of the primary and key secondary endpoints.

If the primary endpoint test is positive, superiority of satralizumab compared with placebo for the following key secondary endpoints will be tested at the two-sided 5% significance level in the order as shown below:

- Proportion of participants achieving proptosis response from baseline (Day 1) at Week 24 in the *Part I FAS (*overall *population)*
- Change in proptosis from baseline (Day 1) to Week 24 in the *Part I FAS (*active *population)*
- Proportion of participants with Grade ≥ 1 reduction/improvement in diplopia from baseline (Day 1) at Week 24 in the *Part I* FAS among participants with diplopia present at baseline *(active population)*
- *Change in proptosis from baseline (Day 1) to Week 24 in the Part I FAS (overall population)*
- Proportion of participants with Grade ≥ 1 reduction/improvement in diplopia from baseline (Day 1) at Week 24 in the *Part I* FAS among participants with diplopia present at baseline *(overall population)*
- Proportion of participants achieving absence of motility-induced pain from baseline (Day 1) at Week 24 in the *Part I* FAS among participants with motility-induced pain present at baseline *(active population)*
- Proportion of participants achieving absence of spontaneous pain from baseline (Day 1) at Week 24 in the *Part I* FAS among participants with spontaneous pain present at baseline *(active population)*

For hypotheses that use binary endpoints, the corresponding estimand framework will follow the primary estimand framework.

The continuous key secondary endpoints will be tested using the mixed-effect model for repeated measures method. The respective estimand framework can be found in Table 2.

9.2.1 Sample Size Determination

A total of *approximately* 120 participants including 25% chronic inactive participants will be enrolled in this study and randomized at baseline in a 1:1 ratio (stratified by current smoking status [current smoker, including the use of e-cigarettes vs. former smoker vs. never smoked] and TED disease activity status [active vs. inactive]).

A total of 90 participants with active TED will provide > 90% power to show superiority of satralizumab compared with placebo in PR at Week 24. The following assumptions are used:

- Response ratio of [redacted] in the satralizumab arm
- Response ratio of [redacted] in the placebo arm
- Fisher exact test for two proportions

- 5% two-sided type I error rate
- 10% dropout rate

While the *test for the common risk difference by using MH stratus weights (Mantel and Haenszel 1959) and the Sato variance estimator (Sato 1989)* will be used as the main analysis method, the Fisher exact test is expected to be less sensitive and a more conservative way to estimate the sample size.

A total of 120 active and chronic inactive participants (overall FAS) will provide > 90% power to show superiority of satralizumab compared with placebo in PR at Week 24. The following assumptions are used:

- Response ratio of [redacted] in the satralizumab arm
- Response ratio of [redacted] in the placebo arm
- Fisher exact Test for two proportions
- 5% two-sided type I error rate
- 10% dropout rate

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan for Part I *and Part II* will be finalized prior to Sponsor unmasking, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of selected endpoints, including primary and key secondary endpoints. Secondary endpoints assessing the efficacy in Part II will be tested on a nominal two-sided αlevel of 5%. The analyses specified in the Statistical Analysis Plan supersede those specified here.

9.3.1 Estimation Methods for the Primary Estimand

The primary estimand is defined in Table 2. The main analysis for the primary endpoint will be the test *for the common risk difference using MH stratum weights (Mantel and Haenszel 1959) (*stratified by smoking status: current smoker, including the use of *ecigarettes* vs. former smoker vs. never smoked*) and the Sato variance estimator (Sato 1989*), and the p-value will be provided. The proportion of participants in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by smoking status using the *MH* weights. *The confidence interval* for the difference in proportions between treatment groups will be calculated using the method *proposed by Sato (1989).* Missing values will be imputed using multiple imputation methods.

A supplementary analysis will be performed using the same intercurrent events, analysis methods and missing data handling approach as the main analysis of the primary

endpoint, with the exception that participants with any intercurrent event will be treated as non-responders.

A sensitivity analysis will be performed using the same intercurrent events, handling of intercurrent events and analysis methods as the main analysis of the primary endpoint, with the exception that missing data will not be imputed and participants with missing data will be excluded from the analysis.

9.3.2 Safety Analyses

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

9.3.3 Analyses for the European Medicines Agency

To support registration in the European Union, a separate set of hypotheses will be tested in the active and overall population after the primary hypothesis. For the European Medicines Agency, the following hypotheses will be tested hierarchically at an overall significance level of $\alpha = 0.05$ to control the overall type I error rate:

- [redacted]
-
-
-

- [redacted]

Intercurrent events will be defined as in the primary estimand definition. A treatment policy approach will be used for handling all intercurrent events.

9.3.4 Analyses for the Japan Pharmaceuticals and Medical Devices Agency

To support registration in Japan, a separate set of hypotheses will be tested in the active and overall population after the primary hypothesis. For the Pharmaceuticals and Medical Devices Agency, the following hypotheses will be tested hierarchically at an overall level of $\alpha = 0.05$ to control the overall type I error rate:

- [redacted]

- [redacted]
- [redacted]

9.3.5 Other Analyses

9.3.5.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.5.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, race/ethnicity and region) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment (satralizumab or placebo). Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.5.3 Pharmacokinetic Analyses

The PK analysis population consists of all participants in the safety analysis set with at least one valid post-dose concentration result with a dosing record and sampling time. The trial will evaluate the PK characteristics of satralizumab treatment over 24 weeks in Part I of the study by summary statistics. PK samples will also be taken during Part II of the study, to further characterize the pharmacokinetics of satralizumab in TED over longer-term treatment. The serum concentration at each sampling timepoint will be described with means and standard deviation of C_{trough} irrespective of whether participants receive rescue therapy, miss a dose, or if study drug administration is delayed, or if they withdraw from treatment before data collection at Week 24. Individual and mean serum-concentration-versus-time curves will be plotted. Non-linear mixed effects analysis will be performed to analyze the satralizumab concentration–time data collected in the trial. The model to be used was previously developed on the basis of PK data from adult healthy volunteers and adult and adolescent participants with NMOSD. Further model development may be undertaken if needed in order to achieve a satisfactory description of the data, and the data from this study may be pooled with data from other studies with satralizumab. Population and individual PK and exposure parameters will be generated based on the model. Covariate analysis, including demographic factors and ADA status, will also be performed. Both the satralizumab concentration data and the results of the pop PK analysis will be reported separately from the CSR.

Further details are described in a separate Data Analysis Plan.

9.3.5.4 Immunogenicity Analyses

The immunogenicity analysis population will consist of all participants with at least one ADA assessment. Participants will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The number and proportion of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, participants are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60-titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

The percentage of participants who have positive or negative ADA results for satralizumab will be tabulated. PK, PD, efficacy parameters, and safety will be summarized by anti-satralizumab antibody (i.e., satralizumab ADA) status.

Pharmacodynamic Analyses

Serum IL-6 and sIL-6R levels will be summarized by treatment group and timepoint graphically and descriptively, as appropriate.

9.4 INTERIM ANALYSES

Safety data will be reviewed regularly in an ongoing manner by the iDMC. No further interim analyses are planned.

10. REFERENCES

Allen RC, Bradley EA, Fante, RG, et al. A Perspective on the Current Role of Teprotumumab in Treatment of Thyroid Eye Disease. Ophthalmology. 2021;128(8):1125–8.

Anvari M, Khalilzadeh O, Esteghamati A, et al. Genetic susceptibility to Graves' ophthalmopathy: the role of polymorphisms in proinflammatory cytokine genes. Eye (Lond). 2010;24(6):1058–63.

Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362(8):726–38.

Bahn RS. Autoimmunity and Graves' disease. Clin Pharmacol Ther. 2012;91(4):577–9.

Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012;97(12):4454–63.

Bartalena L. Graves' orbitopathy: imperfect treatments for a rare disease. Eur Thyroid J. 2013b;2(4):259–69.

Bartalena L, Kahaly GJ, Baldeschi L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021;185(4):G43-G67. Published 2021 Aug 27. doi:10.1530/EJE-21-0479

Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5(1):9–26.

Bartalena L, Baldeschi L, Dickinson A, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008;158(3):273–85.

Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Trans Am Ophthalmol Soc. 1994;92:477–588.

Barrio-Barrio J, Sabater AL, Bonet-Farriol E, et al. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. J Ophthalmol. 2015;2015:249125.

Belinsky I, Creighton FX Jr, Mahoney N, et al. Teprotumumab and Hearing Loss: Case Series and Proposal for Audiologic Monitoring. Ophthalmic Plast Reconstr Surg. 2022;38(1):73–8.

Chow A, Silkiss RZ. Teprotumumab-associated chronic hearing loss screening and proposed treatments. BMJ Case Rep. 2022;15(4):e248335. Published 2022 Apr 13.

Dik WA, Virakul S, van Steensel L. Current perspectives on the role of orbital fibroblasts in the pathogenesis of Graves' ophthalmopathy. Exp Eye Res. 2016;142:83–91.

Ding AS, Mahoney NR, Campbell AA, Creighton FX. Sensorineural Hearing Loss After Teprotumumab Therapy for Thyroid Eye Disease: A Case Report. Otol Neurotol. 2022;43(2):e148–52.

Dolman PJ, Cahill K, Czyz CN, et al. Reliability of estimating ductions in thyroid eye disease: an International Thyroid Eye Disease Society multicenter study. Ophthalmology. 2012;119(2):382–9.

Douglas RS, Kossler AL, Abrams J, et al. Expert Consensus on the Use of Teprotumumab for the Management of Thyroid Eye Disease Using a Modified-Delphi Approach. J Neuroophthalmol. 2022a;42(3):334–9.

Douglas RS, Dailey R, Subramanian PS, et al. Proptosis and Diplopia Response With Teprotumumab and Placebo vs the Recommended Treatment Regimen With Intravenous Methylprednisolone in Moderate to Severe Thyroid Eye Disease: A Meta-analysis and Matching-Adjusted Indirect Comparison. JAMA Ophthalmol. 2022b;140(4):328–35.

Draman MS, Ludgate M. Thyroid eye disease- an update. Expert Rev Ophthalmol. 2016:1–12.

European Group on Graves' Orbitopathy (EUGOGO*). Clinical evaluation: EUGOGO ATLAS [resource on the Internet]. 2001. Available from: http://www.associazionemediciendocrinologi.it/images/clinica/ausilii/EUGOGO_Atlas.pdf*

European Group on Graves' Orbitopathy (EUGOGO), Wiersinga WM, Perros P, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. Eur J Endocrinol. 2006;155(3):387–9.

Ezra DG, Krell J, Rose GE, et al. Transcriptome-level microarray expression profiling implicates IGF-1 and Wnt signalling dysregulation in the pathogenesis of thyroid-associated orbitopathy. J Clin Pathol. 2012;65(7):608–13.

Gerding MN, Terwee CB, Dekker FW, et al. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. Thyroid. 1997;7(6):885–9.

Gillespie EF, Smith TJ, Douglas RS. Thyroid eye disease: towards an evidence base for treatment in the 21st century. Curr Neurol Neurosci Rep. 2012;12(3):318–24.

Gupta S, Douglas RS. The pathophysiology of thyroid eye disease: implications for immunotherapy. Curr Opin Ophthalmol 2011;22:385–90.

Highland J, Gordon S, Reddy D, Patel N. Ototoxicity and Teprotumumab. Ann Otol Rhinol Laryngol. 2022;131(8):910–3.

Hiromatsu Y, Yang D, Bednarczuk T, et al. Cytokine profiles in eye muscle tissue and orbital fat tissue from patients with thyroid-associated ophthalmopathy. J Clin Endocrinol Metab. 2000;85(3):1194–9.

ICH International Council for Harmonisation. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1) [resource on the Internet]. November 201]. Available at: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

Kahaly GJ, Hardt J, Petrak F, et al. Psychosocial factors in subjects with thyroidassociated ophthalmopathy. Thyroid. 2002;12(3):237–9.

Kahaly GJ, Pitz S, Hommel G, et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005;90(9):5234–40.

Khong JJ, McNab AA, Ebeling PR, et al. Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. Br J Ophthalmol. 2016;100(1):142–50.

Kumar S, Schiefer R, Coenen MJ, et al. A stimulatory thyrotropin receptor antibody (M22) and thyrotropin increase interleukin-6 expression and secretion in Graves' orbital preadipocyte fibroblasts. Thyroid. 2010;20(1):59–65.

Mantel, N., and Haenszel, W. Statistical Aspects of Analysis of Data from Retrospective Studies of Disease. Journal of the National Cancer Institute 1959;22:719–748.

Patel A, Yang H, Douglas RS. A new era in the treatment of thyroid eye disease. Am J Ophthalmol. 2019;208:281–8.

Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. Ophthalmic Plast Reconstr Surg. 2014;30(2):162–167.

Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. Am J Ophthalmol. 2018;195:181-90.

Ponto KA, Merkesdal S, Hommel G, et al. Public health relevance of Graves' orbitopathy. J Clin Endocrinol Metab. 2013;98(1):145–52.

Sánchez-Bilbao L, Martínez-López D, Revenga M, et al. Anti-IL-6 Receptor Tocilizumab in Refractory Graves' Orbitopathy: National Multicenter Observational Study of 48 Patients. J Clin Med. 2020;9(9):2816.

Sato T. On the Variance Estimator of the Mantel-Haenszel Risk Difference.(Letter to the editor). Biometrics. 1989;45:1323–1324.

Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the ocular surface disease index. Arch Ophthalmol. 2000;118:615–621.

Sears CM, Azad AD, Amarikwa L, et al. Hearing Dysfunction After Treatment With Teprotumumab for Thyroid Eye Disease. Am J Ophthalmol. 2022;240:1–13.

Slowik M, Urbaniak-Kujda D, Bohdanowicz-Pawlak A, et al. CD8+CD28-lymphocytes in peripheral blood and serum concentrations of soluble interleukin 6 receptor are increased in patients with Graves' orbitopathy and correlate with disease activity. Endocr Res. 2012;37(2):89–95.

Weetman AP, Cohen S, Gatter KC, et al. Immunohistochemical analysis of the retrobulbar tissues in Graves' ophthalmopathy. Clin Exp Immunol. 1989;75(2):222-7.

Wiersinga WM. Quality of life in Graves' ophthalmopathy. Best Pract Res Clin Endocrinol Metab. 2012;26:359-70.

Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. Thyroid. 2002;12(10):855-60.

Terwee CB, Prummel MF, Gerding MN, et al. Measuring disease activity to predict therapeutic outcome in Graves' ophthalmopathy. Clin Endocrinol (Oxf). 2005;62(2):145-55.

UpToDate, Inc. Treatment of Graves' orbitopathy (ophthalmopathy) [resource available on the internet]. 2020 [updated 14 May 2020; cited 13 September 2022]. Available from: https://www.uptodate.com/contents/treatment-of-graves-orbitopathy-ophthalmopathy.

Yu CY, Correa T, Simmons BA, Hansen MR, Shriver EM. Audiology findings in patients with teprotumumab associated otologic symptoms. Am J Ophthalmol Case Rep. 2021;24:101202. Published 2021 Sep 16.

Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab. 2011;96(2):320-32.

Zhang-Nunes SX, Dang S, Garneau HC, et al. Characterization and outcomes of repeat orbital decompression for thyroid-associated orbitopathy. Orbit. 2015;34(2):57-65.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Up to *approximately 70* sites globally will participate to enroll approximately 120 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring.

An iDMC will be employed to monitor and evaluate participant safety throughout the study. An independent review facility will collect, store, and review imaging data.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website: https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–6 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). *The eCRF system utilized in this clinical trial is RAVE.* The

investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or onsite monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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A1–7 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–8 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–9 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–10 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local or central laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Urine pregnancy test* • Urine pregnancy tests will be performed at specified study visits in the schedule of activities. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis* • Dipstick urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood. If any abnormalities are detected on urine dipstick tests, a complete urinalysis (including microscopic examination of urine and/or urine culture) is to be performed as deemed necessary. • Tuberculosis test*
Central Laboratory Tests
• Serum pregnancy test*: All female participants of childbearing potential will have a serum pregnancy test performed at screening. A serum pregnancy test may also be required during the study to confirm a positive urine pregnancy test. • Hematology: hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), quantitative platelet count, fibrinogen and INR • Chemistry panel (serum or plasma): albumin, total protein, total bilirubin, ALP, AST, ALT, GGT, LDH, ferritin, BUN, creatinine, sodium, Cl, K, Ca, P, lipase, CRP, and serum CK. • Complements C3, C4, and CH50 • Quantitative immunoglobulins: IgA, IgE, IgG, and IgM • Thyroid function testing: thyroid stimulating hormone, free T3 and free T4 • HIV testing • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test • Lipids: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides

Note: Local laboratory tests will need to be performed in clinic.
*These lab tests may be conducted at the local or central laboratory

Investigators must document their review of each laboratory safety report. Laboratory results that could unmask the study (CRP, fibrinogen, complement [C3, C4, and CH50]), and non-safety results including satralizumab pharmacokinetics, IL-6, sIL-6R, ADAs, and

immunoglobulins will not be reported to investigative sites or other masked personnel *from baseline/Day 1 and post-baseline measurements* until the study has been unmasked. The iDMC will perform periodic unmasked safety reviews, which will include the laboratory parameters that are masked to the Sponsor and site.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, 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 drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Caser Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5 .

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5 , to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken offline, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 28 weeks after the final dose of study treatment (i.e. until Week 72 [which is 28 weeks after the final dose of study treatment at Week 44]). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event /Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 28 weeks after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined in Section 8.3.1) or after the final dose of study treatment, if the event is believed to be related to prior exposure to study treatment. These events should be reported through

use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 INJECTION REACTIONS

Adverse events that occur during or within 24 hours after study drug administration and are considered to be related to study drug injection should be captured as a diagnosis (e.g., “injection-related reaction”/“injection site reaction”/"anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.3 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an

adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.8 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.9 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.10 LACK OF EFFICACY OR WORSENING OF THYROID EYE DISEASE

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of Thyroid Eye Disease on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "dysthroid optic neuropathy, choroidal folds and corneal ulceration"). Acronyms or abbreviations should not be used when reporting adverse events. Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These

data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Clinical Measures of Severity scale (based on EUGOGO consensus) see Section 8.1.2.5. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through the use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required to perform any of the procedures required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours.

A3–8 SPECIAL SITUATIONS: ACCIDENTAL OVERDOSE AND/OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)

After initiation of the study drug, special situations associated with satralizumab/ matching placebo and any associated adverse events will be reported until 28 weeks after the final dose of the study drug.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A3-8).

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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Appendix 4: Safety Plan: Management of Identified and Potential Risks

A4–1 RISKS ASSOCIATED WITH SATRALIZUMAB

Satralizumab is not approved for the treatment of thyroid eye disease. The safety plan for participants in this study is based on clinical experience with satralizumab in completed and ongoing studies with neuromyelitis optica spectrum disorder (NMOSD) and safety risks observed with medicines in the same class (i.e., anti–interleukin[IL]-6 receptor [IL-6R]R antibodies). The anticipated important safety risks for satralizumab are outlined below. Please refer to the most recent Satralizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

A4–1.1 INFECTIONS

Treatment with IL-6R inhibitors may increase the risk of infections, including serious infections. Treatment with IL-6R inhibitors suppresses acute-phase reactions (e.g., fever, increase in C-reactive protein [CRP]) induced by IL-6 and accordingly suppresses signs and symptoms associated with infection, which may delay the detection of infection.

Reactivation of chronic hepatitis B virus has been observed with other treatments that affect the immune system. Tuberculosis (TB) activation has been reported with other anti–IL-6R antibodies.

The following patients will be excluded from this study (see Section 5.2).

- Patients with active or presence of recurrent bacterial, viral, fungal, mycobacterial infection, or other infection (excluding fungal infection of nail beds or dental caries) at baseline
- Patients with infection requiring hospitalization or treatment with IV anti-infective agents within 4 weeks prior to baseline visit
- Patients with positive hepatitis B (HBV) test at screening, defined as either of the following:
  - Positive hepatitis B surface antigen (HBsAg)
  - Positive total hepatitis B core antibody (total HBcAb) confirmed by a positive viral DNA polymerase chain reaction test
- Patients with positive hepatitis C (HCV) test at screening (defined as positive HCV antibody and detectable HCV RNA)

- Patients with evidence of latent or active TB (excluding patients receiving chemoprophylaxis for latent TB infection)
- Patients who received any live or live attenuated vaccine within 6 weeks prior to baseline visit

    No data are available on the effects of vaccination in patients receiving satralizumab. In general, it is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating satralizumab therapy. However, patients are not eligible to be enrolled in the study if live or live-attenuated vaccines are received within 6 weeks prior to baseline.

Management of Infections and Serious Infections

Guidelines for management of infections are outlined below:

- Participants should be closely monitored for the development of signs and symptoms of infection because signs and symptoms of acute inflammation may be attenuated as a result of suppression of the acute-phase reactants.
- Participants must be instructed to contact their physician immediately when any symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment.
- If a participant develops an infection, administration of study drug should be interrupted until the infection is controlled. Upon resolution of the infection, the treating physician should conduct a benefit-risk assessment before resuming treatment with study drug.
- If a participant develops hepatitis B infection (new onset or reactivation), study drug should be discontinued.
- Live or live attenuated vaccines should not to be given during the study or within 6 weeks prior to baseline as clinical safety has not been established.

A4–1.2 HYPERSENSITIVITY

Anaphylaxis and hypersensitivity reactions are considered a potential risk for all biologic medications, including satralizumab.

The symptoms or signs of hypersensitivity include, but are not limited to, blood pressure decrease, dyspnea, loss of consciousness, dizziness, nausea, vomiting, fever, chills, urticaria, itchiness, flushing, etc.

A decision to continue or discontinue treatment with satralizumab should be made taking into account the potential benefits and risks, if any of these events are observed.

Appendix 4: Safety Plan: Management of Identified and Potential Risks

Management of Possible Hypersensitivity Reactions to Satralizumab

Guidelines for management of hypersensitivity reactions are outlined below:

- SC injections should be administered at the study sites. Participants should stay in the clinic or hospital for at least 1 hour after study drug administration for the first five doses in Part 1 and Part 2 in order to receive treatment immediately in case anaphylaxis occurs (see Section 6.1). Study sites should have medications (e.g., corticosteroid, antihistamine, and epinephrine) and access to resuscitation facilities.
- Participants and caregivers will be provided with emergency contact information by the site. Participants and caregivers should be instructed to recognize the signs and symptoms of hypersensitivity reactions and to seek immediate medical attention if the participant develops symptoms of acute hypersensitivity reactions. Participants and caregivers should confirm with the investigator whether treatment with study drug may be continued.
- If an anaphylactic reaction or other serious hypersensitivity reaction occurs, study drug should be discontinued.
- For other hypersensitivity reactions, a decision to continue or discontinue treatment with study drug will be made by the investigator in consultation with the Medical Monitor, taking into account the benefits and risks.

A4–1.3 LIVER ENZYME AND BILIRUBIN ELEVATION

It has been reported that IL-6 appears to have a hepato-protective effect on various forms of liver injury and promotes hepatocyte regeneration.

In the double blind (DB) period of the Phase III studies in patients with NMOSD, mild and moderate elevations of liver transaminases (ALT or AST) were observed with satralizumab treatment. Elevations of ALT or AST $\geq 3 \times$ upper limit of normal (ULN) were not associated with increases in bilirubin.

Participants with AST or ALT $> 1.5 \times$ ULN at screening will be excluded from the study (see Section 5.2).

Liver function markers should be closely monitored, especially when satralizumab is administered concomitantly with anti-thyroid drugs (ATDs), or to participants with elevated transaminases (in the range of ULN to $1.5 \times$ ULN). Some of the allowed background ATDs e.g. methimazole (MMI) and propylthiouracil (PTU) may cause hepatotoxicity. Please refer to the local prescribing information of the background treatment(s) for details on their individual safety profile(s).

Recommended dose interruption or discontinuation for elevated liver enzymes are provided in Table A4-1.

Appendix 4: Safety Plan: Management of Identified and Potential Risks

Table A4-1 Management of Participants with Elevated Transaminases (ALT and/or AST)

ALT or AST Values	Action to Be Taken
>1 to $3\times$ ULN	• Reduction (interruption if necessary) of concomitant hepatotoxic drugs (if applicable). • For persistent increases in this range, study drug could be interrupted until AST and ALT is below ULN [a].
>3 to $5\times$ ULN	• Do not administer study drug. Laboratory tests (ALT, AST, ALP, and TBL) should be repeated within 72 hours to confirm value. Participants who cannot return to the trial site promptly may repeat the test locally. • The presence of clinical symptoms should be queried. • Study drug should be interrupted until AST and ALT is below $3\times$ ULN and follow recommendations above for >1 to $3\times$ ULN. • If at least one of following is associated with the ALT/AST increase, study drug should be discontinued immediately: – TBL $>2\times$ ULN and/or – INR $>1.5\times$ ULN and/or – Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
$>5\times$ ULN	• Do not administer study drug. Laboratory tests (ALT, AST, ALP, and TBL) should be repeated within 72 hours. If value is confirmed, study drug should be discontinued immediately and a gastroenterologist should be contacted. Participants who cannot return to the trial site promptly may repeat the test locally. • The presence of clinical symptoms should be queried. • Repeat test weekly until AST or ALT are $\leq 1.5\times$ ULN.

TBL = total bilirubin; ULN = upper limit of normal.

[a] ULN or participant's baseline value, whichever is higher.

A4–1.4 NEUTROPENIA

In the DB period of the Phase III studies in patients with NMOSD, decreases in neutrophil counts (including Grades 3 and 4 events) occurred following treatment with satralizumab. The majority of neutrophil decreases were transient or intermittent.

Patients with a low neutrophil count ($<2\times10^3/\mu L$) at screening will be excluded from this study (see Section 5.2).

Recommended dose interruption or discontinuation for ANC decreases are provided in Table A4-2.

Table A4-2 Management of Low Neutrophil Count

ANC ($\times 10^3/\mu L$)	Action to Be Taken
>1.0	Article I. Maintain the dose.
0.5–1.0	Article II. If neutropenia persists, study drug should be interrupted until ANC is above 1,000/μL. For restarting study drug administration after event resolution, please refer to Section 6.1. Article III. If ANC was $<1{,}000/\mu L$ at the previous laboratory test, ANC must be checked before treatment with the study drug (e.g., ANC test at site).
<0.5	• Study drug should be discontinued.

A4–1.5 THROMBOCYTOPENIA

In the DB period of the Phase III studies in patients with NMOSD, decreases in platelet counts were observed in patients treated with satralizumab. The majority of the decreased platelets were transient and not $<7.5\times10^4/\mu L$.

Participants with platelet count $<10\times10^4/\mu L$ at screening will be excluded from the study (see Section 5.2).

Recommended dose interruption on the basis of platelet counts are provided in Table A4-3.

Table A4-3 Management of Low Platelet Count

Platelet Count ($\times 10^4/\mu L$)	Action to Be Taken
>7.5	Article IV. Maintain the dose.
5.0–7.5	Article V. If thrombocytopenia persists, study drug should be interrupted until platelet count is $>7.5\times10^4/\mu L$. For restarting study drug administration after event resolution, please refer to Section 6.1.
<5.0	• Study drug should be discontinued.

A4–1.6 ELEVATIONS IN LIPID LEVELS

In the DB period of the Phase III studies in patients with NMOSD, elevations in total cholesterol and triglycerides were observed more often in patients treated with satralizumab compared with placebo.

Elevations in lipid levels in the participants should be managed according to local guidelines.

A4–1.7 LABORATORY ABNORMALITIES ASSOCIATED WITH THE PHARMACODYNAMIC EFFECT OF SATRALIZUMAB

In addition to the above abnormal laboratory parameters, in the Phase III studies with satralizumab in patients with NMOSD, decreases in CRP, fibrinogen, and complements (C3, C4, and CH50) were observed and are anticipated pharmacodynamic effects of satralizumab.

A4–1.8 CYP450 ENZYME NORMALIZATION

Elevation of serum IL-6 levels is known to be associated with inhibition of CYP450 enzyme activity. Blockade of IL-6 signaling by satralizumab may result in normalization of CYP450 activity and therefore increases in the metabolism of CYP450 substrates.

When starting or discontinuing satralizumab treatment, the participants who are receiving substrates of CYP450 3A4, 1A2, 2C9, or 2C19, and particularly those with a narrow therapeutic index (such as carbamazepine and phenytoin) should be carefully monitored and the serum level monitoring of the CYP substrates should be considered. Doses should be adjusted if needed to maintain their therapeutic effect.

Given the prolonged terminal drug-elimination half-life of satralizumab (approximately 30 days), the effect of satralizumab may persist for several months after stopping therapy.

A4–2 OTHER RISKS ASSOCIATED WITH DRUGS IN THE SAME CLASS

A4–2.1 GASTROINTESTINAL PERFORATIONS (COMPLICATIONS OF DIVERTICULITIS)

Gastrointestinal (GI) perforations have been reported rarely in patients with rheumatoid arthritis (RA) treated with other anti–IL-6R antibodies. IL-6R inhibition may suppress the acute symptoms (e.g., abdominal pain, pyrexia) associated with diverticulitis, causing delayed diagnosis and progression to perforation.

Patients with a history of diverticulitis or concurrent severe GI disorders (such as symptomatic diverticulosis) that, in the investigator's opinion, may lead to increased risk of complications such as GI perforation are excluded from the study (see Section 5.2).

Special caution should be exercised in those patients who receive concomitant therapies that have been associated with a risk of GI perforation. Please refer to the local prescribing information of the therapy for additional details on the risk of GI perforation.

Management of Participants with (Suspected) Gastrointestinal Perforation

Participants presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, hemorrhaging, and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with GI perforation, and appropriate measures taken. Study drug and suspected therapy should be discontinued for participants who develop GI perforation. Participants should be made aware of the symptomatology potentially indicative of complicated diverticular disease, and they should be instructed to alert their health care provider as soon as possible if these symptoms arise.

In participants who receive glucocorticoids and/or non-steroidal anti-inflammatory drugs, prophylactic treatment with proton pump inhibitors, or H_2 blocker should be considered.

A4–2.2 MALIGNANCIES

Although malignancies have been reported in patients given other IL-6R antibodies, there have been no reports to date that there is an appreciable increase in the occurrence of malignancies. No increased risk of malignancies has been observed in clinical trials with satralizumab.

Patients with history of carcinoma or malignancy, unless deemed cured by adequate treatment with no evidence of recurrence for $\geq$5 years before screening (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured) will be excluded from the study (see Section 5.2).

Management of Participants with Malignancies

Study drug should be discontinued in participants with malignancies with the exception of local basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix uteri that have been completely excised and cured.

A4–2.3 DEMYELINATING DISORDERS

Demyelinating diseases, including multiple sclerosis and chronic inflammatory demyelinating polyneuropathy, have been reported in patients with rheumatoid arthritis administered with another anti–IL-6R antibody, but it is not known whether there is a causal relationship. If symptoms suggestive of a demyelinating disorder are reported, a complete neurological examination should be performed and additional diagnostic studies performed if indicated.

Appendix 4: Safety Plan: Management of Identified and Potential Risks

A4–3 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–3.1 TREATMENT INTERRUPTION

Satralizumab may be withheld in participants who experience toxicity considered to be related to study drug. Satralizumab may be withheld for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A4–3.2 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events are presented in Section A4–1.

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Collection of Pregnancy Information

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Appendix 5: Collection of Pregnancy Information

A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 12 weeks after the final dose of satralizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

Appendix 5: Collection of Pregnancy Information

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–3 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

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Appendix 6: Reporting Requirements for Medical Device Complaints

A6–1 REPORTING REQUIREMENTS FOR MEDICAL DEVICE COMPLAINTS

In this study, the prefilled syringe and needle safety device are considered medical devices. The investigator must report all device deficiencies to the Sponsor in the form of a medical device complaint. A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, and it can include malfunctions, use errors, and inadequate labeling. In reporting a medical device complaint, the investigator should forward as much information as possible to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event); the Sponsor will then fill out the IMP Deviation form (refer to the pharmacy manual for further details). If the medical device deficiency results in an adverse event to the study participant, the event must be reported on the Adverse Event electronic Case Report Form (eCRF) and submitted through the electronic data system. If the event fulfills seriousness criteria, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as outlined in Section A3–5.

Appendix 7
Instructions for Tuberculosis Screening and Treatment

INTERPRETATION OF TUBERCULOSIS SCREENING RESULTS

Immunosuppressant biologic treatments have been shown to increase the risk of tuberculosis (TB) infection or to cause conversion from latent to active TB in some circumstances. Because of this, patients must be screened for active or latent TB prior to entry to this study.

DEFINITIONS

Active TB is a disease caused by Mycobacterium tuberculosis (M. tuberculosis) in any part of the body and that is in an active state, as determined by either a smear or culture taken from any source which tests positive for TB or if there is radiographic evidence of TB. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine, or elsewhere) and can spread the infection to others.

Diagnosis of latent TB is established when an individual is infected with M. tuberculosis, as evidenced by a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA; e.g., QuantiFERON-TB Gold In-Tube assay®), but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others. Appropriate anti-mycobacterial therapy must start for such individuals at least 4 weeks before initiating study drug administration in this study, because the effect of anti-mycobacterial therapy may not appear immediately after initiating.

TUBERCULOSIS SCREENING

TB screening must be performed prior to initiation of study drug treatment. TB screening should be conducted per local guidance. For reference, the U.S. Centers for Disease Control's (CDC) guidance on TB testing may be found at http://www.cdc.gov/TB/TOPIC/testing/default.htm.

- As part of recording the patient's medical history, the patient will be asked if he or she has had either active or latent TB, and whether the patient has received a bacille Calmette-Guérin (BCG) vaccination. The patient will also be asked if he or she has been in contact with any individuals known to have active TB.
- TB test (e.g., TST [using purified protein derivative] and/or IGRA [e.g., QuantiferonTB Gold]) is required at screening according to local guidance.

A chest X-ray or chest computed tomography (CT) scan should be performed in participants with positive TB test or in participants who are at potential risk for TB infection or TB reactivation (e.g., on immunosuppressive therapies, recently in contact with a person who has infectious TB disease, live in or recently traveled to a high-prevalence region/countries, etc.), or according to local guidance.

Notes:

1. The TST may be positive if the patient has had a BCG vaccination or has been infected with TB in the past; IGRA results may also be positive in some cases of previous infection.

1) Positive results of the TST and IGRA test may be reduced by immune suppression.

2) Local guidance may vary depending upon the sensitivity of strains of M. tuberculosis present locally.

In case of any doubt as to the diagnosis of latent TB, it is advised that a local physician with expertise in the treatment of TB or the Medical Monitor is consulted.

A combination of the medical history, the results of the TST test and/or, IGRA test and any other investigations deemed appropriate by the investigator on the basis of clinical signs and symptoms indicative of TB infection elsewhere in the body will be used by the investigator to determine study eligibility at screening for this study.

TUBERCULOSIS TREATMENT

If the patient is positive for latent TB, then appropriate anti-mycobacterial therapy must start for the patient at least 4 weeks before initiating study drug administration in this study because the effect of anti-mycobacterial therapy may not appear immediately after initiating. Treatment regimens should be followed by the local guidance. If no local guidance exists for treatment of immunocompromised individuals, then the U.S. CDC's guidance must be followed (http://www.cdc.gov/TB/publications/LTBI/default.htm). In patients who test positive for latent TB and undergo anti-TB treatment per protocol, TB re-testing is not required as part of the re-screening process if the original TB test was conducted within 12 weeks prior to baseline.

In case of any doubt as to the appropriate course of anti-mycobacterial therapy of latent TB, it is advised that a local physician with expertise in the treatment of TB or the Medical Monitor be consulted.

MANAGEMENT OF SIGNS AND SYMPTOMS OF TUBERCULOSIS DURING THE STUDY

If new signs and symptoms of TB infection develop during the study, perform diagnostic tests as above. If TB infection is diagnosed, interrupt study drug and consult the Medical Monitor. Report TB infection as a "selected adverse event" (see Section 8.3.8.2). If TB infection is resolved completely, benefit–risk assessment should be done by the investigator before treatment with the study drug.

Appendix 8
Normal Exophthalmometry Values *(Mean and Range)* for Race and Gender

	Female (mm)		Male (mm)	
Race	*Mean ± SD*	*Range*	*Mean±SD*	*Range*
Black/African American [1]	*17.73 ± 2.53*	*12.6−23.04*	*18.41 ± 3.08*	*12.3 −24.65*
Asian Chinese [2]	*15.8 ± 1.8*	*10−22*	15.8±1.8	10–22
Hispanic/*Latino* [3]	16.2±2.2	*10.3 −22*	*17.6± 2.5*	10.5–25.5
Japanese [4]	15.*13 ± 2.31*	10.5–19.7	15.*35 ± 2.31*	10.7–19.9
Korean [5]	*13.6 ± 1.9*	*8 −19.5*	*13.6± 1.8*	*8 −19.5*
White [1]	*15.46 ± 2.34*	10.74–20.8	16.47±2.6	*11.31* −21.*71*

Note: *The method used to determine the 3 mm minimum proptosis level is at the investigator's discretion and can be based on patient-specific parameters such as differences in study eye versus non-study eye for unilateral TED, prior exophthalmometry measurement, or prior photograph, or referencing normal ranges listed in Appendix 8. It is important to note that this* table represents approximate values reported in literature. *and it is not encompassing.* It is meant for *information* purposes only.

[1] *Migliori* et. al. 2021

[2] *Wu* et. al. *2015*

[3] *Cheng* et. al

[4] *Nakayama et. al.1992*

[5] *Kwak et.* al. *1974*

REFERENCE

Cheng T, Wang F, Denisova K, et al. Normative exophthalmometry values in Hispanic individuals. Arch Soc Esp Oftalmol (Engl Ed). 2023 Apr;98(4):199-205.

Kwak YJ. Normal range of exophthalmos in Korea. J Korean Ophthalmol Soc. 1974;15(4):312-315.

Migliori, M.E. and Gladstone, G.J., 1984. Determination of the normal range of exophthalmometric values for black and white adults. Am J Ophthamol 98(4), pp.438-442.

Nakayama et al. Exophthalmometric values in contemporary Japanese population. Jpn J Clin Ophthalmol 1992.

Wu, D., Liu, X., Wu, D. et al. Normal Values of Hertel Exophthalmometry in a Chinese Han Population from Shenyang, Northeast China. Sci Rep 5, 8526 (2015).

Appendix 9
Order of Key Assessments

Order	*Assessment*
I	*PROs [a]: GO-QoL [b] & OSDI*
II	*ECG [c]*
III [d]	*Visual Acuity, IOP, Pupillary reaction, and Anterior segment examination*
IV [e]	*Posterior segment examination*

Note: This is not a comprehensive list of assessments. Please refer to the schedule of activities Section 1.3 for information on all assessments. All assessments should be performed prior to study drug administration (aside from the post-dose vital signs mentioned below). Ocular assessments will be performed for both eyes, unless otherwise indicated, at specified time points according to the schedule of activities in Section 1.3.

[a] PROs should be performed prior to all non-PRO assessments. Refer to A12–1.

[b] The GO-QoL questionnaire can be completed up to 48 hours prior to dosing

[c] ECG recordings should be performed at baseline prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Must be done prior to IxRS being recorded

[d] Should be performed prior to dilating eyes. Refer to Section 8.1.1.

[e] Dilated examination of the posterior segment should be performed with either binocular indirect ophthalmoscopy or on a slit lamp with a high-power lens per Section 8.1.1.

Appendix 10
Clinical Measures of Severity

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Table A10-1 Clinical Measures of Severity

Item and Assessment Scale	Minimum change required for classifying overall response
Exophthalmos (measured in mm using the same Hertel exophthalmometer provided by the Sponsor for consistency in measurement and same base setting for each individual patient)	Decrease ≥ 2mm
Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed and with distant fixation)	Decrease ≥ 2mm
Swelling of the eyelids (absent, mild, moderate, severe)*	Decrease ≥ One grade
Redness of the eyelids (absent, present)	Decrease ≥ One grade
Conjunctival edema (absent, present)	Decrease ≥ One grade
Conjunctival redness (absent; mild (equivocal or minimal redness), moderate (<50% of definite conjunctival redness, severe (>50% of definite conjunctival redness)*	Decrease ≥ One grade
Inflammation of the caruncle or plica (absent, present)	Decrease ≥ One grade
Subjective diplopia score 0 = no diplopia; 1 = intermittent (diplopia in primary position of gaze, when tired or when first awakening; 2 = inconstant (diplopia at extremes of gaze); 3 = constant (continuous diplopia in primary or reading position	Decrease ≥ One grade
Eye muscle involvement (ductions in degrees)	Increase ≥ 8° in at least one direction of gaze
Corneal involvement (absent/ punctate keratopathy/ ulcer)	Decrease ≥ One grade
Optic nerve involvement Best corrected visual acuity Color vision Optic disc Relative afferent pupillary defect (absent/ present) Visual fields if optic nerve compression is suspected	Change of best corrected visual acuity by ≥ 2 lines on Snellen chart, or substantial color vision change, or significant change in optic disc appearance, or (dis-)appearance of relative afferent pupillary defect

Appendix 10: Clinical Measures of Severity

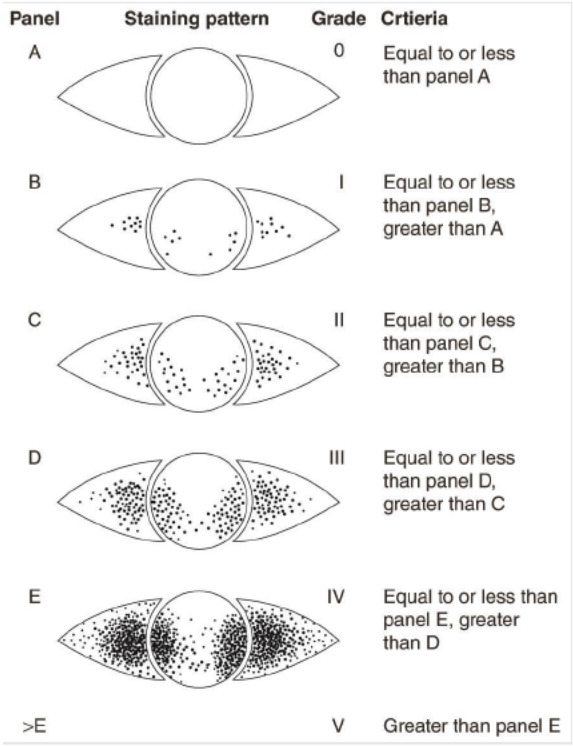
Item and Assessment Scale	Minimum change required for classifying overall response

Source: Bartalena et al. 2008.

* *For mild eyelid swelling and mild conjunctival redness on the clinical measures of severity scale, the CAS score must be recorded as absent (negative) in accordance with the EUGOGO Clinical Evaluation Atlas (EUGOGO 2021)).*

Appendix 11
Oxford Grading Chart

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Source: Bron et al. 2003.

Appendix 12
Clinical Outcome Assessments

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Appendix 12: Clinical Outcome Assessments

A12–1 CLINICAL OUTCOME ASSESSMENT INSTRUMENT(S)

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the appropriate instruments to be administered in the correct order at each specified timepoint.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 15 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

  Site staff should review all completed instruments and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participants to complete the item or confirm that the item was intentionally left blank.

  PRO data will be collected on paper questionnaires. The data from these questionnaires will be entered into the electronic case report forms (eCRFs) by site staff.

  ClinRO instruments will be completed at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). ClinRO instruments will be administered *before* the *participant receives any information on disease status*, prior to the *performance of non-ClinRo assessments, and prior to the* administration of

study treatment. The instruments will be completed on the designated eCRF/provided by the Sponsor in pre-printed booklets. *Healthcare professionals* must complete the official version of each ClinRO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol. *ClinRO data will be collected on paper questionnaires. The data from these questionnaires will be entered into the electronic case report forms (eCRFs) by site staff.*

A12–1.1 OCULAR SURFACE DISEASE INDEX

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Appendix 12: Clinical Outcome Assessments

Protocol #: GP44467 Screening No.: ☐☐☐☐☐☐ Subject No.: ☐☐☐☐☐☐

Site No.: ☐☐☐☐☐☐ Visit: _____ DATE: ☐☐-☐☐☐-20☐☐

Administrator Initials _____

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned? . . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D (D = sum of scores for all questions answered) (D)

Total number of questions answered (do not include questions answered N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

Appendix 12: Clinical Outcome Assessments

Protocol #: GP44467 Screening No.: ☐☐☐☐☐ Subject No.: ☐☐☐☐☐

Site No.: ☐☐☐☐☐☐ Visit: DATE: ☐☐-☐☐☐-20☐☐

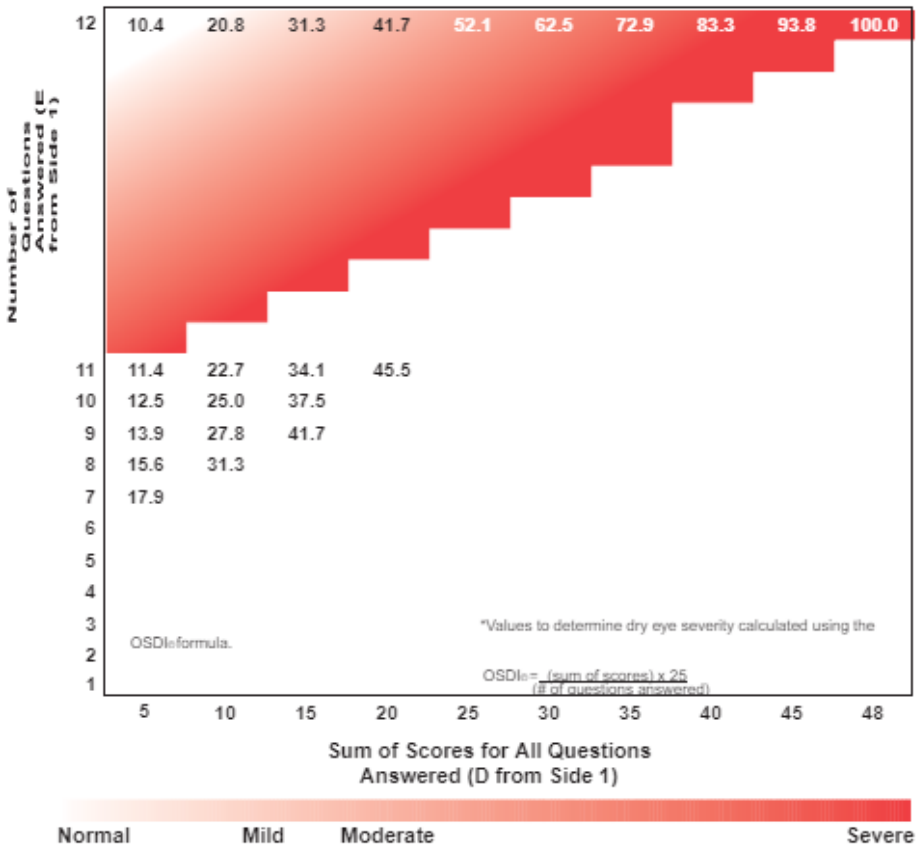
Administrator Initials _

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1,2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



Source: Schiffman et al. 2000.

Appendix 12: Clinical Outcome Assessments

A12–1.2 GRAVES' OPHTHALMOPATHY QUALITY OF LIFE

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Appendix 12: Clinical Outcome Assessments

Protocol #: GP44467 Screening No.: ☐☐☐☐☐☐ Subject No.: ☐☐☐☐☐

Site No.: ☐☐☐☐☐☐ Visit: _____ DATE: ☐☐-☐☐☐-20☐☐

GO-Quality Of Life Questionnaire ☐ **Initial** ☐ **follow-up** Administrator Initials _____

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 in general

	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

Appendix 13
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

3) Stop the study treatment administration, if possible.
4) Call for additional medical assistance.
5) Maintain an adequate airway.
6) Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
7) Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
8) Continue to observe the participant and document observations.

Appendix 14
Investigational and Auxiliary Medicinal Product Designations (for Use in European Economic)

Table A14-1 presents the Investigational and Auxiliary Medical Products Designations for the European Economic Area.

Table A14-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Satralizumab (RO5333787)	IMP (test product)	Authorized	No[a]
Satralizumab (RO5333787)	IMP (placebo)	Unauthorized	Not applicable
rituximab	AxMP (rescue therapy)	Authorized	No[b]
tocilizumab	AxMP (rescue therapy)	Authorized	No[b]
cyclosporine	AxMP (rescue therapy)	Authorized	No[b]
azathioprine	AxMP (rescue therapy)	Authorized	No[b]
oral glucocorticoids	AxMP (rescue therapy)	Authorized	No[b]
mycophenolate mofetil	AxMP (rescue therapy)	Authorized	No[b]
intravenous glucocorticoids	AxMP (rescue therapy)	Authorized	No[b]

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

[a] Satralizumab is approved as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.

[b] Rituximab, tocilizumab, cyclosporine, azathioprine, oral glucocorticoids, mycophenolatemofetil, intravenous glucocorticoids are classified as authorized AxMP based on the 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy (European Journal of Endocrinology 2021) even though not authorized in EEA for this indication.

Appendix 15
Grading Scale for Assessment of Anterior Chamber Cells and Flare, Vitreous Cells, Vitreous Haze, and Vitreous Haemorrhage

Table A15-1 Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field[a]
0	<1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

Note: Reproduced from Foster et al. 2016. The Standardization of Uveitis Nomenclature (SUN) Working Group criteria.

Reference: Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016;61:1-17.

[a] Field size is a 1-mm slit beam.

Table A15-2 Grading Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Note: Reproduced from Foster et al. 2016. The Standardization of Uveitis Nomenclature (SUN) Working Group criteria.

Reference: Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016;61:1-17.

Appendix 15 Grading Scale for Assessment of Anterior Chamber Cells and Flare, Viterous Cells, Vitreous Haze, and Vitreous Haemorrhage

Table A15-3 Grading Scheme for Vitreous Cells

Grade	Number of Vitreous Cells
0	No cells
0.5+	1–10
1+	11–20
2+	21–30
3+	31–100
4+	>101[a]

Note: Reproduced from Foster et al. 2016. The Standardization of Uveitis Nomenclature (SUN) Working Group criteria.

Reference: Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016;61:1-17.

[a]There is an error in the publication. This should read ≥101.

Table A15-4 Grading Scheme for Vitreous Haze

Grade	Clinical Findings
0	None. No Inflammation.
0.5+	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fiber layer reflex)
1+	Posterior pole clearly visible. Mild blurring of the retinal vessels and optic nerve
2+	Moderate blurring of the optic nerve head
3+	Posterior pole details very hazy. Marked blurring of the optic nerve head
4+	Posterior pole details barely visible. Optic nerve head not visible

Nussenblatt et al. 1985; adapted in Jabs et al. 2005; updated in Lowder et al. 2011.

Appendix 15 Grading Scale for Assessment of Anterior Chamber Cells and Flare, Viterous Cells, Vitreous Haze, and Vitreous Haemorrhage

Table A15-5 Grading Scheme for Vitreous Hemorrhage

Grade	Clinical Findings
None (0)	Retina is visible.
1+	Retinal detail is visible; some hemorrhage is visible by ophthalmoscopy.
2+	Large retinal vessels are visible, but central retinal detail is not visible by ophthalmoscopy.
3+	Red reflex is visible, but no central retinal detail is seen posterior to the equator by ophthalmoscopy.
4+	No red reflex by ophthalmoscopy.

Excerpted from: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis. Fundamentals and clinical practice. 2nd rev.ed. New York: Mosby, 1996, p. 64.

Appendix 16 Abbreviations

Abbreviation or Term	Definition
ADA	anti-drug antibody
AUC	area under the concentration-time curve
AxMP	axiliary medicinal product
C_{max}	maximum concentration
C_{trough}	steady-state concentration at the end of the dosing interval
CAS	Clinical Activity Score
CIV ID	Clinical Investigation Identification Number
CMH	Cochran-Mantel-Haenszel (test)
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRC	central reading center
CRO	contract research organization
CRP	C-reactive protein
CS	corticosteroids
CSR	Clinical Study Report
DAIDS	Division of AIDS
DB	double blind
DM	double-masked
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EUGOGO	European Group on Grave's Orbitopathy
FAS	full analysis set
GO	Grave's ophthalmopathy/ orbitopathy
GO-QoL	Grave's orbitopathy- Quality of Life
HBV	hepatitis B
HBsAg	hepatitis B surface antigen
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IL	interleukin
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure

Appendix 16 Abbreviations

Abbreviation or Term	Definition
IRB	Institutional Review Board
IST	immunosuppressant
IVT	intravitreal
IxRS	interactive voice or web-based response system
LPLV	last participant, last visit
MRD	margin reflex distance
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMOSD	neuromyelitis optica spectrum disorder
NSD	needle safety device
OSDI	Ocular Surface Disease Index
PD	pharmacodynamic
pop-PK	population-pharmacokinetic
PK	pharmacokinetic
PRO	patient-reported outcome
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RA	rheumatoid arthritis
RBR	Research Biosample Repository
RO	receptor occupancy
sIL-6R	soluble interleukin-6 receptor
TB	tuberculosis
TED	thyroid eye disease
TSHR	thyroid stimulating hormone receptor
ULN	upper limit of normal
VA	visual acuity
WES	whole exome sequencing
WGS	whole genome sequencing

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