CLINICAL STUDY PROTOCOL

Title:	ASCEND GO 2: A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled Study of RVT-1401 for the Treatment of Patients with Active, Moderate to Severe Graves' Ophthalmopathy
Sponsor	Immunovant Sciences GmbH, a Swiss Limited Liability Company, is the Sponsor of this study. Immunovant, Inc., an affiliate of Immunovant Sciences GmbH, has been engaged by Immunovant Sciences GmbH to manage the day-to-day operations of the study. All references to "Sponsor" contained herein shall refer to Immunovant, Inc., acting pursuant to a services agreement with Immunovant Sciences GmbH.
Compound Name:	RVT-1401
Protocol Number	RVT-1401-2001
Indication	Graves' Ophthalmopathy
Development Phase	2b
Regulatory #s	IND: 141988 CTA: 226455 EUDRA CTA: 2018-004676-35
Version/ **Effective Date:**	Amendment 02: Version 3.0 09-AUG-2019 Amendment 01: Version 2.0 12-FEB-2019 Original: Version 1.0 14-DEC-2018
Immunovant, Inc. Study Director	[redacted], [redacted] Telephone: [redacted] Email: [redacted]

NCT Number: NCT03938545

Confidentiality Statement

The information contained in this document, particularly unpublished data, is the property or under control of Sponsor, and is provided to you in confidence as an investigator, potential investigator or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Sponsor, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE:

Study title: A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled Study of RVT-1401 for the Treatment of Patients with Active, Moderate to Severe Graves' Ophthalmopathy

Protocol Number: RVT-1401-2001

This protocol has been approved by Sponsor's representative. The following signatures document this approval.

[redacted]

Immunovant, Inc.

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Contact	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number
Primary Medical Monitor	[redacted]	Office: [redacted]	Cell: [redacted]
SAE contact information	[redacted]		

Study Sponsor:

Immunovant Sciences GmbH Registered Address:

Viaduktstrasse 8
4051 Basel
Switzerland

Immunovant, Inc. Address:

320 W. 37th St.
New York, NY 10018
USA

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations and comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Principal Investigator Name (Printed)	Signature
Site	Date

1. TABLE OF CONTENTS

PAGE

2. PROTOCOL SUMMARY FOR STUDY RVT-1401-2001

Study Title	A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled Study of RVT-1401 for the Treatment of Patients with Active, Moderate to Severe Graves' Ophthalmopathy
Objectives	**Primary** To examine the effects of RVT-1401 versus placebo on proptosis responder rate at week 13 To assess the safety and tolerability of RVT-1401 in patients with active, moderate to severe GO **Secondary** To examine the effect of RVT-1401 versus placebo on proptosis responder rate at weeks 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 20 To examine the effect of RVT-1401 versus placebo on proportion of patients with a CAS score of 0 or 1 To examine the effect of RVT-1401 versus placebo on mean change from baseline in proptosis To examine the effect of RVT-1401 versus placebo on mean change from baseline in CAS To examine the effect of RVT-1401 versus placebo on overall ophthalmic improvement To examine the effect of RVT-1401 versus placebo on diplopia To examine the effect of RVT-1401 versus placebo on the Graves' Ophthalmopathy Quality of Life (GO-QOL) score in the visual functioning and appearance subscales To assess the change in serum levels of anti-TSHR antibodies and total IgG & IgG subclasses (1-4) To examine RVT-1401 PK following repeated doses in patients with active, moderate to severe GO To measure anti-RVT-1401 antibodies following repeated doses in patients with moderate to severe

	active GO
Study Phase	Phase 2b
Target Population	Graves' Ophthalmopathy
Number of Participants Planned	Approximately 77 participants
Number of Study Centers Planned	Approximately 20 centers
Study Design	Randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of RVT-1401 in GO patients
Duration of Treatment	12 weeks
Criteria for Evaluation (Endpoints)	**Primary** Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye). Assessment of safety and tolerability by analysis of adverse event (AE) data and changes from baseline in vital signs, ECGs, and clinical laboratory values **Secondary** Proportion of participants with CAS of 0 or 1 Change from baseline in proptosis Change from baseline in CAS Proportion of patients with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye: • Reduction in proptosis by at least 2 mm; • Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree); • Improvement in CAS by at least 2 points

	Change from baseline in the Gorman Score for Diplopia Change from baseline in the GO-QOL visual functioning and appearance subscale scores Change from baseline in levels of anti-TSHR antibodies Change from baseline in levels of total IgG and IgG subclasses (1-4) Concentration of RVT-1401 pre-dose (Ctrough) Immunogenicity determined by number of participants with treatment-emergent positive anti-RVT-1401 antibodies

3. INTRODUCTION

3.1. Background

RVT-1401 is a fully human anti-neonatal FC receptor (FcRn) monoclonal antibody. FcRn is critical to the regulation of Immunoglobulin G (IgG) [Roopenian, 2007]. In addition to its central role in mediating the transport of IgG within and across cells of diverse origin, it also serves to rescue IgG from degradation, thereby prolonging its circulating half-life [Roopenian, 2007]. Targeting the FcRn pathway has been shown to dramatically reduce circulating IgG, thus supporting its use in the treatment of auto-Ab mediated autoimmune diseases. RVT-1401 functions by inhibiting the binding of IgG to FcRn, resulting in the rapid catabolism of IgG via lysosomal degradation.

3.1.1. Graves' Ophthalmopathy

Graves' disease is characterized by hyperthyroidism with concomitant low levels of thyroid stimulating hormone (TSH). Specifically, the hyperthyroidism is caused by antibodies that bind to and are agonists at the TSH receptors (TSHR) in the thyroid [Smith, 2017]. TSH receptors are also located in non-thyroid tissues including dermal fibroblasts, orbital fibroblasts, and adipocytes. Upregulation of TSHR in these tissues is believed to be responsible for Graves' dermopathy (pretibial myxedema) and Graves' ophthalmopathy (GO) associated with Graves' disease [Bahn, 2010].

In addition to pathogenic autoantibodies directed at TSHR, IgG that activate insulin-like growth factor receptor (IGF-1R) signalling in patients with Graves' disease has also been suggested as contributing to GO [Pritchard, 2003]. Studies investigating this pathway have led to the discovery that the IGF-1R and TSHR form a receptor complex where IGF-1R can augment the signalling of TSHR [Tsui, 2008]. A recent clinical trial assessing the efficacy of teprotumumab, an IGF-1R inhibitory monoclonal antibody (MAb) in patients with active, moderate-to severe GO demonstrated positive clinical benefit lending support to the role of this pathway [Smith, 2017].

The exact nature of the interaction between IGF-1R and TSHR continues to be investigated. Some data suggest synergistic activation of hyaluronan secretion with simultaneous activation of TSHR and IGF-1R, and that the effects of TSHR stimulating antibodies are only partially blocked by an IGF-1R antagonist while it can be completely blocked with a TSHR antagonist [Krieger, 2015]. These data indicate that both TSHR and IGF-1R play a critical role in the pathogenesis of GO.

GO is characterized by enlarged extraocular muscles and an increased volume of orbital fat. In severe cases, this can lead to diplopia and/or loss of vision. The disease passes through several phases; from the onset, the first phase involves worsening of symptoms and signs in the active/inflammatory phase. This is followed by gradual improvement in the inflammatory signs and congestive symptoms until eventually no further changes occur. It is in the final stable (inactive) state where abnormalities in both function and appearance may persist indefinitely. Therefore, treatments should be aimed at the active phase of GO to ideally prevent the occurrence of permanent changes.

RVT-1401 will reduce levels of all pathogenic IgG, while teprotumumab is limited to preventing signalling through IGF-1R. Thus, RVT-1401 is hypothesized to be more effective than teprotumumab for the treatment of GO due to a broader effect on multiple targets important in the pathophysiology of this disease. In addition, RVT-1401 is expected to have effects on both ocular and thyroid manifestations of Graves' disease. No other anti-FcRn compounds are currently in clinical development for the treatment of GO, giving RVT-1401 the potential to be first-in-class with broader application using a convenient subcutaneous (SC) mode of administration.

3.2. Rationale

3.2.1. Study Rationale

The purpose of the current study is to assess the efficacy and safety/tolerability of three dose regimens of RVT-1401 in the treatment of active, moderate to severe GO patients. In addition, the study is designed to characterize RVT-1401 exposure to reduction in anti-TSHR IgG.

3.2.2. Dose Rationale

An autoimmune response against the TSHR plays a major role in the development of GO. This is supported by studies that have shown elevated TSHR expression in the orbital tissues from patients with GO as well as the fact that anti-TSHR IgG antibodies are detectable in the majority of patients with GO [Starkey, 2003; Bahn, 1998; Wakelkamp, 2003; Bahn, 2010]. Anti-TSHR antibody serum levels have also been shown to be directly associated with GO clinical features and have prognostic value such that patients with persistently high TSHR titers have a greater risk of severe disease course and outcome [Lytton, 2010; Ponto, 2011; Eckstein, 2006]. In GO, RVT-1401 treatment is expected to lead to a reduction in the levels of pIgG such as anti-TSHR antibodies and thus provide therapeutic benefit to these patients.

RVT-1401 is designed to provide patients with a treatment option that can allow home administration via SC injection. This significantly reduces the burden that an IV infusion treatment (e.g., teprotumumab) places on patients who will be required to go to an infusion center to receive their treatment.

Three dosing regimens of RVT-1401 will be assessed in this study. All dosing regimens will involve once weekly SC injections:

- Dosing Regimen A - 680 mg weekly for 12 weeks
- Dosing Regimen B - 340 mg weekly for 12 weeks
- Dosing Regimen C - 255 mg weekly for 12 weeks

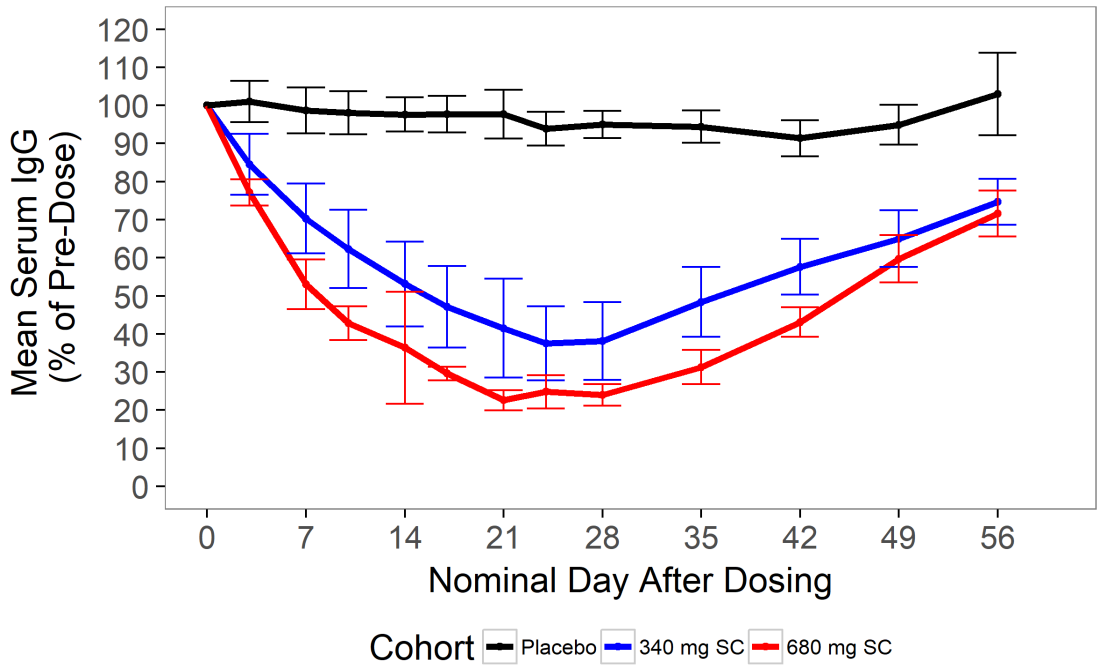
Given that there is a practical limit on the volume that can be administered via SC injection, the two higher doses represent what can be administered as a single SC injection (340 mg) and two SC injections (680 mg) per week with the current formulation.

As it is unknown how much IgG reduction is needed to show clinical benefit, three dosing regimens are proposed to explore the relationship between IgG reduction and clinical effect compared to placebo. The 680 mg/weekly dose will provide the maximum reduction in total IgG and is thus expected to have the greatest potential for demonstrating maximum clinical benefit. The other two RVT-1401 doses (340 mg/weekly and 255/weekly) will allow characterization of clinical benefit at lower doses.

The proposed weekly doses are expected to provide an average total IgG reduction of approximately 75-80%, 65-70%, and 45-55% for 680 mg, 340 mg, and 255 mg respectively, by the fourth or fifth dose. It is predicted that the nadir IgG reduction will be achieved by the 3rd-5th dose (depending on dose studied) and maintained following the remaining doses before rising back to baseline over the next 6 to 8 weeks after stopping treatment.

These assumptions are supported by preliminary PD results, shown in Figure 1**,** of the ongoing Phase 1 clinical study RVT-1401-1001 (Section 3.2.3). In healthy participants, 4 weekly SC injections of 680 mg of RVT-1401 produced an average total IgG percent reduction from baseline of 78%.

Figure 1: Serum IgG (Mean +/-SD) Reduction Following Multiple Doses of RVT-1401 (Study RVT-1401-1001)



In study RVT-1401-1001, the inter-individual variability in IgG reduction and PK was larger in the 340 mg cohort vs. the 680 mg cohort; this difference can be explained by lower receptor occupancy in the 340 mg cohort throughout the dosing interval across all individuals. It is also noteworthy that, with both doses, the variability in exposure decreased with repeat dosing. This may indicate that full receptor occupancy is not lost

within the dosing interval, and that with subsequent doses, more receptors are being occupied or remain occupied.

In the repeat dose 340 mg cohort, there were some individuals who did not achieve nadir IgG concentration until after the last dose, indicating they may have not reached steady state. In contrast, most subjects in the 680 mg cohort achieved nadir concentration prior to the last dose and maintained that response until after the last dose, indicating steady state response was achieved. These data will be used to support dose selection in future studies.

Since a weekly 340 mg and 680 mg dose of RVT-1401 produce a significant reduction in total serum IgG levels, which in GO patients would also include anti-TSHR IgG, it is expected that RVT-1401 treatment will provide therapeutic benefit to these patients. As it is unknown to what extent reduction of anti-TSHR IgG is needed to translate into clinical efficacy, this trial has been designed to assess multiple dosing regimens to further assess a minimum effective dose.

3.2.3. Clinical Experience

RVT-1401 has been studied in two Phase 1 clinical studies (HL161BKN-001 and RVT-1401-1001) designed to assess the safety, tolerability, PK, and PD following single (IV and SC) and multiple (SC) doses in healthy participants. As of December 14, 2018, RVT-1401 has been administered to 65 healthy participants at the following doses: 0.1 mg/kg as a 1-hour IV infusion (n=4), 100 mg as a 1-hour IV infusion (n=6), 340 mg as a 1-hour IV infusion (n=6), 0.5 mg/kg SC injection (n=3), 1.5 mg/kg SC injection (n=6), 5 mg/kg SC (n=6), 340 mg SC injection (n=6), 500 mg SC injection (n=6), 765 mg SC injection (n=6). Eight participants have received repeated 340 mg SC injections weekly for 4 weeks and 8 participants have received repeated 680 mg SC injections weekly for 4 weeks.

3.2.3.1. Safety

See Investigator's Brochure (IB) for Details.

RVT-1401 has been well tolerated with no Grade 3 or 4 adverse events (AEs), and no withdrawals due to AEs. There was one SAE (Malpighian carcinoma in left side of the neck) considered unrelated to study drug.

All AEs in subjects receiving RVT-1401 have been reported as mild or moderate. One subject who received placebo experienced severe (Grade 3) pain from urinary lithiasis.

The most frequent AE for both groups was injection site reactions (erythema/ and or swelling). Overall, injection site reactions have resolved within a few hours after dosing; there were two exceptions of mild swelling (one RVT-1401 and one placebo subject) that resolved after 3 and 4 days, respectively. The frequency of injection site reactions was not dose-related and similar reactions were observed with placebo. Additionally, injection site reactions were not consistently observed following every injection in the repeat dose cohorts.

Preliminary data suggest no subject who has received RVT-1401 had clinically relevant changes in laboratory findings, electrocardiograms (ECGs), or vital signs.

3.2.3.2. Pharmacokinetics

3.2.3.3. Pharmacodynamic

Following the administration of single SC doses of RVT-1401, total IgG reduction increased with increasing dose, with a maximum reduction of 47% observed after a fixed dose of 765 mg. The nadir for IgG reduction following single SC dosing occurred between days 8-15 in most individuals. IgG serum levels on average returned to within 90% of baseline by 43 days after drug administration. Albumin levels were also reduced from baseline when compared to placebo showing a similar dose related trend. The highest reduction occurring following the 765 mg SC dose [redacted] but were not considered to be clinically significant reductions as all patients remained within normal limits (3.5 g/dL to 5.5 g/dL) and levels recovered quickly, returning to baseline ~ 2 weeks after nadir.

The amount of IgG reduction has also been assessed following weekly SC administration of 340 and 680 mg of RVT-1401 or placebo for 4 weeks. There were 8 subjects with data out to day 35, that were included in the preliminary PD analysis for the 680 mg cohort and 7 subjects with data out to day 49 that were included in the analysis for the 340 mg cohort. One subject only received 2 doses of 340 mg prior to withdrawing due to personal reasons, their data was not included in the preliminary PD analysis. There were 4 placebo subjects with data out to day 35 pooled across two cohorts for analysis of the PD endpoints. Figure 1 presents the mean IgG concentration-time profiles for both weekly SC administration of 340 mg and 680 mg doses. Figure 1 shows a reduction in serum IgG

as a percent of pre-dose across both 340 mg and 680 mg cohorts. In contrast, the placebo group demonstrated minimal changes in serum IgG as a percent of pre-dose. The reduction in serum IgG was more rapid following the 680 mg SC compared to the 340 mg SC. The median IgG nadir concentration occurred prior to the last dose in the 680 mg cohort whereas for the 340 mg it occurred approximately 3 days after the last dose. The finding that the 680 mg cohort achieved nadir concentration following the 3rd dose and maintained serum IgG reduction after the 4th dose, indicates a maximum response has likely been achieved, and that higher doses or more frequent dosing would yield little additional benefit. This is consistent with data from other anti-FcRn agents in development that have observed a maximum percent reduction in serum IgG from baseline of ~ 75-80%.

Preliminary data following the last dose across both cohorts shows that IgG levels were within normal range and within 30% of the baseline value by 5 weeks after the last dose (average (SD) IgG concentration was 8.64 (2.73) g/L, and 8.95 (2.03) g/L for the 340 mg and 680 mg cohorts, respectively). The return towards baseline indicates the effect is reversible.

Additional information is available in the current IB.

3.3. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with RVT-1401 can be found in the IB.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	**Mitigation Strategy**	
	Impact on Eligibility	**Monitoring and Stopping Criteria OR Management Criteria**
The potential for allergic reactions exists following administration of any protein to human participants.	Participants with history of significant allergic reactions are ineligible.	Participants will be closely monitored for reactions for up to 30 min post-dose. If during the course of study drug administration, the participant experiences a drug related AE of Grade 3 (severe) or greater severity, study drug administration will be stopped.
Changes in circulating complement	None	Serum complement will be monitored throughout the study (Section 8.1). Abnormal values will be discussed with the study medical monitor.
Sustained hypogammaglobulinemia	The following participants will be ineligible: -Participants with a total IgG level of <6g/L at screening -Participant has had their spleen removed. -Participant has a past medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency. - History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or Mycobacterium tuberculosis: - Participants must have negative test results for HBV surface antigen, HBV core antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON-TB Gold test at Screening. - Hepatitis C virus (HCV): - Participants must have a negative	Total IgG levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Transient depletion of IgG following administration of certain drugs (e.g., corticosteroids) are not generally associated with an increased risk of infections [Furst, 2008]. Furthermore, available data from other FcRn antagonists in development have not reported an increased risk of infection in short-term trials similar to RVT-1401-2001.

	test result for HCV antibody or - Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection that is confirmed with a negative HCV RNA test at Screening. -Absolute neutrophil count <1500 cells/mm^3	
Sustained hypoalbuminemia	Participants with baseline albumin levels <3.5 g/dL will be ineligible. Subjects with advanced liver disease including any diagnosis of cirrhosis of any stage will be ineligible. Non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the subject may be enrolled if s/he has a normal range fibroscan for liver fibrosis. AST or ALT ≥1.5x ULN at Screening. The subject may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the subject may be enrolled if s/he has a normal range fibroscan for liver fibrosis.	Serum albumin levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Treatment of any clinical signs/symptoms suspected to be associated with hypoalbuminemia will be left to the discretion of the investigator and decision on dosing will be discussed with the study medical monitor (Section 6.8.4).

4. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To examine the effects of RVT-1401 versus placebo on proptosis responder rate at week 13	Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye).
To assess the safety and tolerability of RVT-1401 in patients with active, moderate to severe GO	Assessment of safety and tolerability by analysis of adverse event (AE) data and changes from baseline in vital signs, ECGs, and clinical laboratory values
Secondary	
To examine the effect of RVT-1401 versus placebo on proptosis responder rate at weeks 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 20	Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye).
To examine the effect of RVT-1401 versus placebo on proportion of patients with a CAS score of 0 or 1	Proportion of patients with CAS of 0 or 1
To examine the effect of RVT-1401 versus placebo on mean change from baseline in proptosis	Change from baseline in proptosis
To examine the effect of RVT-1401 versus placebo on mean change from baseline in CAS	Change from baseline in CAS
To examine the effect of RVT-1401 versus placebo on overall ophthalmic improvement	Proportion of patients with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye: • Reduction in proptosis by at least 2 mm; • Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree); • Improvement in CAS by at least 2 points
To examine the effect of RVT-1401 versus placebo on diplopia	Change from baseline in the Gorman Score for Diplopia

To examine the effect of RVT-1401 versus placebo on the Graves' Ophthalmopathy Quality of Life (GO-QOL) score in the visual functioning and appearance subscales	Change from baseline in the GO-QOL visual functioning and appearance subscale scores
To assess the change in serum levels of anti-TSHR antibodies and total IgG & IgG subclasses (1-4)	Change from baseline in levels of anti-TSHR antibodies Change from baseline in levels of total IgG and IgG subclasses (1-4)
To examine RVT-1401 PK following repeated doses in patients with active, moderate to severe GO	Concentration of RVT-1401 pre-dose (Ctrough)
To measure anti-RVT-1401 antibodies following repeated doses in patients with active moderate to severe GO	Immunogenicity determined by number of participants with positive anti-RVT-1401 antibodies
Exploratory	
[redacted]	

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2b, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of RVT-1401 in GO patients. The study design is illustrated in Section 5.2**.**

Participants will screen to determine eligibility 3 to 6 weeks prior to first dose/baseline visit. Once eligibility is confirmed, on Day 1 participants will begin to receive RVT-1401 as weekly SC injections for 12 weeks. No dose adjustments of RVT-1401 are allowed during the study. See Section 6.8 for additional information on stopping criteria.

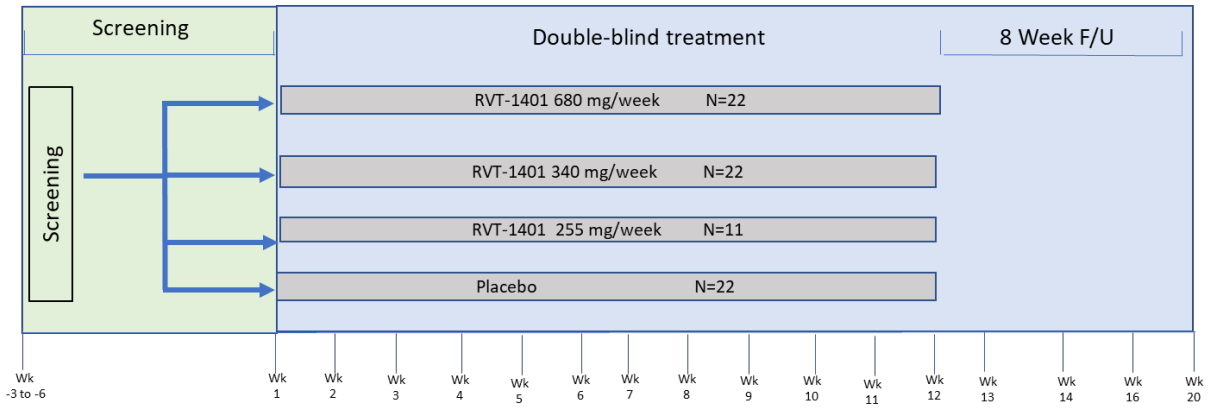
Following the initial dose at the Baseline Visit (Day 1), study visits will occur weekly throughout the treatment period. Following the final dose at Week 12, visits will occur weekly through Week 14 and then at Week 16 and Week 20. Refer to Section 8.1, Time and Events Table.

Optional home visits will be offered to collect (at a minimum) blood samples, vital signs, and review adverse events and concomitant medications. Alternatively, the participants will attend the clinic on the visits that could optionally be scheduled for home visits.

Each participant will participate in the study for up to approximately 23-26 weeks i.e., 3-6 week screening period (prior to baseline), a 12-week treatment period, and an 8-week follow up period.

5.2. Study Schematic

Figure 2 Study Design



Regimen A= RVT-1401 680 mg weekly for 12 weeks
Regimen B= RVT-1401 340 mg weekly for 12 weeks
Regimen C= RVT-1401 255 mg weekly for 12 weeks

5.3. Treatment Arms and Duration

Participants will be randomized 2:2:1:2 to RVT-1401 or placebo. Randomization will be stratified based on smoking status at the screening visit. Refer to Figure 2 for dosing regimen details.

6. PARTICIPANT POPULATION

6.1. Type and Number of Participants

A sufficient number of participants will be enrolled to achieve approximately 77 evaluable participants. Enrollment is competitive.

In order to manage the total study enrollment, the Sponsor may suspend screening and/or enrollment at any site or study-wide at any time.

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the Sponsor.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

To determine participant eligibility at screening, a single repeat of certain tests such as laboratory values, vital signs, or ECGs is allowed at the discretion of the Principal Investigator.

6.2. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female ≥ 18 years of age.
2. A female participant is eligible to participate if she is of:
    a. Non-childbearing potential defined as pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; hysteroscopic sterilization, or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) in the post-menopausal range is confirmatory].
    b. Child-bearing potential and agrees to use one of the contraception methods listed in Section 6.6.1 for an appropriate period of time (as determined by the product label or Principal Investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female participants must agree to use contraception until 90 days after the last dose of study treatment.
3. Male participants must agree to use one of the contraception methods listed in Section 6.6.1. This criterion must be followed from the time of the first dose of study treatment until 90 days after the last dose of study treatment.
4. Clinical diagnosis of Graves' disease with hyperthyroidism associated with active, moderate to severe GO with a CAS ≥ 4 for the most severely affected eye at Screening and Baseline.
5. Onset of active GO within 9 months of screening.
6. Documented evidence at Screening of detectable anti-TSHR-Ab.
7. Participant does not require immediate surgical intervention and is not planning corrective surgery/irradiation or medical therapy for GO during the course of the study.
8. Moderate-to-severe active GO (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, proptosis ≥ 3 mm above normal for race and gender (see study specific manual), and/or inconstant or constant diplopia.
9. Stable medical regimen; unlikely to require adjustment of thyroid medications during the 12-week treatment period.
10. Participants 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) at Screening. Every effort

should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the entire duration of the clinical trial.

11. Stable dose of allowed concomitant medications (e.g. antidepressants) for 3 months from Baseline.
12. Participants who are rendered euthyroid by the block-and-replace regimen e.g., methimazole + adding levothyroxine) when FT4 and T3 have become normal are allowed.
13. Participants who have received radioactive iodine treatment for Graves' hyperthyroidism >6 months from Screening are allowed.
14. Willing and capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

6.3. Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria apply:

1. Use of any steroid (IV, oral, steroid eye drops) for the treatment of GO or other conditions within 3 weeks prior to Screening. Steroids cannot be initiated during the trial. Exceptions include topical and inhaled steroids which are allowed.
2. Use of rituximab, tocilizumab, or any monoclonal antibody/Fc-fusion biologic for immunomodulation within the past 9 months prior to Baseline.
3. Use of selenium within 3 weeks prior to Baseline and use during the clinical trial (multivitamins that include selenium are allowed).
4. Use of biotin within 48 hours prior to any laboratory collection (this includes multivitamins that include biotin).
5. Participants with at least a 2-point decrease in CAS or 2 mm decrease in proptosis between screen & baseline assessments.
6. Total IgG level < 6g/L at Screening.
7. Absolute neutrophil count <1500 cells/mm^3 at Screening.
8. Albumin level <3.5 g/dL at Screening.
9. Known advanced liver disease including any diagnosis of cirrhosis of any stage.

   Non- alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.
10. AST or ALT ≥1.5x ULN at Screening. The participant may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.

11. Participants with decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months at Screening.

12. Previous orbital irradiation or surgery for GO.

13. Participant has any laboratory abnormality (at screening) that, in the opinion of the investigator, is clinically significant, has not resolved at baseline, and could jeopardize or would compromise the participant's ability to participate in this study.

14. Have known autoimmune disease other than GO, that would in the opinion of the Investigator and Medical Monitor, that would interfere with the course and conduct of the study.

15. Medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.

16. Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening.

17. History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or Mycobacterium tuberculosis:

    -Participants must have negative test results for HBV surface antigen, HBV core antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON-TB Gold test at Screening.

    -Participants with an indeterminate QuantiFERON-TB Gold test result will be allowed one retest; if not negative on retesting, the participant will be excluded.

18. Hepatitis C virus (HCV):

    -Participants must have a negative test result for HCV antibody

    or

    -Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection. This is defined as undetectable or unquantifiable HCV RNA at least 12 weeks after stopping HCV treatment (HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2014-2018, AASLD and IDSA). This should be confirmed with a negative HCV RNA test at Screening.

19. Participant has any clinically significant history of allergic conditions (including drug allergies, anaphylactic reactions), that would in the opinion of the Investigator, contraindicates their participation.

20. Participant has any medical condition (acute or chronic illness) or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the participant's ability to participate in this study

21. Body Mass Index (BMI) at Screening ≥ 40 kg/m^2.

22. Enrollment in a previous RVT-1401 clinical trial.

23. Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
24. Currently participating or has participated in another GO clinical study within 28 days prior to signing the informed consent form.
25. Participant has received a live vaccination within 8 weeks prior to the Baseline Visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of study treatment.
26. Participant has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to baseline and during the treatment period.
27. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
28. Pregnant or lactating females as determined by positive serum or urine human chorionic gonadotropin test at screening or baseline.
29. Participant has had their spleen removed.
30. QTcF interval >450 milliseconds for males and >470 milliseconds for females at Screening (a single repeat is allowed for eligibility determination). QTcF >480 msec in participants with Bundle Branch Block.

6.4. Other Eligibility Criteria Considerations

To assess any potential impact on participant eligibility with regard to safety, the Principal Investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product(s) being used in this study:

RVT-1401 Investigator's Brochure.

6.5. Screening/Baseline Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently treated. A minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and any SAEs. Screen failure data will be recorded within the electronic Case Report Form (eCRF).

6.6. Lifestyle Restrictions

6.6.1. Contraception

Female participants of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or agree to use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year).

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulations methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of <1%

- Combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female participant's entry into the study, and this male is the sole partner for that participant. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the participant or review of the participant's medical history for study eligibility, as obtained via a verbal interview with the participant or from the participant’s medical records.
- Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for an appropriate period of time (as determined by the product label or Principal Investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point.
- Sterilized male participants who have had vasectomy with documented azoospermia post procedure can be included.
- Non-sterilized male participants who are sexually active with a female partner of childbearing potential must use effective method of double barrier contraception. Male participants practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. In addition, male participants must be advised not to donate sperm during this period from signing of Informed Consent Form (ICF), throughout the duration of the study, and for 90 days after the last administration of study drug.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring participants understand how to properly use these methods of contraception.

Participants must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this study. If there is any question that a participant will not be reliable in the use of appropriate contraceptive

methods, they should not be entered into the study.

6.7. Withdrawal Criteria

6.7.1. Reasons for Withdrawal

A Principal Investigator may discontinue/withdraw a study participant's participation in the study if any of the following criteria apply:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Participant pregnancy
- Significant protocol violation
- Behavioral or administrative reason
- Participant request to discontinue/withdraw consent for any reason. It is important to document whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason.
- Discontinuation of the study at the request of the Sponsor, regulatory agency or an Institutional Review Board / Independent Ethics Committee
- Stopping criteria, as noted in Section 6.8

If a participant meets a withdrawal criterion during treatment, an Early Termination visit will be required (Section 6.7.2).

6.7.2. Participant Withdrawal Procedures

If a participant is prematurely discontinued from investigational product(s), the Principal Investigator must make every effort to perform an Early Termination Visit per Section 8.1, Time and Events Table and document the primary reason for withdrawal.

Should a participant fail to attend the clinic for a required study visit, the site should attempt to contact the participant and re-schedule the missed visit as soon as possible. The site should also counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study based on previous non-compliance. In cases where the participant does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the participant (3 documented telephone calls and if necessary a certified letter to the participant's last known mailing address) so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up".

6.8. Stopping Criteria for Individual Participants

6.8.1. Liver Chemistry Stopping Criteria

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, Study Treatment should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status), and the event reported as an SAE:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)> 8 x upper limit of normal (ULN); or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5 or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Re-challenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The Investigator and sponsor must discuss and agree with any decision to re-challenge.

Re-challenge should not occur when the etiology of the liver test abnormalities is considered possibly drug induced.

6.8.2. Criteria for Permanent Discontinuation of Study Treatment in Association with Liver Test Abnormalities

Study treatment should be discontinued permanently if all of the following 4 criteria are met (i.e., potential severe drug-induced liver injury/Hy's law case):

1. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
2. AST or ALT increases to ≥ 3 x ULN; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
    - Hepatobiliary tract disease;
    - Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr virus);
    - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;

- Alcoholic hepatitis;
- Non-alcoholic steatohepatitis; or
- Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether Study Treatment should be withheld or permanently discontinued as appropriate for the safety of the participant.

6.8.3. QTc Withdrawal Criteria

- QTc prolongation defined as QTcF >500 ms, or an increase of QTcF >60 ms above baseline on the 12-lead ECG, confirmed (persistent for >5 minutes) on repeated 12-lead ECGs

6.8.4. Albumin Monitoring Criteria

6.8.5. Other Individual Stopping Criteria

- Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy.
- Participant has a severe systemic allergic reaction (i.e., anaphylaxis) to study therapy.
- Participant requires rescue therapy for GO (e.g., corticosteroids).

6.9. Toxicity Management Criteria

6.9.1. Toxicity Management Criteria (AEs, Cardiovascular, and Injection Site Reactions)

The severity of each AE will be graded and managed according to the criteria in Table 1.

Table 1 Criteria for Determining the Grade/Severity of Adverse Event Terms

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Limiting age-appropriate instrumental activities of daily living; minimal, local, or noninvasive intervention as indicated
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living, intervention as indicated
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Injection Site Reactions

Injection site evaluations will be made by clinical staff following administration of study treatment as described below. Additional details related to the specific injection site location will be included within a study specific manual or Study Reference Manual (SRM). If an injection site reaction is observed, a physician will characterize and document the reaction as an AE. Review of the injection site will continue until the AE is resolved. Symptomatic treatment (e.g. antihistamines, NSAIDs, IV fluids) may be provided for any injection site reactions based on the discretion of the Investigator.

The injection sites will be monitored for pain, tenderness, erythema and swelling. Each injection site reaction will be categorized using the intensity grading scheme presented in Table 2.

Table 2: Criteria for Determining the Grade/Severity of Injection Site Reactions

Grade	Criteria
1/Mild	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
2/Moderate	Pain; lipodystrophy; edema; phlebitis
3/Severe or medically significant	Ulceration or necrosis; severe tissue damage; operative intervention indicated

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

6.9.2. Other Management Criteria

For an individual study participant, medical monitor notification criteria include, but are not limited to:

- Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. laboratory tests or vital signs, etc.) as judged by the Investigator.

6.10. Participant and Study Completion

A completed participant is one who has completed all phases of the study including the follow-up visits.

The end of the study is defined as the last participant's last visit.

7. STUDY TREATMENT

7.1. Investigational Product

The term study treatment is used throughout the protocol to describe RVT-1401.

To maintain the study blind, all participants will receive two injections by an unblinded designee (Section 7.6); participants receiving the 680 mg dose will receive two injections of RVT-1401, while participants receiving the 340 mg or the 255 mg dose will receive one injection with RVT-1401 and one placebo injection. Participants receiving placebo will receive two injections of placebo.

Study Treatment Name:	**RVT-1401**	**Placebo**
Manufacturer:	[redacted]	[redacted]
Dosage formulation:	Sterile solution for injection.	Sterile solution for injection.
Unit dose strength(s)/Dosage level(s):	680 mg: 2 mL RVT-1401 in two syringes for a total of 4 mL 340 mg: 2 mL RVT-1401 in one syringe and 2 mL placebo in the second syringe for a total of 4 mL 255 mg: 1.5 mL RVT-1401 in one syringe and 1.5 mL placebo in the second syringe for a total of 3 mL	2 mL placebo in two syringes for a total of 4 mL
Route of Administration	SC injection	
Dosing instructions:	The detailed methods are indicated in the Pharmacy Manual. Participants will be closely monitored for reactions for up to 30 minutes post-dose before they leave the clinic.	
Dose Preparation	The preparation procedure and expiry details will be included in the Pharmacy manual/product label.	

7.2. Treatment Assignment

Randomization will occur centrally using an interactive web response system (IXRS) using central randomization. Participants will be assigned in accordance with the randomization schedule, prepared prior to the start of the study.

7.3. Blinding

This will be a double-blind study. The investigator and study site will also remain blinded to the IgG, albumin, total protein, alkaline phosphatase (ALP), anti-TPO, anti-

thyroglobulin, and anti-TSHR, and anti-IGF-1R antibody data post screening as this could potentially unblind them. An unblinded Medical Monitor will review the lab data for IgG, albumin, total protein, and ALP on an ongoing basis for safety.

The following will apply throughout the study:

- The Investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the Investigator. Emergency unblinding will be available via the IXRS or via the unblinded pharmacist.
- The Investigator should make every effort to first contact the Medical Monitor or appropriate study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If the Medical Monitor is not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding.
- The date and reason for the unblinding (the event or condition which led to the unblinding) must be fully documented in the eCRF

A participant will be withdrawn if the participant's treatment code is unblinded..

The Sponsor or their designee may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to Investigator in accordance with local regulations.

7.4. Packaging and Labeling

RVT-1401 will be supplied to the study site as a sterile liquid formulation with a nominal fill of at least 1 mL in Nuova Ompi 2R clear glass vials with a flip-off cap. The solution is clear to slightly yellow, essentially free of visible particles, for SC administration. The formulation consists of 170 mg/mL RVT-1401 in 100 mM L-Histidine/Histidine HCl, 100 mM L-Arginine HCl and 0.02% Polysorbate 20, pH 6.0.

Placebo will be provided as a sterile liquid formulation with at least a 1 mL fill in Nuova Ompi 2R clear glass vials with a flip-off cap. The solution is clear, essentially free of visible particles, for SC administration. The placebo formulation consists of 100 mM L-Histidine/Histidine HCl, 100 mM L-Arginine HCl and 0.02% Polysorbate 20, pH 6.0.

Doses will be prepared by the unblinded pharmacist or designee with a label that includes at a minimum the study number, participant number, kit number and vial number. Doses are administered to participants by pre-identified unblinded clinic staff or designee.

See Pharmacy Manual for exact instructions on dose preparation.

All labels will meet all local applicable requirements and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

7.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation will be detailed in the pharmacy manual.

- Only participants enrolled in the study may receive study treatment and only authorized site staff may prepare, handle, supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- While the Investigator is ultimately responsible, study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records) can be designated to the Pharmacist or other designee.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or the Sponsor study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from the Sponsor.

7.6. Compliance with Study Treatment Administration

The individual dose for a participant is prepared by an Unblinded Pharmacist, licensed Pharmacy Technician, or designee. The preparation of the dose will be reviewed and confirmed by a second unblinded member of the study site staff.

The study treatment will be administered by an unblinded designee not involved in the assessment of the participant. The date and time of each dose administered along with the location of each injection will be recorded in the source documents. The location of each injection and study participant identification will be confirmed at the time of dosing by another member of the study site staff (this person can be blinded or unblinded to study treatment) other than the person administering the study drug.

7.7. Treatment of Study Treatment Overdose

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose the Investigator or treating physician should:

- contact the Medical Monitor immediately,

- closely monitor the participant for AEs/SAEs and laboratory abnormalities.
- obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

7.8. Treatment After the End of the Study

Participants will not receive any additional treatment with the study treatment from the Sponsor after completion of the study because the long-term safety and efficacy of RVT-1401 have not been established.

The Principal Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not the Sponsor is providing specific post-study treatment.

7.9. Concomitant Medications and Non-Drug Therapies

7.9.1. Permitted Medications and Non-Drug Therapies

Any concomitant medication should be recorded in the study records, including the doses administered, the dates and times of administration and the reason for administration.

Refer to Section 6.2 and Section 6.3 in the study inclusion and exclusion criteria for permitted standard of care GO treatments.

7.9.2. Prohibited Medications and Non-Drug Therapies

Refer to the exclusion criteria (Section 6.3) and the SRM for a list of prohibited medications.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table, Section 8.1.

The following points must be noted:

- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- The total blood volume collected will be specified within the ICF.

8.1. Time and Events Table

	Screening[1]	**Treatment Period Weekly Visit**												**Follow-up Period Weekly Visit (Weeks)**				**Early Withdrawal Visit**
Study Timepoint W=Weeks D=Day	Within 3-6 weeks	W1 D1 BL	W2 D8	W3 D15	W4 D22	W5 D29	W6 D36	W7 D43	W8 D50	W9 D57	W10 D64	W11 D71	W12 D78	W13	W14	W16	W20	
Time Window (days)			+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-3 days	+/-3 days	+/-3 days	+/-3 days	
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Demographic, medical/thyroid history, and smoking status	X																	
Height	X																	
Body weight	X	X																
Complete physical examination	X	X																
Brief physical examination																	X	X
Ophthalmic examination[9]	X	X	X		X		X		X		X		X		X	X	X	X
Dilated indirect ophthalmoscopy		X			X				X				X				X	X
Color vision		X			X				X				X				X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram[2]	X	X	X		X		X			X			X				X	X
Pregnancy test[3] (females)	X	X	X	X	X	X	X		X		X		X		X		X	X
Viral Serology	X																	
Vaccine Titers		X												X			X	X

	Screening[1]	**Treatment Period Weekly Visit**												**Follow-up Period Weekly Visit (Weeks)**				**Early Withdrawal Visit**
Study Timepoint W=Weeks D=Day	Within 3-6 weeks	W1 D1 BL	W2 D8	W3 D15	W4 D22	W5 D29	W6 D36	W7 D43	W8 D50	W9 D57	W10 D64	W11 D71	W12 D78	W13	W14	W16	W20	
Time Window (days)			+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-3 days	+/-3 days	+/-3 days	+/-3 days	
QuantiFERON® – TB GOLD	X																	
Urinalysis[2]	X	X	X	X	X	X	X		X		X		X		X		X	X
Blood chemistry and hematology[2]	X	X	X	X	X	X	X		X		X		X		X		X	X
Hemoglobin A1c		X											X					X
Fasting lipid panel		X											X				X	X
Serum complement (CH50, C3)[2]		X	X	X	X	X	X		X		X		X		X		X	X
Immunoglobulins (IgM, IgA)[2]		X		X			X		X		X		X		X		X	X
Anti-TPO and anti-thyroglobulin antibodies[2]		X		X					X		X			X			X	X
TSH, Free T3, Free T4[2]	X	X	X	X	X	X	X		X		X			X		X	X	X
Anti-TSHR[2]	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Anti-TSHR (Cell based) [2]		X												X		X	X	X
Anti-IGF-1R[2]		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Anti-IGF-1R (Cell based) [2]		X												X		X	X	X
RVT-1401 PK sampling[2]		X	X	X	X	X	X		X		X		X	X				X
Total IgG[2]	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Immunoglobins (IgG subclasses)[2]		X	X	X	X		X		X		X			X	X	X	X	X

	Screening[1]	**Treatment Period Weekly Visit**												**Follow-up Period Weekly Visit (Weeks)**				**Early Withdrawal Visit**
Study Timepoint W=Weeks D=Day	Within 3-6 weeks	W1 D1 BL	W2 D8	W3 D15	W4 D22	W5 D29	W6 D36	W7 D43	W8 D50	W9 D57	W10 D64	W11 D71	W12 D78	W13	W14	W16	W20	
Time Window (days)			+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-3 days	+/-3 days	+/-3 days	+/-3 days	
Gene Expression Analysis[2]		X		X			X							X		X	X	X
Pro-Inflammatory Biomarker Multiplex[2]		X		X			X							X		X	X	X
Anti- RVT-1401antibody[2, 4]		X		X		X			X					X			X	X
Nab Assessment[2, 4]		X		X		X			X					X			X	X
Drug administration		X	X	X	X	X	X	X	X	X	X	X	X					
Injection site reactions[5]		X	X	X	X	X	X	X	X	X	X	X	X					
Clinical Activity Score (CAS)[6]	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X
Proptosis[6]	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X
Motility[6]		X	X	X	X	X	X		X		X		X	X	X	X	X	X
Lid retraction		X	X	X	X	X	X		X		X		X	X	X	X	X	X
Gorman Score for Diplopia[6]		X	X	X	X	X	X		X		X		X	X	X	X	X	X
GO-QOL[6]		X	X		X		X		X		X		X	X	X	X	X	X
External Photographs[7]		X	X	X	X	X	X		X		X		X	X	X	X	X	X
Orbital CT Scan[8]		X												X			X	
Collect Methimazole (or other anti-thyroid medication) dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Satisfaction Questionnaire														X				X

	Screening[1]	**Treatment Period Weekly Visit**												**Follow-up Period Weekly Visit (Weeks)**				**Early Withdrawal Visit**
Study Timepoint W=Weeks D=Day	Within 3-6 weeks	W1 D1 BL	W2 D8	W3 D15	W4 D22	W5 D29	W6 D36	W7 D43	W8 D50	W9 D57	W10 D64	W11 D71	W12 D78	W13	W14	W16	W20	
Time Window (days)			+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-3 days	+/-3 days	+/-3 days	+/-3 days	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Screening can take place over multiple days.
2. Vitals, ECG, safety labs, PK, and PD assessments will be collected pre-dose on dosing days where specified. Microalbumin/creatinine ratio at baseline, week 12, and week 20 only (if urine protein abnormal).
3. Pregnancy tests will be collected pre-dose (via urine dipstick) on dosing days where specified. Serum pregnancy tests should be collected at screening, Week 20, and early withdrawal.
4. Participants with treatment emergent positive results (change from baseline) for anti- RVT-1401 antibody at Week 20 will be requested to return at approximately 6, 9, and 12 months post-dose for additional samples or until their result is no longer positive. However, for purposes of safety follow-up and database lock participation ends at the Week 20 visit.
5. Local injection site reactions will be assessed at approximately 10 minutes post dose and participants will be monitored for 30 minutes post dose.
6. GO assessments will be assessed pre-dose when collected on dosing days.
7. Photographs can be assessed pre or post each dose when performed (for participating sites).
8. The baseline orbital scan should be scheduled once all entry criteria have been met. Scans can be performed within +/- 7 days of the scheduled visit (for participating sites). **Note:** Week 13 and Week 20 visit scans should only be completed for participants who are considered proptosis responders at Week 13.
9. See Section 8.3.2 for details of Ophthalmic Examination.

8.2. Screening and Critical Baseline Assessments

Screening assessments are outlined in the Time and Events Table, (Section 8.1). The following demographic parameters will be captured: year and month of birth, sex, race and ethnicity. Smoking status will also be collected.

Medical/medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Written informed consent must be obtained prior to performance of any study related procedures. Screening can take place over multiple days.

8.3. Study Assessments and Procedures

8.3.1. Physical Exams

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems and skin. Height will also be measured and recorded at screening only and weight at screening and baseline only.

A brief physical examination will include, at a minimum, assessments of the skin, Respiratory, Cardiovascular system, and abdomen (liver and spleen).

8.3.2. Ophthalmic Exams

Ophthalmic exams will consist of:

- best corrected visual acuity (Snellen chart)
- automated perimetry to include a minimum of 24 degrees of visual field
- pupil assessment to include swinging flashlight test for afferent pupillary defect
- anterior segment slit lamp exam
- intraocular pressure
- posterior exam including dilated indirect ophthalmoscopy with optic disc and retinal/choroid assessment of posterior pole as well as periphery
- color vision (Ishihara plates or equivalent).

The exams will be conducted at the times indicated in the Time and Events Table (Section 8.1). Please note that the timing for 2 ophthalmic assessments: (1) dilated indirect ophthalmoscopy and (2) color vision, are listed separately in the T&E table as they have a different schedule than the other assessments that comprise the ophthalmic

exam. Results for all ophthalmic assessments will be recorded in the participant's source document.

If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities, clinically significant rise in intraocular pressure, or other abnormalities of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist's clinical judgment.

8.3.3. Vital Signs

Vital signs will be measured in supine position and will include temperature, systolic and diastolic blood pressure and pulse rate.

8.3.4. Electrocardiogram (ECG)

ECGs will be measured in supine position.

Twelve-lead ECGs will be obtained during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 6.8.3 for QTcF criteria and additional QTcF readings that may be necessary.

8.3.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments must be conducted in accordance with the SRM or Laboratory Manual, and Protocol Time and Event Table (Section 8.1). Laboratory requisition forms must be completed, and samples must be clearly labelled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested by central laboratory are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
Red Blood Cell (RBC)Count	Mean corpuscular volume (MCV)	Neutrophils

White Blood Cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils
Hemoglobin A1c		

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Total carbon dioxide (CO_2)	Gamma glutamyltransferase (GGT)	Albumin	Total Protein
Sodium	Calcium (corrected)	Alkaline phosphatase (ALP)	TSH, Free T3, Free T4
Serum complement (CH50, C3)	Immunoglobulin M (IgM)	Immunoglobulin A (IgA)	Immunoglobulin G (IgG)
Fasted labs			
Glucose (fasted) **Baseline and Week 12 only**			
Lipid Panel (fasted) **Baseline, weeks 12, 20, and Early Withdrawal only**	Total cholesterol Triglycerides HDL cholesterol LDL cholesterol (calculated using Martin-Hopkins equation) Cholesterol/HDL ratio Non-HDL cholesterol (calculated)		

Since changes in IgG, ALP, total protein and albumin level can potentially unblind the investigator to which dose the participant has been randomized to, post-screening values for IgG, ALP, total protein, and albumin levels will be blinded to the site. An unblinded Medical Monitor will review this lab data on an ongoing basis for safety.

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Appendix 2: Liver Safety Required Actions and Follow up Assessments.

Routine Urinalysis

Specific gravity, pH
glucose, protein, blood and ketones by dipstick

Microscopic examination (if blood or urine protein is abnormal)
Microalbumin/creatinine ratio at baseline, week 12, and week 20 only (if urine protein is abnormal)

Other tests

Viral Serology [HIV1/HIV2, Hepatitis B (HBsAg), Hepatitis B (Core antibody), Hepatitis C (Hep C antibody]
Vaccine titers for: tetanus, diphtheria, Hepatitis A, Hepatitis B, Pneumococcal
FSH (as needed for confirmation of postmenopausal status)
Pregnancy Tests: serum test at screening and Week 20, and early withdrawal and urine dipstick pre-dose at other timepoints. Positive urine tests should be confirmed with a serum test.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Principal Investigator, the etiology should be identified, if possible and the Sponsor notified.

8.3.6. Pharmacokinetics

Blood samples for PK analysis of RVT-1401 will be collected at the time points indicated in Section 8.1, Time and Event Table. The actual date and time of each blood sample collection will be recorded.

Processing, storage and shipping procedures are provided in the SRM or lab manual.

Serum analysis will be performed under the control of the Sponsor. Concentrations of RVT-1401 will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical.

8.3.7. Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb)

Blood samples for ADA and NAb analysis will be collected at the time points indicated in Section 8.1, Time and Event Table. The actual date and time of each blood sample collection will be recorded.

Processing, storage and shipping procedures are provided in the SRM or lab manual.

ADA analysis will be performed under the control of the Sponsor. Anti-RVT-1401 antibody titers will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. If Anti-RVT-1401 antibody titers are detected, they will be further characterized using a validated Nab assay.

8.3.8. Pharmacodynamics

Blood samples for PD analysis will be collected at times indicated in the Time and Event Table (Section 8.1).

Pharmacodynamic Markers

Total IgG, and differentiation by class: IgG subclasses (IgG1, 2, 3, and 4)
Anti-TSHR

The actual date and time of each blood sample collection will be recorded. These samples may be used for the analysis of exploratory biomarkers. Samples will be collected, labelled, stored, and shipped as detailed in the SRM or lab manual.

8.3.9. Exploratory Biomarkers

[redacted]

8.4. Graves' Ophthalmopathy Assessments

8.4.1. Clinical Activity Score (CAS)

The CAS measures the classical signs of acute inflammation (pain, redness, swelling, and impaired function) in GO [Mourits, 1989]. One point is given for the presence of each of the parameters assessed. The sum of all points defines clinical activity: active GO if the score is ≥ 4. At all visits the 7-item scale will be utilized. Specific details on scoring the CAS can be found within the SRM or study specific manual.

8.4.2. Lid Retraction

Lid retraction occurs when the eyelid is pulled away from the eyeball, either too far up in the case of the upper eyelid or too far down in lower eyelid. The assessment of lid retraction will be collected at the times indicated in the Time and Events Table (Section 8.1).

8.4.3. Proptosis

Proptosis will be assessed using the same instrument (provided by sponsor) and ideally with the same examiner for each participant. The same intercanthal distance should be used on each occasion. Proptosis will be assessed at the times indicated in the Time and Events Table (Section 8.1).

8.4.4. Motility

Motility will be assessed by the examiner by estimating the degrees of restriction in eye movements. Ideally, the same examiner should be used for each participant. Motility will be assessed at the times indicated in the Time and Events Table (Section 8.1).

8.4.5. GO-Quality Of Life (GO-QOL)

The GO-QOL is a patient-reported questionnaire designed to assess how their GO affects different aspects related to quality of life (visual functioning and psychosocial consequences) [Terwee, 1998]. There are 16 items that are graded on a 3-point Likert scale. The points given to questions 1-8 and 9-16 are added to obtain 2 raw scores ranging from 8-24; one for visual functioning and one for appearance. Specific details on scoring the GO-QOL can be found within the SRM or study specific manual.

8.4.6. External Photographs (For participating sites only)

External photographs of the participant's eyes will be taken at the time points indicated in Section 8.1, Time and Event Table. Approximately 7 digital images will be taken at each visit according to a standardized protocol. Images will be used to document changes in GO symptoms at the same time points when the CAS is assessed. Specific details on the photograph procedure can be found within the SRM or study specific manual.

8.4.7. Orbital CT Scan (For participating sites only)

CT-measured muscle volume, fat volume, total orbital volume, and proptosis will be assessed at the time points indicated in Section 8.1, Time and Event Table. Note: post-baseline orbital CT scans will only be conducted for proptosis responders (i.e., participants with a reduction of 2 or more mm of proptosis as assessed by exophthalmometer at Week 13).

Dedicated orbital CT scans will be collected locally at each site and provided to a central reader for analysis. Specific details can be found within the SRM or study specific manual.

8.4.8. Gorman Score for Diplopia

Diplopia will be assessed at the time points indicated in Section 8.1, Time and Event Table, based on three grades [Bahn, 1987]:

Grade I - Intermittent diplopia: This is present only when the patient is fatigued

Grade II – Inconstant diplopia: This is present only on lateral or upward gaze

Grade III – Constant diplopia: This is present on straight and level gaze

Specific details can be found within the SRM or study specific manual.

8.4.9. Satisfaction Questionnaire

A brief survey asking participants for feedback on their experience with the SC injections during the course of the study will be completed at the end of the treatment period. The survey will take less than 2 min to complete by the participant.

9. DATA MANAGEMENT

For this study, participant data will be entered into a Sponsor-approved electronic database and combined with data provided from other sources (e.g., safety laboratory, PK and PD vendor, etc.) in validated datasets then transmitted electronically to the Sponsor or designee.

Management of clinical data will be performed in accordance with applicable Sponsor approved standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced (WHO-DDE), respectively.

The Principal Investigator will retain original source documents and the Sponsor will receive eCRF-required data as electronic datasets. Participant initials will not be collected or transmitted to the Sponsor.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Sample Size Considerations

For the primary endpoint, proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye. It will be assumed that the placebo arm will have a 5% response rate and the highest dosing arm (680 mg) will have a 50% response rate. Assuming a dropout rate of 15%, approximately

22 participants are to be randomized to the 680 mg, 340 mg, and placebo groups. Eleven subjects are to be randomized to the 255 mg dose group. Using these assumptions, 19 participants per arm will be sufficient to detect this treatment group difference with approximately 85% power using a two-sided Fisher's Exact Test assuming an alpha of 0.05.

10.2. Data Analysis Considerations

10.2.1. Analysis Populations

Intention-To-Treat (ITT) Population

All enrolled participants who take at least one dose of study medication will be included in the ITT population. Participants will be summarized by randomized treatment group.

This will be the population for all PD parameters.

Safety Population

All participants enrolled in the study and receive at least one dose of study treatment will be included in the Safety Population. Participants will be summarized by actual treatment group.

This will be the population for the safety analyses, as well as for presentation and summarization of baseline/demographic characteristics.

Pharmacokinetic Population

The PK Population will include all participants who undergo plasma PK sampling and have evaluable concentration-time data for analysis.

Pharmacodynamic Population

The PD population will include all participants who have baseline measure, along with a post baseline measure and receive at least one dose of study treatment

10.3. Final Analysis

Final analysis will be performed after the completion of the study and the database is locked.

Data will be listed and summarized. Treatment will be assigned based on the dosing schedule and included in the data listings. Listings will be sorted by participant, day, and time; summaries will be presented by treatment, day, and time.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum. The geometric mean with associated 95% confidence interval (CI), and the between-participant CV (%CVb) for PK parameters only will also be included. For categorical variables, n and percent will be used as summary statistics. Baseline is the last

available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.4 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings.

Complete details will be documented in the Statistical Analysis Plan (SAP).

10.3.1. Primary Efficacy Endpoint

The primary endpoint is defined as the Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye at the end of treatment (Week 13). The study eye is defined as the most severely affected eye at the baseline visit. In the event of both eyes being affected the same, then the right eye will be used as the study eye. The proportion of responders will be summarized for all participants in the ITT population by treatment group at each visit. A fixed, sequential testing procedure will be used to test the three active treatment groups vs placebo. The highest dose will be tested vs placebo at a significance level of 0.05. If that test is significant, then the middle dose will be tested against placebo at a significance level of 0.05. If this test is significant, the smallest dose level will be tested against placebo at a significance level of 0.05. Testing will stop when a non-significant test occurs.

10.3.2. Secondary Efficacy Endpoints

All secondary endpoints will be evaluated with the end of the treatment period (Week 13), unless otherwise specified.

The following secondary endpoints will be evaluated:

- Proportion of participants with ≥2-point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20

- Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye) at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 20

- Proportion of participants with CAS of 0 or 1 at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20
- Change from baseline in proptosis at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20
- Change from baseline in CAS at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20
- Proportion of participants with overall ophthalmic improvement at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20 defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye:
    - Reduction in proptosis by at least 2 mm;

    - Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree);
    - Improvement in CAS by at least 2 points
- Change from baseline in the Gorman Score for diplopia at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20
- Change from baseline in the GO-QOL visual and appearance subscale scores at Weeks 2, 4, 6, 8, 10, 12, 13, 14, 16, and 20

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Treatment group differences will be evaluated using a mixed model for repeated measurements (MMRM) techniques with terms in the model for baseline treatment, visit, and treatment by visit interaction. Pairwise differences comparing both active arms to placebo will be performed assuming an alpha of 0.05.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Treatment group differences will be evaluated using a two-sided Fisher's Exact test assuming an alpha of 0.05.

10.3.3. Safety Analyses

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements, and ECG readings at various time points during the study, and by the documentation of AEs.

AE verbatim text will be coded and classified by body system and preferred (coded) term using the MedDRA. All AEs, both serious and non-serious will be listed. AE summaries by study part and treatment group, of the number and percent of participants reporting each event at least once will be generated.

Clinical chemistry, hematology, and urinalysis values will be listed for each participant and flagged high or low relative to the normal range where appropriate. Descriptive summary statistics will be created by study part, treatment and assessment time.

Other safety data will be summarized descriptively by treatment and time. Details will be provided in the SAP.

10.3.4. Pharmacokinetic Analyses

Serum compound concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin or other PK software programs. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following primary PK parameters will be determined (if possible):

Ctrough

Additional PK parameters may be calculated. PK data will be presented in graphical and tabular form and will be summarized descriptively

10.3.5. Pharmacodynamic Analyses

All participants in the ITT population will be included in the summaries of PD data. The actual value, change from baseline and percentage change from baseline for all PD parameters will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Statistical testing may be performed between the two treatment groups using mixed models. Details will be provided in the Statistical Analysis Plan.

Serum IgG, IgG subclass (1-4), anti-TSHR levels will be summarized as both raw values as well as percent change from baseline (intra-participant assessment). Additional PK/PD and PD/PD relationships may be evaluated. PD data will be presented in graphical and tabular form and will be summarized descriptively.

10.3.6. Other Analyses

11. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAES)

The Principal Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All SAEs must be reported to the Sponsor or Sponsor designee within 24 hours of awareness of the event (Section 11.2).

Once former study participants have completed the study, the Principal Investigator is not obligated to actively seek AEs or SAEs. However, if the Principal Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the Principal Investigator must promptly notify the Sponsor.

11.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE 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 a medicinal product.

Events meeting the definition of an AE **include but are not limited to**:

- Any clinically significant, new or worsened, abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements). Clinical significance is determined based on the medical and scientific judgement of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition.
- Signs, symptoms, or the clinical sequelae of a suspected interaction (e.g. with medications or food).

- Signs, symptoms, or the clinical sequelae of an overdose of either investigational product or a concomitant medication (overdose without an AE should be reported as a protocol deviation).

Events that **do not** meet the definition of an AE include:

- Anticipated day-to-day fluctuations of pre-existing condition(s), including the disease under study, that do not represent a clinically significant exacerbation or worsening.
- Abnormal or worsening laboratory, imaging, or other safety findings that are not clinically significant.
- Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

11.2. Definition and Reporting of Serious Adverse Events

Serious adverse events must be marked as an SAE within the AE eCRF form, which will send an immediate auto notification **to** [redacted] **and the Medical Monitor.**

If the eCRF is not available, the site must email [redacted] **and the Medical Monitor within 24 hours of the study site personnel's knowledge of the event**.

An SAE is 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, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

Hospitalization planned prior to signing the informed consent is not considered an SAE. Surgeries and other interventions that were under consideration prior to signing the informed consent are not considered an SAE if the underlying condition has not changed from baseline.

"Hospitalization" includes admission to the hospital of any duration. It does not include emergency room visits. Complications that occur during hospitalization are AEs and are SAEs if they prolong hospitalization or fulfill any other serious criteria.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in disability/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) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are allergic bronchospasm, blood dyscrasias or convulsions where treatment prevents the need for hospitalization.

The following should always be considered serious: invasive or malignant cancers, and development of drug dependency or drug abuse.

11.3. Time Period and Frequency for Collecting AE and SAE Information

- AEs will be collected from the time of informed consent until the follow-up contact, at the timepoints specified in the Section 8.1, Time and Events Table.
- Medical occurrences that begin prior to any study procedure but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to the Sponsor within 24 hours of site awareness.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to investigational product will be recorded from the time a participant consents to participate in the study up to and including any follow-up contact.
- Once former study participants have completed the study, the Principal Investigator is not obligated to actively seek AEs or SAEs. However, if the Principal Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product or study participation, the Principal Investigator must promptly notify the Sponsor.

11.4. Method of Detecting and Reporting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"

- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

All AEs and SAEs should be promptly recorded in the eCRF, completing all fields for which data is available. When known, the diagnosis should be entered as the event term in the eCRF, rather than individual symptoms. When the diagnosis is unclear, key symptoms may be entered, and the investigator should obtain appropriate tests to establish a diagnosis, if possible. Discharge summaries should be requested for all hospitalizations.

For SAEs, the eCRF will send an auto notification to [redacted] and the Medical Monitor when the form is saved. Each SAE should be assigned a causality at the time of entry, as this is required to determine regulatory reporting. Follow-up information regarding the SAE, including hospital discharge summary, should be emailed to [redacted]

11.5. Assessing Severity of AEs and SAEs

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on participant/event outcome or action taken.

The Investigator must determine the severity of each AE according to the following criteria:

Criteria for Determining the Grade/Severity of Adverse Event Terms

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the AE eCRF and in the participant's source documents.

11.6. Assessing Causality of AEs and SAEs

Regulatory authorities require that both investigator and sponsor assess whether there is a reasonable possibility that the study treatment caused each AE. This assessment requires

careful medical consideration of each event in relationship to the timing of drug administration, the presence of other factors which may have caused the event (underlying illness, concomitant medication, complications, exposure to other toxins or allergens, environmental factors, etc.), and the effects of stopping and/or restarting the study treatment. The following definitions are to be used for the relationship of the AE to Study Treatment:

The investigator will assess the causality of each reported AE as follows:

- Probably related: an AE occurring at a reasonable time following administration of a drug, where other causes are unlikely, there is evidence to suggest that the drug caused the event, and/or where the event recurs after reintroduction of the drug (without other explanation for the recurrence).
- Possibly related: an AE occurring at a reasonable time following administration of a drug and for which there is a reasonable possibility that the drug caused the event, e.g. there is some evidence to suggest a causal relationship.
- Not related: an AE with poor or no relationship to the timing of drug administration, or where another cause such as underlying disease, complications, or other medications reasonably explains the event, or where the event does not recur after continued administration or reintroduction of the drug for an adequate period.

11.7. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Principal Investigator is required to proactively follow each event at subsequent visits/contacts until the event resolves. All SAEs and AEs will be followed until resolution, or until the condition stabilizes or until the participant is lost to follow-up. Where necessary, repeated laboratory testing should be requested to confirm resolution. Ongoing AEs where no further information is likely to be available may be closed after consultation between the Sponsor and Medical Monitor.

11.8. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of SAEs/adverse event of special interest (AESIs) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigator.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and are forwarded to the Investigators in accordance with local regulations.

The Investigator who receives an Investigator safety report describing an SAE(s)/AESI(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the IB and will notify the IRB/IEC, as appropriate according to local requirements.

11.9. Overdose

Overdose is less likely in a study where the drug is administered within a clinical unit by a healthcare provider. If there are no symptoms of an overdose, it may be recorded as a protocol deviation. Overdose with symptoms should be recorded as an AE or SAE, as appropriate.

12. PREGNANCY REPORTING

All female participants will be tested for pregnancy prior to study drug dosing. Participants testing positive for pregnancy will be ineligible for study participation.

Any pregnancies in a participant, or the partner of a participant, between the time of informed consent and study termination must be reported to the Sponsor within 24 hours of learning of the pregnancy. Information on the status and health of the mother, the pregnancy and its outcome, and the child will be recorded on the form provided. In case of a partner pregnancy, the partner of the study participant will be asked to sign a partner pregnancy consent form in order to collect pregnancy and outcome information. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

13. RESPONSIBILITIES

13.1. Principal Investigator Responsibilities

13.1.1. Good Clinical Practice (GCP)

The Principal Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States IND, the Principal Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the Principal Investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in

humans submitted in a marketing application or reclassification petition participant to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Principal Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Principal Investigator and any sub-investigator. The Principal Investigator and sub-investigator agree to notify the Sponsor of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last participant has completed the protocol defined activities.

13.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the participant (such as informed consent form, advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Principal Investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the Principal Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC on an annual basis or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC, where applicable.
- Notifying the IRB/IEC of SAEs or other significant safety findings when required by procedures established by the IRB/IEC.

13.1.3. Informed Consent

The Principal Investigator or designee is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Principal Investigator must utilize an IRB or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the participant and the person obtaining consent.

Participants must be re-consented to continue their participation in the study if a protocol amendment is made that substantially alters the study design or the potential risks or burden to the participant.

13.1.4. Confidentiality

The Principal Investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only participant number (i.e., not names) and month and year of birth (as allowed) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Principal Investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial.

The Principal Investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial.

The Principal Investigator agrees that all information received from the Sponsor, including but not limited to the IB, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Principal Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13.1.5. Study Files and Retention of Records

The Principal Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) Investigator's study file, and (2) participant clinical source documents.

The Investigator's study file will contain the IB, protocol/amendments, eCRF forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization and training forms, and other appropriate documents and correspondence.

The required source data should include the following for each participant:

- participant identification (name, month and year of birth, gender);
- documentation that participant meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial discussed and date of informed consent;
- dates of all visits;
- documentation that protocol specific procedures were performed;

- results of efficacy parameters, as required by the protocol;
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- record of all AE and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the Principal Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The Principal Investigator may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Principal Investigator must notify the Sponsor before destroying any clinical study records.

Should the Principal Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Principal Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Principal Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Principal Investigator in case of a regulatory audit. When source documents are required for the continued care of the participant, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years for purposes of this study.

13.1.6. Electronic Case Report Forms (eCRF)

For each participant enrolled, an eCRF must be completed and signed by the Principal Investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those participants who fail to complete the study (even during the screening period if an eCRF was initiated). If a participant withdraws from the study, the reason must be noted on the eCRF. If a participant is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

13.1.7. Drug Accountability

The Principal Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), participant dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to participants, including lot number, date dispensed, participant identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. Used investigational product and supplies may be returned or destroyed on an ongoing basis during the study, following review and verification from study monitor, as appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will return, all unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13.1.8. Inspections

The Principal Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

13.1.9. Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

13.2. Sponsor Responsibilities

13.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by the Sponsor.

13.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

13.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers within 21 days of enrollment of the first participant. Results will be posted as required.

13.3. Joint Investigator/Sponsor Responsibilities

13.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the Principal Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries on the eCRFs. The Principal Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the Sponsor may conduct inspections or audits of the clinical study. If the Principal Investigator is notified of an inspection by a regulatory authority the Principal Investigator agrees to notify the Sponsor medical monitor immediately. The Principal Investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13.3.3. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority (ies), IRBs, and IECs. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

Reasons for stopping the study may include but are not limited to:

- New evidence that, in the opinion of the sponsor, makes continuation of the study unnecessary or unethical
- The sponsor discontinues development of RVT-1401
- Insufficient patient enrollment

14. REFERENCES

Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010 Feb 25;362(8):726-38.

Bahn RS, Dutton CM, Natt N, Joba W, Spitzweg C, Heufelder AE. Thyrotropin receptor expression in Graves' orbital adipose/connective tissues: potential autoantigen in Graves' ophthalmopathy. J Clin Endocrinol Metab. 1998 Mar;83(3):998-1002.

Bahn RS, Gorman CA. Choice of therapy and criteria for assessing treatment outcome in thyroid-associated ophthalmopathy. Endocrinol Metab Clin North Am. 1987 Jun;16(2):391-407.

Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, Heckmann C, Esser J, Morgenthaler NG. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab. 2006 Sep;91(9):3464-70. Epub 2006 Jul 11.

FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009.

Furst, DE. Serum Immunoglobulins and Risk of Infection: How Low Can You Go? 2008 Elsevier Inc. Semin Arthritis Rheum 39:18-29.

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2014-2018, AASLD and IDSA. www.hcvguidelines.org (last updated: May 24, 2018)

Hendrikx J, Haanen J, Voest E, Schellens J, Huitema A, Beijnen J. Fixed Dosing of Monoclonal Antibodies in Oncology. The Oncologist 2017; 22:1212-1221.

Investigator's Brochure RVT-1401.

Krieger CC1, Neumann S, Place RF, Marcus-Samuels B, Gershengorn MC. Bidirectional TSH and IGF-1 receptor cross talk mediates stimulation of hyaluronan secretion by Graves' disease immunoglobins. J Clin Endocrinol Metab. 2015 Mar;100(3):1071-7.

Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD, Kahaly GJ. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. J Clin Endocrinol Metab. 2010 May;95(5):2123-31. doi: 10.1210/jc.2009-2470. Epub 2010 Mar 17.

Mourits, M.P., Koornneef, L, Wiersinga W.M., Prummel, M.F, Berghout, A and van der Gaag, R "Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach," British Journal of Ophthalmology, vol. 73, no. 8, pp. 639–644, 1989.

Paunkovic N, Paunkovic J. The diagnostic criteria of Graves' disease and especially the thyrotropin receptor antibody; our own experience. Hell J Nucl Med. 2007 May-Aug;10(2):89-94.

Ponto KA, Kanitz M, Olivo PD, Pitz S, Pfeiffer N, Kahaly GJ. Clinical relevance of thyroid-stimulating immunoglobulins in graves' ophthalmopathy. Ophthalmology. 2011 Nov;118(11):2279-85. doi: 10.1016/j.ophtha.2011.03.030.

Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. J Immunol. 2003 Jun 15;170(12):6348-54.

Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007 Sep;7(9):715-25.

Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, Harris GJ, Antonelli A1, Salvi M, Goldberg RA, Gigantelli JW, Couch SM, Shriver EM, Hayek BR, Hink EM, Woodward RM, Gabriel K, Magni G, Douglas RS. Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med. 2017 May 4;376(18):1748-1761.

Starkey KJ, Janezic A, Jones G, Jordan N, Baker G, Ludgate M. Adipose thyrotrophin receptor expression is elevated in Graves' and thyroid eye diseases ex vivo and indicates adipogenesis in progress in vivo. J Mol Endocrinol. 2003 Jun;30(3):369-80.

Terwee, C.B., Gerding, M.N., Dekker, F.W., Prummel, M.F., Wiersinga, W.M. Development of a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy (The GO-QOL) . Br J Ophthalmol. 1998;82:773–779.

Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, Gianoukakis AG, Douglas RS, Smith TJ. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. J Immunol. 2008 Sep 15;181(6):4397-405.

Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. Clin Endocrinol (Oxf). 2003 Mar;58(3):280-7.

15. APPENDICES

15.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC (0-t)	Area under the concentration-time curve from time zero to time
AUC (0-168)	Area under the concentration-time curve from time zero to 168 hours
BMI	Body mass index
BUN	Blood urea nitrogen
CAS	Clinical activity score
CI	Confidence intervals
Cmax	Maximum concentration
CO_2	Carbon dioxide
CPK	Serum creatine phosphokinase
$C\tau$	Concentration at end of dosing interval
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	Electronic case report form
FcRn	fully human anti-neonatal FC receptor
FDA	U.S. food and drug administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GO	Graves' ophthalmopathy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference on harmonisation
IEC	Independent ethics committee
IgA	Immunoglobulin A
IGF-1R	Insulin-like growth factor receptor
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product

IRB	Institutional review board
IS	Immunosuppressive
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MAb	Monoclonal antibody
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MSDS	Material safety data sheet
NAb	Neutralizing Antibody
NSAID	Non-steroidal anti-inflammatory agents
PD	Pharmacodynamic
PE	Plasma exchange
pIgG	Pathogenic IgG
PIS	Post-Intervention Status
PK	Pharmacokinetic
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Elimination half-life
TB	Tuberculosis
Tmax	Time to maximum concentration
TPO	Thyroperoxidase
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
ULN	Upper limit of normal
WBC	White blood cell
WHO-DDE	World health organization drug dictionary enhanced

Trademark Information

Trademarks of Immunovant Sciences GmbH

Trademarks not owned by Immunovant Sciences GmbH
WinNonlin
SAS
FlowJo
nSolver

15.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with the FDA Drug-induced Liver Injury: Premarketing Clinical Evaluation).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Liver Safety Process

The procedures listed below are to be followed if a participant has ALT, bilirubin and/or INR elevations that meet the definition of an SAE (as defined in Section 11):

- Notify the medical monitor within 24 hours of learning of the abnormality to confirm follow-up.
- Complete the liver event case report forms.
- Upon completion of the safety follow-up withdraw the participant from the study unless further safety follow up is required.
- Make every reasonable attempt to have participants return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor participants twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- Obtain viral hepatitis serology including:
    - Hepatitis A IgM antibody.
    - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
    - Hepatitis C ribonucleic acid (RNA).
    - Cytomegalovirus IgM antibody.
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
    - Hepatitis E IgM antibody.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE eCRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications eCRF.

- Record alcohol use on the Liver Events eCRF.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China** Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

The Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

15.3. Appendix 3: Protocol Amendment Summary of Changes

Amendment 02 Changes

Rationale for the amendment: Dosing was extended from 6 to 12 weeks in order to maximize the potential benefit of RVT-1401 treatment. The follow up period was shortened from 12 weeks to 8 weeks to decrease the overall visit schedule for participants while still allowing sufficient time for PD effects to return back to normal range and near baseline values. Associated changes related to the updated study design have also been made to the objectives and endpoints, entry criteria, and the timing of assessments in the Time and Events Table. Additional laboratory tests were also included in order to characterize the impact of possible changes in albumin on other parameters, HbA1c and the [redacted]. Repeat CT scans will only be completed for week 13 proptosis responders instead of for all participants. Other administrative changes have also been made throughout. The detailed changes are listed below:

Change #1: Title Page

Added ASCEND GO2 to study title

Change #2: Title Page

Added all regulatory #s to the title page, including moving the EUDRA CTA # from page 4 to the title page:

IND: 141988

CTA: 226455

EUDRA CTA: 2018-004676-35

Change #3: Title Page, Sponsor Signature Page

Updated [redacted] title:

[redacted]

Change #4: Medical Monitor/Sponsor Information Page

Updated the Medical Monitor contact from [redacted] to [redacted]

Change #5: Section 2 Protocol Summary, Section 4 Objectives and Endpoints, Section 10.3.1 Primary Efficacy Endpoint, Section 10.3.2 Secondary Efficacy Endpoint

Updated the primary endpoint from Week 7 to Week 13

Updated the secondary endpoints based on 12 weeks of dosing where appropriate

Change #6: Section 2 Protocol Summary and Section 6.1 Type and Number of Participants

Updated the number of participants from 70 to approximately 77

Change #7: Section 2 Protocol Summary, Section 3.2.2 Dose Rationale, Section 5.2 Study Schematic

Updated the duration of treatment from 6 weeks to 12 weeks

Change #8: Section 2 Protocol Summary and Section 8.1 Time and Events Table (footnote 4)

Clarified the anti-RVT-1401 antibodies as "treatment emergent"

Change #9: Section 3.2.2 Dose Rationale, 6th paragraph

Previous text:

The proposed weekly doses are expected to provide an average total IgG reduction of approximately 75-80%, 65-70%, and 45-55% for 680 mg, 340 mg, and 255 mg respectively, by the fourth or fifth dose. It is predicted that the nadir IgG reduction will be achieved by the 5th dose and maintained following the sixth dose before rising back to baseline over the next 6 to 8 weeks.

Current text:

The proposed weekly doses are expected to provide an average total IgG reduction of approximately 75-80%, 65-70%, and 45-55% for 680 mg, 340 mg, and 255 mg respectively, by the fourth or fifth dose. It is predicted that the nadir IgG reduction will be achieved by the **3rd-**5th dose **(depending on dose studied)** and maintained following the **remaining** dose**s** before rising back to baseline over the next 6 to 8 weeks **after stopping treatment**.

Change #10: Section 3.3.1 Risk Assessment, Sustained hypogammaglobulinemia and Sustained hypoalbuminemia

Previous text:

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	Monitoring and Stopping Criteria OR Management Criteria
Sustained hypogammaglobulinemia	The following participants will be ineligible: -Participants with a total IgG level of <6g/L at screening -Participant has had their spleen	Total IgG levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Transient depletion of IgG following administration of certain drugs (e.g., corticosteroids) are

	removed. -Participant has a past medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency. -History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Mycobacterium tuberculosis. Participants must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®- tuberculin (TB) Gold test at Screening. Participants with an indeterminate QuantiFERON®-TB Gold test result will be allowed one retest; if not negative on retesting, the participant will be excluded. -Absolute neutrophil count <1500 cells/mm^3	not generally associated with an increased risk of infections [Furst, 2008]. Furthermore, available data from other FcRn antagonists in development have not reported an increased risk of infection in short-term trials similar to RVT-1401-2001.
Sustained hypoalbuminemia	Investigator discretion	Serum albumin levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Treatment of hypoalbuminemia will be left to the discretion of the investigator and decision on dosing discussed with the study medical monitor (Section 6.8.4).

Current text:

Potential Risk of Clinical Significance	**Mitigation Strategy**	
	Impact on Eligibility	**Monitoring and Stopping Criteria OR Management Criteria**
Sustained hypogammaglobulinemia	The following participants will be ineligible: -Participants with a total IgG level of <6g/L at screening -Participant has had their spleen removed. -Participant has a past medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.	Total IgG levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Transient depletion of IgG following administration of certain drugs (e.g., corticosteroids) are not generally associated with an increased risk of infections [Furst, 2008]. Furthermore, available data from other FcRn antagonists in development have not reported an increased risk of infection

	- **History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or Mycobacterium tuberculosis:** **– Participants must have negative test results for HBV surface antigen, HBV core antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON-TB Gold test at Screening.** **- Hepatitis C virus (HCV):** **- Participants must have a negative test result for HCV antibody** **or** **- Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection that is confirmed with a negative HCV RNA test at Screening.** -Absolute neutrophil count <1500 cells/mm^3	in short-term trials similar to RVT-1401-2001.
Sustained hypoalbuminemia	**Participants with baseline albumin levels <3.5 g/dL will be ineligible.** **Subjects with advanced liver disease including any diagnosis of cirrhosis of any stage will be ineligible.** **Non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the subject may be enrolled if s/he has a normal range fibroscan for liver fibrosis.** **AST or ALT ≥1.5x ULN at Screening.**	Serum albumin levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Treatment of **any clinical signs/symptoms suspected to be associated with** hypoalbuminemia will be left to the discretion of the investigator and decision on dosing **will be** discussed with the study medical monitor (Section 6.8.4).

	The subject may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the subject may be enrolled if s/he has a normal range fibroscan for liver fibrosis.	

Change #11: Section 4 Objective and Endpoints and Section 10.3.6 Other Analyses

[redacted]

Change #12: Section 5.1 Overall Design

Previous text:

This is a Phase 2b, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of RVT-1401 in GO patients. The study design is illustrated in Section 5.2.

Participants will screen to determine eligibility 3 to 6 weeks prior to first dose/baseline visit. Once eligibility is confirmed, on Day 1 participants will begin to receive RVT-1401 as weekly SC injections for 6 weeks. No dose adjustments of RVT-1401 are allowed during the study. See Section 6.8 for additional information on stopping criteria.

Following the initial dose at the Baseline Visit (Day 1), study visits will occur weekly throughout the treatment period. Following the final dose at Week 6, visits will occur weekly through Week 10 and then every 2 weeks until Week 18. Refer to Section 8.1, Time and Events Table.

Optional home visits will be offered to collect (at a minimum) blood samples, vital signs, and review adverse events and concomitant medications. Alternatively, the participants will attend the clinic on the visits that could optionally be scheduled for home visits.

Each participant will participate in the study for up to approximately 21-24 weeks i.e., 3-6 week screening period (prior to baseline), a 6-week treatment period, and a 12-week follow up period.

Current text:

This is a Phase 2b, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of RVT-1401 in GO patients. The study design is illustrated in Section 5.2.

Participants will screen to determine eligibility 3 to 6 weeks prior to first dose/baseline visit. Once eligibility is confirmed, on Day 1 participants will begin to receive RVT-1401 as weekly SC injections for **12** weeks. No dose adjustments of RVT-1401 are allowed during the study. See Section 6.8 for additional information on stopping criteria.

Following the initial dose at the Baseline Visit (Day 1), study visits will occur weekly throughout the treatment period. Following the final dose at **Week 12**, **visits will occur weekly through Week 14 and then at Week 16 and Week 20.** Refer to Section 8.1, Time and Events Table.

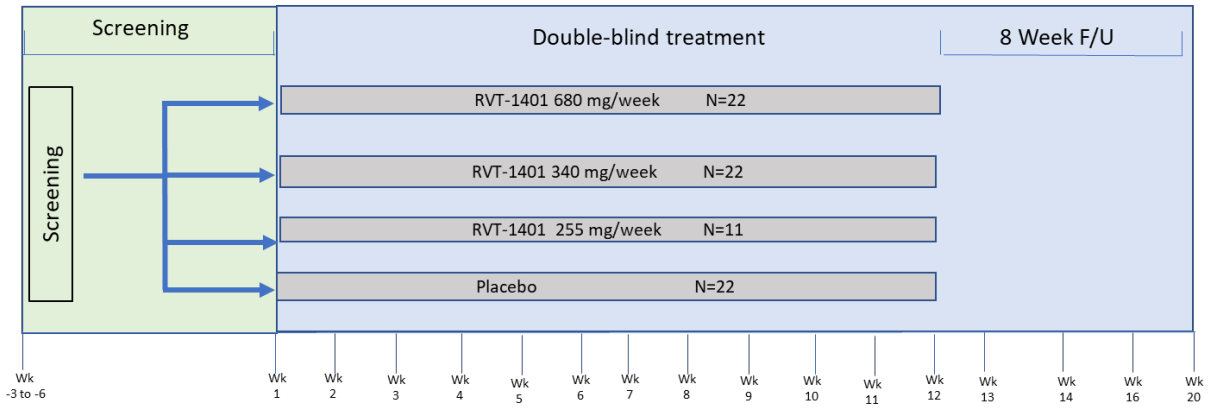
Optional home visits will be offered to collect (at a minimum) blood samples, vital signs, and review adverse events and concomitant medications. Alternatively, the participants will attend the clinic on the visits that could optionally be scheduled for home visits.

Each participant will participate in the study for up to approximately **23-26 weeks** i.e., 3-6 week screening period (prior to baseline), a **12-week** treatment period, and a **8-week** follow up period.

Change #13: Section 5.2 Study Schematic. Figure 2

Updated the schematic (Figure 2) from 6 weeks to 12 weeks of dosing

Figure 3 Study Design



Regimen A= RVT-1401 680 mg weekly for 12 weeks
Regimen B= RVT-1401 340 mg weekly for 12 weeks
Regimen C= RVT-1401 255 mg weekly for 12 weeks

Change #14 Section 6.2 Inclusion Criteria

Updated criteria # 9 to include the 12-week dosing period

Added new criteria # 13 for radioactive iodine treatment:

13. Participants who have received radioactive iodine treatment for Graves' hyperthyroidism >6 months from Screening.

Change #15: Section 6.3 Exclusion Criteria

Combined criteria #1 through criteria #3

Previous text:

1. Use of oral and/or IV corticosteroid use for conditions other than GO within 3 weeks prior to Screening (topical steroids for dermatological conditions are allowed). These cannot be initiated during the trial.
2. Use of any steroid (IV or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of GO within 3 weeks prior to Screening.
3. Previous steroid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of GO and previous use of steroid eye drops is allowed if the corticosteroid was discontinued at least 3 weeks prior to Screening.

Current text:

1. Use of any steroid (IV, oral, steroid eye drops) for the treatment of GO or other conditions within 3 weeks prior to Screening. Steroids cannot be initiated during the trial. Exceptions include topical and inhaled steroids which are allowed.

Clarified the CAS criteria:

Previous text:

Participants with ≥ 2 pts (CAS) or 2 mm (proptosis) decrease between screen & baseline.

Current text:

Participants with **at least a 2-point decrease in CAS or 2 mm decrease in proptosis** between screen & baseline **assessments**.

Added criteria for albumin, liver disease, AST and ALT

Albumin level <3.5 g/dL at Screening.

Known advanced liver disease including any diagnosis of cirrhosis of any stage.

Non- alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.

AST or ALT ≥1.5x ULN at Screening. The participant may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.

Updated criteria for HIV, HBV, and HCV

Previous text:

History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Mycobacterium tuberculosis. Participants must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®-TB Gold test at Screening. Participants with an indeterminate QuantiFERON®-TB Gold test result

will be allowed one retest; if not negative on retesting, the participant will be excluded.

Current text:

History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or Mycobacterium tuberculosis:

-Participants must have negative test results for HBV surface antigen, HBV core antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON-TB Gold test at Screening.

- Participants with an indeterminate QuantiFERON-TB Gold test result will be allowed one retest; if not negative on retesting, the participant will be excluded.

Hepatitis C virus (HCV):

-Participants must have a negative test result for HCV antibody

or

-Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection. This is defined as undetectable or unquantifiable HCV RNA at least 12 weeks after stopping HCV treatment (HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2014-2018, AASLD and IDSA). This should be confirmed with a negative HCV RNA test at Screening.

Updated criteria for allergic reactions:

Previous text:

Participant has any clinically significant history of allergic conditions (including drug allergies, anaphylactic reactions), that would in the opinion of the Investigator or Medical Monitor, contraindicates their participation.

Current text:

Participant has any clinically significant history of allergic conditions (including drug allergies, anaphylactic reactions), that would in the opinion of the **Investigator,** contraindicates their participation.

Updated BMI criteria:

Previous text:

Body Mass Index (BMI) at Screening ≥ 35 kg/m^2.

Current text:

Body Mass Index (BMI) at Screening ≥ **40** kg/m^2.

Added criteria for enrollment into a study with RVT-1401

Enrollment in a previous RVT-1401 clinical trial.

Updated criteria for blood transfusion or blood product donation

Previous criteria:

Participant has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to baseline.

Current criteria:

Participant has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to baseline **and during the treatment period.**

Change # 16: Section 6.6.1 Contraception: Contraceptive Methods with a Failure Rate of <1%, 5th bullet

Previous text:

Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for at least 4 weeks before Screening.

Current text:

Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment **for an appropriate period of time (as determined by the product label or Principal Investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point.**

Change #17: Section 6.8.4 Albumin Monitoring Criteria

[redacted]

Change #18 Section 6.8.5 Other Individual Stopping Criteria

Added text:

- Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy.
- Participant has a severe systemic allergic reaction (i.e., anaphylaxis) to study therapy.
- Participant requires rescue therapy for GO (e.g., corticosteroids).

Change #19: Section 6.9.1. Toxicity Management Criteria (AEs, Cardiovascular, and Injection Site Reactions), Table 2

Removed Grade 4 and Grade 5 events

Change #20: Section 7.1 Investigational Product

Updated the dosing instructions so that participants are closely monitored for reactions for up to 30 minutes post dose instead of 1 hour

Change #21: Section 7.3 Blinding

Previous text:

This will be a double-blind study. The investigator and study site will also remain blinded to the IgG, albumin, total protein, alkaline phosphatase (ALP), anti-TPO, anti-thyroglobulin, and anti-TSHR and anti-IGF-1R antibody data post screening as this could potentially unblind them. An unblinded Medical Monitor will review this lab data on an ongoing basis for safety, with the exception of the anti-TPO and anti-thyroglobulin data which are exploratory endpoints.

The following will apply throughout the study:

- The Investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the Investigator. Emergency unblinding will be available via the IXRS or via the unblinded pharmacist.

- The Investigator should make every effort to first contact the Medical Monitor or appropriate study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If the Medical Monitor is not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding.
- The date and reason for the unblinding (the event or condition which led to the unblinding) must be fully documented in the eCRF

A participant will be withdrawn if the participant's treatment code is unblinded by the Investigator or treating physician.

Current text:

This will be a double-blind study. The investigator and study site will also remain blinded to the IgG, albumin, total protein, alkaline phosphatase (ALP), anti-TPO, anti-thyroglobulin, and anti-TSHR, and anti-IGF-1R antibody data post screening as this could potentially unblind them. An unblinded Medical Monitor will review the lab data for **IgG, albumin, total protein, and ALP** on an ongoing basis for safety.

The following will apply throughout the study:

- The Investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the Investigator. Emergency unblinding will be available via the IXRS or via the unblinded pharmacist.
- The Investigator should make every effort to first contact the Medical Monitor or appropriate study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If the Medical Monitor is not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding.
- The date and reason for the unblinding (the event or condition which led to the unblinding) must be fully documented in the eCRF

A participant will be withdrawn if the participant's treatment code is unblinded.

Change #22: Section 7.5 Preparation/Handling/Storage/Accountability, bullet 2

Previous text:

- The Pharmacist or designee is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Current text:

- **While the Investigator is ultimately responsible**, study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records) **can be designated to the Pharmacist or other designee.**

Change #23: Section 7.6 Compliance with Study Treatment Administration

Previous text:

The individual dose for a participant is prepared by a Pharmacist, licensed Pharmacy Technician, or designee. The preparation of the dose will be reviewed and confirmed by a second member of the study site staff.

The IP will be administered by an unblinded designee. The date and time of each dose administered along with the location of each injection will be recorded in the source documents. The location of each injection and study participant identification will be confirmed at the time of dosing by a member of the study site staff (blinded to study treatment) other than the person administering the study drug.

Current text:

The individual dose for a participant is prepared by an Unblinded Pharmacist, licensed Pharmacy Technician, or designee. The preparation of the dose will be reviewed and confirmed by a second **unblinded** member of the study site staff.

The **study treatment** will be administered by an unblinded designee **not involved in the assessment of the participant**. The date and time of each dose administered along with the location of each injection will be recorded in the source documents. The location of each injection and study participant identification will be confirmed at the time of dosing by **another** member of the study site staff **(this person can be blinded or unblinded to study treatment)** other than the person administering the study drug.

Change #24: Section 8.1 Time and Events Table

Updated visit schedule and assessments to reflect 12 weeks of dosing and an 8 week follow up period

Added the following assessments: dilated indirect ophthalmoscopy assessment, color vision assessment, vaccine titers, lipid panel, and, and microalbumin/creatinine ratio if urine protein abnormal.

Added Hemoglobin A1c sampling at baseline, Week 12 and early withdrawal

[redacted]

Changed the observation post dose period from 1 hour to 30 minutes

Removed IGF1-R sampling from screening visit

Change #25: Section 8.3.2 Ophthalmic Exams

Previous text:

Ophthalmic exams will consist of cornea, lens, intraocular pressure, and optic neuropathy assessments (disc, choroidal folds). The exams will be conducted at the times indicated in the Time and Events Table (Section 8.1). If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities, rise in intraocular pressure, or other abnormalities of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.

Current text:

Ophthalmic exams will consist of:

- best corrected visual acuity (Snellen chart)
- automated perimetry to include a minimum of 24 degrees of visual field
- pupil assessment to include swinging flashlight test for afferent pupillary defect
- anterior segment slit lamp exam
- intraocular pressure
- posterior exam including dilated indirect ophthalmoscopy with optic disc and retinal/choroid assessment of posterior pole as well as periphery
- color vision (Ishihara plates or equivalent).

The exams will be conducted at the times indicated in the Time and Events Table (Section 8.1). Please note that the timing for 2 ophthalmic assessments: (1) dilated indirect ophthalmoscopy and (2) color vision, are listed separately in the T&E table as they have a different schedule than the other assessments that comprise the ophthalmic exam. Results for all ophthalmic assessments will be recorded in the participant's source document.

If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities, clinically significant rise in intraocular pressure, or other abnormalities of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist's clinical judgment.

Change #26: Section 8.3.3 Vital Signs and Section 8.3.4 Electrocardiogram

Changed the position for these assessments from semi-supine to supine.

Change #27: Section 8.3.5 Clinical Safety Laboratory Assessments

Added Hemoglobin A1c to the hematology panel

Added a fasted lipid panel, clarified the timepoints for fasted glucose, updated the urinalysis with microalbumin/creatinine ratio, and added vaccine titers.

Clinical Chemistry

Fasted labs	
Glucose (fasted) **Baseline and Week 12 only**	
Lipid Panel (fasted) **Baseline, weeks 12, 20, and Early Withdrawal only**	Total cholesterol Triglycerides HDL cholesterol LDL cholesterol (calculated using Martin-Hopkins equation) Cholesterol/HDL ratio Non-HDL cholesterol (calculated)

Routine Urinalysis

Specific gravity, pH
glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or urine **protein** is abnormal)
Microalbumin/creatinine ratio at baseline, week 12, and week 20 only (if urine protein is abnormal)

Other tests

Viral Serology [HIV1/HIV2, Hepatitis B (HBsAg), Hepatitis B (Core antibody), Hepatitis C (Hep C antibody]
Vaccine titers for: tetanus, diphtheria, Hepatitis A, Hepatitis B, Pneumococcal
FSH (as needed for confirmation of postmenopausal status)
Pregnancy Tests: serum test at screening and **Week 20,** and early withdrawal and urine dipstick pre-dose at other timepoints. Positive urine tests should be confirmed with a serum test.

Change #28: Section 8.3.5 Clinical Safety Laboratory Assessments, 4th paragraph

Added IgG to the blinded lab parameters

Previous text:

Since changes in ALP, total protein and albumin level can potentially unblind the investigator to which dose the participant has been randomized to, values for ALP, total protein, and albumin levels will be blinded to the site. An unblinded Medical Monitor will review this lab data on an ongoing basis for safety.

Current text:

Since changes in **IgG**, ALP, total protein and albumin level can potentially unblind the investigator to which dose the participant has been randomized to, **post-screening** values for **IgG**, ALP, total protein, and albumin levels will be blinded to the site. An unblinded Medical Monitor will review this lab data on an ongoing basis for safety.

Change #29: Section 8.3.9 Exploratory Biomarkers

[redacted]

Change #30: Section 8.4.3 Proptosis

Removed Hertel from the type of instrument used to measure proptosis

Change #31: Section 8.4.7 Orbital CT Scan (For participating sites only)

Previous text:

CT-measured muscle volume, fat volume, total orbital volume, and proptosis will be assessed at the time points indicated in Section 8.1, Time and Event Table.

Dedicated orbital CT scans will be collected locally at each site and provided to a central reader for analysis. Specific details can be found within the SRM or study specific manual.

Current text:

CT-measured muscle volume, fat volume, total orbital volume, and proptosis will be assessed at the time points indicated in Section 8.1, Time and Event Table**. Note: post-baseline orbital CT scans will only be conducted for proptosis responders (i.e., participants with a reduction of 2 or more mm of proptosis as assessed by exophthalmometer at Week 13).**

Dedicated orbital CT scans will be collected locally at each site and provided to a central reader for analysis. Specific details can be found within the SRM or study specific manual.

Change #32: Section 8.4.8 Gorman Score for Diplopia

Updated the grading scale to 3 grades and removed prisms

Previous text:

Diplopia will be assessed at the time points indicated in Section 8.1, Time and Event Table, based on four grades [Bahn, 1987]:

Grade I - Intermittent diplopia: This is present only when the patient is fatigued

Grade II – Inconstant diplopia: This is present only on lateral or upward gaze

Grade III – Constant diplopia: This is present on straight and level gaze and is correctable with prisms.

Grade IV – Constant diplopia: This is present on straight and level gaze but is not correctable with prisms.

Current text:

Diplopia will be assessed at the time points indicated in Section 8.1, Time and Event Table, based on **three** grades [Bahn, 1987]:

Grade I - Intermittent diplopia: This is present only when the patient is fatigued

Grade II – Inconstant diplopia: This is present only on lateral or upward gaze

Grade III – Constant diplopia: This is present on straight and level gaze

Change #33: Section 10.1 Sample Size Considerations

Previous text:

For the primary endpoint, proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye. It will be assumed that the placebo arm will have a 5% response rate and the highest dosing arm (680 mg) will have a 50% response rate. Using these assumptions, 19 participants per arm will be sufficient to detect this treatment group difference with at least 80% power using a two-sided Fisher's Exact Test assuming an alpha of 0.05.

Current text:

For the primary endpoint, proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye. It will be assumed that the placebo arm will have a 5% response rate and the highest dosing arm (680 mg) will have a 50% response rate. **Assuming a dropout rate of 15%, approximately 22 participants are to be randomized to the 680 mg, 340 mg, and placebo groups. Eleven subjects are to be randomized to the 255 mg dose group.** Using these assumptions, 19 participants per arm will be sufficient to detect this treatment group difference with **approximately 85%** power using a two-sided Fisher's Exact Test assuming an alpha of 0.05.

Change #34: Section 10.2.2 Interim Analysis

The interim analysis was removed from the statistical plan

Change #35: Section 10.3.1 Primary efficacy Endpoint

Previous text:

The primary endpoint is defined as the Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye at the end of treatment (Week 7). The proportion of responders will be summarized for all participants in the ITT population by treatment group at each visit. A closed, sequential testing procedure will be used to test the three active treatment groups vs

placebo. The highest dose will be tested vs placebo at a significance level of 0.05. If that test is significant, then the middle dose will be tested against placebo at a significance

Current text:

The primary endpoint is defined as the Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye at the end of treatment (Week 13). **The study eye is defined as the most severely affected eye at the baseline visit. In the event of both eyes being affected the same, then the right eye will be used as the study eye.** The proportion of responders will be summarized for all participants in the ITT population by treatment group at each visit. A **fixed**, sequential testing procedure will be used to test the three active treatment groups vs placebo. The highest dose will be tested vs placebo at a significance level of 0.05. If that test is significant, then the middle dose will be tested against placebo at a significance level of 0.05. If this test is significant, the smallest dose level will be tested against placebo at a significance level of 0.05. Testing will stop when a non-significant test occurs.

Change #36: Section 10.3.2 Secondary Efficacy Endpoints

Previous text:

All secondary endpoints will be evaluated with the end of the treatment period (Week 7), unless otherwise specified.

The following secondary endpoints will be evaluated:

- Proportion of participants with ≥2-point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis

- Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye).
    - (Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, and 18**) [Not Week 7]**

- Proportion of participants with CAS of 0 or 1
- Change from baseline in proptosis
- Change from baseline in CAS
- Proportion of participants with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye:
    - Reduction in proptosis by at least 2 mm;
    - Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree);
    - Improvement in CAS by at least 2 points
- Change from baseline in the Gorman Score for diplopia
- Change from baseline in the GO-QOL visual and appearance subscale scores.

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by

visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Treatment group differences will be evaluated using ANCOVA techniques with terms in the model for baseline and treatment. Pairwise differences comparing both active arms to placebo will be performed assuming an alpha of 0.05.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Treatment group differences will be evaluated using a two-sided Fisher's Exact test assuming an alpha of 0.05.

Current text:

All secondary endpoints will be evaluated with the end of the treatment period (Week 13), unless otherwise specified.

The following secondary endpoints will be evaluated:

- Proportion of participants with ≥2-point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20**
- Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye) **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 20**

- Proportion of participants with CAS of 0 or 1 **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20**
- Change from baseline in proptosis **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20**
- Change from baseline in CAS **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20**
- Proportion of participants with overall ophthalmic improvement **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20** defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye:
- Reduction in proptosis by at least 2 mm;
- Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree);
- Improvement in CAS by at least 2 points
- Change from baseline in the Gorman Score for diplopia **at Weeks 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 16, and 20**
- Change from baseline in the GO-QOL visual and appearance subscale scores **at Weeks 2, 4, 6, 8, 10, 12, 13, 14, 16, and 20**

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Treatment group differences will be evaluated using a **mixed model for repeated measurements (MMRM)** techniques with terms in the

model for baseline treatment, **visit, and treatment by visit interaction**. Pairwise differences comparing both active arms to placebo will be performed assuming an alpha of 0.05.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Treatment group differences will be evaluated using a two-sided Fisher's Exact test assuming an alpha of 0.05.

Change #37: Section 10.3.6 Other Analyses

Previous text:

Current text:

Change # 38: Section 13.1.7 Drug Accountability

Previous text:

The Principal Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), participant dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to participants, including lot number, date dispensed, participant identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study, as appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Current text:

The Principal Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), participant dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to participants, including lot number, date dispensed, participant identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. **Used investigational product and supplies** may be returned or destroyed on an ongoing basis during the study, **following review and verification from study monitor**, as appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will **return**, all unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Change # 39: Section 13.2.3 Posting of Information on Publicly Available Clinical Trial Registers

Previous text:

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins. Results will be posted as required.

Current text:

Study information from this protocol will be posted on publicly available clinical trial registers **within 21 days of** enrollment of **the first** participant. Results will be posted as required.

Change #40 Section 13.3.3 Study Discontinuation

Previous text:

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority (ies), IRBs, and IECs. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

Current text:

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority (ies), IRBs, and IECs. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

Reasons for stopping the study may include but are not limited to:

- **New evidence that, in the opinion of the sponsor, makes continuation of the study unnecessary or unethical**
- **The sponsor discontinues development of RVT-1401**
- **Insufficient patient enrollment**

Change # 41: Section 14 References

Added the following reference:

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2014-2018, AASLD and IDSA. www.hcvguidelines.org (last updated: May 24, 2018)

Amendment 01 Changes

Rationale for the amendment:

The following items were updated based on FDA feedback:

- Definition for proptosis responder was updated to remove subjects with < 3 mm proptosis at baseline
- Additional details on method for primary analysis was added
- Additional information to note that the first interim analysis will be blinded was added

To simplify the CAS administration, this was changed from the 10-item to the 7-item CAS which is more commonly used by physicians. As a result, proptosis and motility assessments have been added.

The clinical experience including safety, PK, and PD sections were updated to reflect current data and an update to the IB.

[redacted]

Other administrative changes were also made.

Change #1: Section 2 Protocol Summary for RVT-1401-2001: Criteria for Evaluation: Primary, Section 4 Objectives and Endpoints

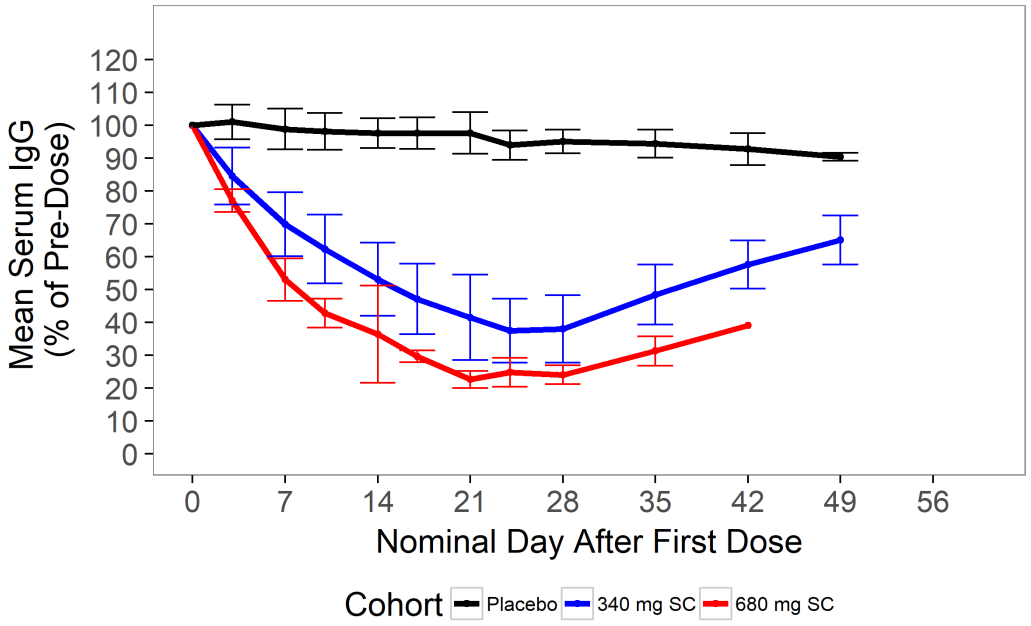
Removed the following text:

Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye).

Change #2: Section 3.2.2 Dose Rationale Figure 1

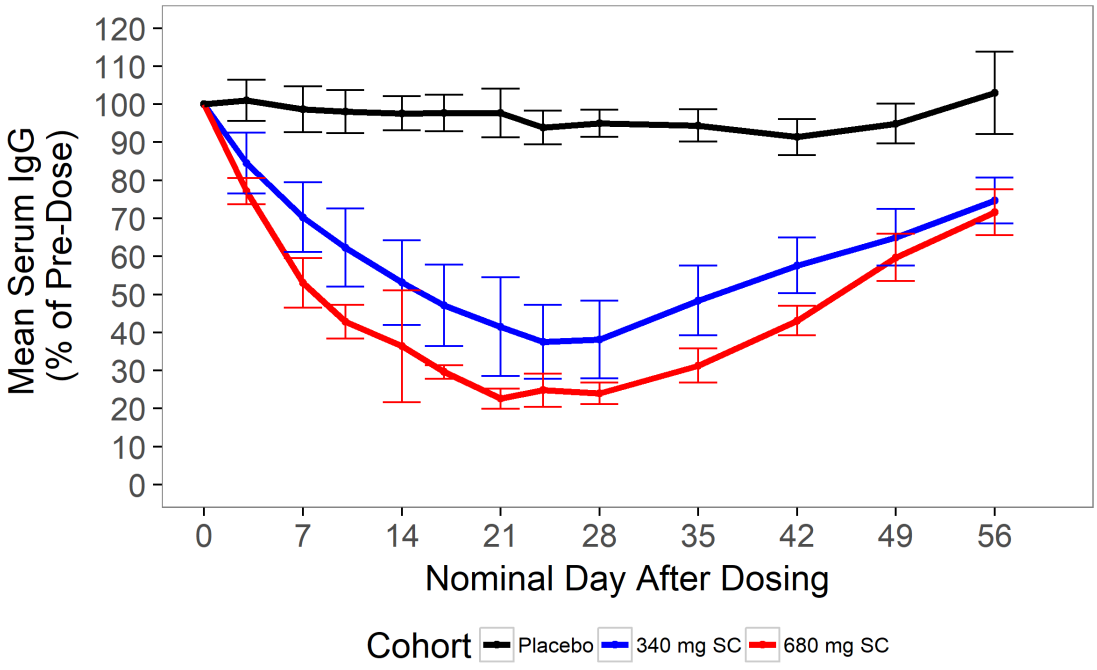
Original text:

Figure 1: Serum IgG (Mean +/-SD) Reduction Following Multiple Doses of RVT-1401 (Study RVT-1401-1001)



Revised text:

Figure 1: Serum IgG (Mean +/-SD) Reduction Following Multiple Doses of RVT-1401 (Study RVT-1401-1001)



Change #3: Section 3.2.2 Clinical Experience, Section 3.2.3.1 Safety, Section 3.2.3.2 Pharmacokinetics, Section 3.2.3.3 Pharmacodynamics

Original text:

RVT-1401 has been studied in two Phase 1 clinical studies (HL161BKN-001 and RVT-1401-1001) designed to assess the safety, tolerability, PK, and PD following single (IV and SC) and multiple (SC) doses in healthy participants. As of November 22, 2018 RVT-1401 has been administered to 65 healthy participants at the following doses: 0.1 mg/kg as a 1-hour IV infusion (n=4), 100 mg as a 1-hour IV infusion (n=6), 340 mg as a 1-hour IV infusion (n=6), 0.5 mg/kg SC injection (n=3), 1.5 mg/kg SC injection (n=6), 5 mg/kg SC (n=6), 340 mg SC injection (n=6), 500 mg SC injection (n=6), 765 mg SC injection (n=6). Eight participants have received repeated 340 mg SC injections weekly for 4 weeks and 8 participants have received repeated 680 mg SC injections weekly for 4 weeks.

3.2.3.1 Safety

RVT-1401 has been well tolerated. There were no Grade 3 or 4 adverse events (AEs), and no withdrawals due to AEs. Note: an SAE (Malpighian carcinoma in left side of the neck) considered unrelated to study drug was received by the sponsor following the data cut-off of Nov 22, 2018 (see Investigator's Brochure for description).

All AEs in subjects receiving RVT-1401 have been reported as mild, except for moderate AEs summarized in Table 1. One subject who received placebo experienced severe (Grade 3) muscular pain that caused the subject to vomit.

Table 1: Moderate AEs Following Administration of RVT-1401 or Placebo

Number of Subjects with Moderate Adverse Events		
Adverse Event	RVT-1401 (N=65)	Placebo (N=18)
Gastroenteritis	1	0
Headache	5	2
Chest pain	1	0
Upper respiratory infection	1	0
Dizziness due to catheter insertion	1	0
Muscular pain	0	3

Mild AEs that were reported in more than 10% of subjects in either RVT-1401 or placebo are presented in Table 2. Table 2 illustrates that the most common mild AEs occurred at similar rates in the placebo and RVT-1401 groups with the only exception being the number of RVT-1401 subjects experiencing a mild headache.

Table 2: Mild AEs Following Administration of RVT-1401 or Placebo

Mild AEs Occurring in >10% of subjects (either RVT-1401 or Placebo)		
Adverse Event	RVT-1401 (N=65)	Placebo (N=18)
Injection site reactions (erythema and/or swelling)	32	11

Headache	7	0
Upper respiratory tract related issues	8	4
Nausea	3	2
Dizziness	2	3
Generalized pain	7	3
Rash	4	2

The most frequent mild AE for both groups was injection site reactions (erythema/ and or swelling). Overall, injection site reactions have resolved within a few hours after dosing; there were two exceptions of mild swelling (one RVT-1401 and one placebo subject) that resolved after 3 and 4 days, respectively. The frequency of injection site reactions was not dose-related and similar reactions were observed with placebo. Additionally, injection site reactions were not consistently observed following every injection in the repeat dose cohorts.

Preliminary data suggest no subject who has received RVT-1401 had clinically relevant changes in laboratory findings, electrocardiograms (ECGs), or vital signs.

An independent safety monitoring committee reviewed safety, PK, and PD data for each cohort prior to every dose escalation and no concerns have been identified with RVT-1401.

3.2.3.2 Pharmacokinetics

[redacted]

3.2.3.3 Pharmacodynamic

Following the administration of single SC doses of RVT-1401, total IgG reduction increased with increasing dose, with a maximum reduction of 47% observed after a fixed dose of 765 mg. The nadir for IgG reduction following single SC dosing occurred between days 8-15 in most individuals. IgG serum levels on average returned to within 90% of baseline by 43 days after drug administration.

Albumin levels were also reduced from baseline when compared to placebo showing a similar dose related trend. The highest reductions occurred following the 765 mg SC dose (average ~14.5%) but were not considered to be clinically significant as all patients remained within normal limits (3.5 g/dL to 5.5 g/dL) and levels recovered quickly, returning to baseline ~ 2 weeks after nadir.

The amount of IgG reduction has also been assessed following weekly SC administration of 340 and 680 mg of RVT-1401 or placebo for 4 weeks. There were 8 subjects with Day 35 data that were included in preliminary PD analysis for 680 mg cohort and 7 subjects with Day 49 data that were included in analysis for the 340 mg cohort. Data from the one subject that only received 2 doses of 340 mg prior to early study withdrawal due to personal reasons was not included. There were 4 placebo subjects with Day 35 data pooled across the two cohorts that were included in the PD analysis.

Figure 1 presents the mean IgG concentration-time profiles for both weekly SC administration of 340 mg and 680 mg doses. A summary of the major PD parameters for IgG are found in Table 4 for placebo, 340, and 680 mg dose groups. Figure 1 shows a reduction in serum IgG as a percent of pre-dose across both 340 mg and 680 mg cohorts. In contrast, the placebo group demonstrated minimal changes in serum IgG as a percent of pre-dose. The reduction in serum IgG was more rapid following the 680 mg SC compared to 340 mg SC. The median IgG nadir concentration occurred prior to the last dose in the 680 mg cohort whereas in 340 mg it occurred approximately 3 days after the last dose.

Table 4 summarizes the changes in IgG across cohorts. The data demonstrate that in addition to greater percent reduction from baseline in serum IgG, there was also less variability around the maximum percent reduction from baseline in IgG for weekly 680 mg doses than for weekly 340 mg doses, even though the baseline IgG levels were higher for the 680 mg cohort. The finding that the 680 mg cohort achieved nadir concentration following the 3rd dose and maintained serum IgG reduction after the 4th dose, indicates a maximum response has likely been achieved, and that higher doses or more frequent dosing would yield little additional benefit. This would be consistent with data from other anti-FcRn agents in development that have observed a maximum percent reduction in serum IgG from baseline of ~ 75-80%. Although there is only preliminary data out to day 35 after the first dose for the 680 mg cohort, this data shows an initial rate of return to baseline for serum IgG that appears to be like the 340 mg cohort. The return towards baseline would suggest the effect is reversible, similar to what has been observed following single dose administration.

The change in serum albumin was also assessed following repeat SC administration of 340 and 680 mg of RVT-1401 as compared to pooled placebo (Table 5). Following both single and repeat dosing RVT-1401 serum albumin concentrations were reduced in a dose dependent fashion, whereas placebo subjects showed little to no change in albumin concentrations. While there was a reduction in albumin concentrations following weekly dosing of 340 mg of RVT-1401, individual concentrations remained within normal limits (>3.5 g/dL or 35 g/L) for serum albumin and recovered back to 90% of baseline in less than 3 weeks after the last dose. Following weekly administration of 680 mg of RVT-1401, serum albumin levels dropped below normal limits (>3.5 g/dL) but remained above 3.0 g/dL for the duration of dosing except in one individual. Most individuals had nadir albumin concentration prior to the last dose, indicating no further reduction occurred after the last dose. The one subject who had albumin concentrations below 3.0 g/dL had a similar percent reduction from baseline, however their baseline albumin level of 4.1 g/dL was lower than rest of the group, which may explain the lower absolute albumin concentration level that was observed. There were no other clinical signs or symptoms reported with transient albumin reduction. In most individuals, albumin levels began to rise within 7 days following the last dose of either 340 mg or 680 mg indicating the reversibility of this effect. Weekly albumin levels will be reviewed throughout the current trial; specific stopping criteria are described in Section 6.8.4.

[redacted]

Additional information is available in the current Investigator's Brochure (IB).

Revised text:

3.2.3 Clinical Experience

RVT-1401 has been studied in two Phase 1 clinical studies (HL161BKN-001 and RVT-1401-1001) designed to assess the safety, tolerability, PK, and PD following single (IV and SC) and multiple (SC) doses in healthy participants. As of December 14, 2018, RVT-1401 has been administered to 65 healthy participants at the following doses: 0.1 mg/kg as a 1-hour IV infusion (n=4), 100 mg as a 1-hour IV infusion (n=6), 340 mg as a 1-hour IV infusion (n=6), 0.5 mg/kg SC injection (n=3), 1.5 mg/kg SC injection (n=6), 5 mg/kg SC (n=6), 340 mg SC injection (n=6), 500 mg SC injection (n=6), 765 mg SC injection (n=6). Eight participants have received repeated 340 mg SC injections weekly for 4 weeks and 8 participants have received repeated 680 mg SC injections weekly for 4 weeks.

3.2.3.1 Safety

See Investigator's Brochure for Details.

RVT-1401 has been well tolerated with no Grade 3 or 4 adverse events (AEs), and no withdrawals due to AEs. There was one SAE (Malpighian carcinoma in left side of the neck) considered unrelated to study drug.

All AEs in subjects receiving RVT-1401 have been reported as mild or moderate. One subject who received placebo experienced severe (Grade 3) pain from urinary lithiasis.

The most frequent AE for both groups was injection site reactions (erythema/ and or swelling). Overall, injection site reactions have resolved within a few hours after dosing; there were two exceptions of mild swelling (one RVT-1401 and one placebo subject) that resolved after 3 and 4 days, respectively. The frequency of injection site reactions was not dose-related and similar reactions were observed with placebo. Additionally, injection site reactions were not consistently observed following every injection in the repeat dose cohorts.

Preliminary data suggest no subject who has received RVT-1401 had clinically relevant changes in laboratory findings, electrocardiograms (ECGs), or vital signs.

3.2.3.2 Pharmacokinetics

3.2.3.3 Pharmacodynamic

Following the administration of single SC doses of RVT-1401, total IgG reduction increased with increasing dose, with a maximum reduction of 47% observed after a fixed dose of 765 mg. The nadir for IgG reduction following single SC dosing occurred between days 8-15 in most individuals. IgG serum levels on average returned to within 90% of baseline by 43 days after drug administration. Albumin levels were also reduced from baseline when compared to placebo showing a similar dose related trend. The highest reduction occurring following the 765 mg SC dose [redacted] but were not considered to be clinically significant reductions as all patients remained within normal limits (3.5 g/dL to 5.5 g/dL) and levels recovered quickly, returning to baseline ~ 2 weeks after nadir.

The amount of IgG reduction has also been assessed following weekly SC administration of 340 and 680 mg of RVT-1401 or placebo for 4 weeks. There were 8 subjects with data out day 35, that were included in preliminary PD analysis for 680 mg cohort and 7 subjects with data out to day 49 were included in analysis for 340 mg cohort. One subject only received 2 doses of 340 mg prior to withdrawing due to personal reasons, their data was not included in the preliminary PD analysis. There were 4 placebo subjects with data out to day 35 pooled across two cohorts for analysis of PD endpoints. Figure 1presents the mean IgG concentration-time profiles for both weekly SC administration of 340 mg and 680 mg doses. Figure 1 shows a reduction in serum IgG as a percent of pre-dose across both 340 mg and 680 mg cohorts. In contrast, the placebo group demonstrated minimal changes in serum IgG as a percent of pre-dose. The reduction in serum IgG was more rapid following the 680 mg SC compared vs 340 mg SC. The median IgG nadir concentration occurred prior to last dose in the 680 mg cohort whereas in 340 mg it

occurred approximately 3 days after the last dose. The finding that the 680 mg cohort achieved nadir concentration following the 3rd dose and maintained serum IgG reduction after the 4th dose, indicates a maximum response has likely been achieved, and that higher doses or more frequent dosing would yield little additional benefit. This is consistent with data from other anti-FcRn agents in development that have observed a maximum percent reduction in serum IgG from baseline of ~ 75-80%.

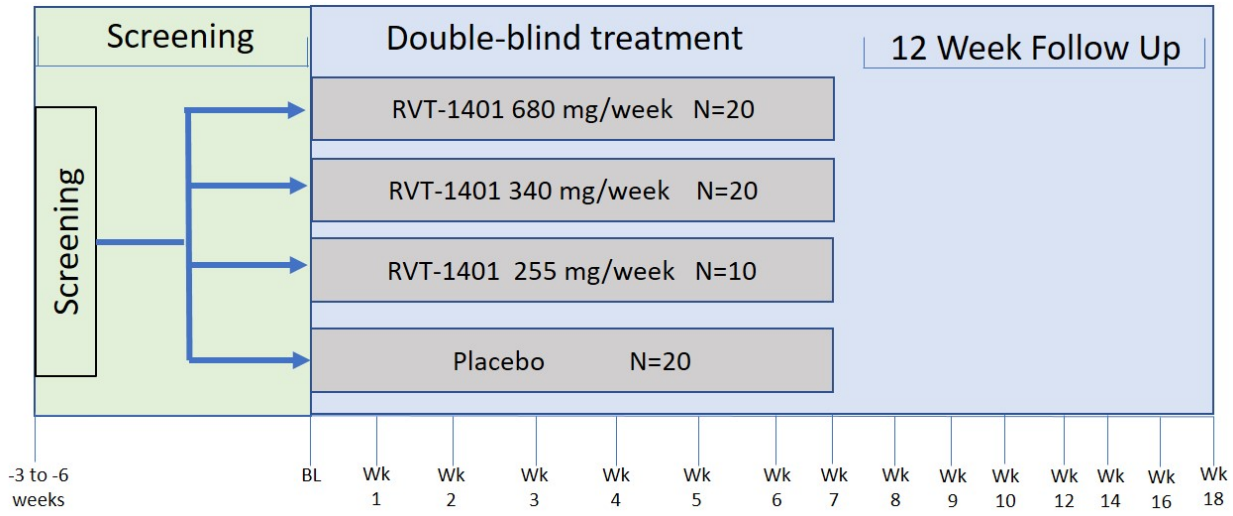
Preliminary data following the last dose across both cohorts shows that IgG levels were within normal range and within 30% of the baseline value by 5 weeks after the last dose (average (SD) IgG concentration was 8.64 (2.73) g/L, and 8.95 (2.03) g/L for the 340 mg and 680 mg cohorts, respectively). The return towards baseline indicates the effect is reversible.

The change in serum albumin was also assessed following repeat SC administration of 340 and 680 mg of RVT-1401 as compared to pooled placebo. Following both single and repeat dosing RVT-1401 serum albumin concentrations were reduced in a dose dependent fashion, whereas placebo subjects showed little to no change in albumin concentrations. While there was a reduction in albumin concentrations following weekly dosing of 340 mg of RVT-1401, individual concentrations remained within normal limits (>3.5 g/dL) for serum albumin. Following weekly administration of 680 mg of RVT-1401, all but 1 individual remained above 3.0 g/dL for the duration of dosing and most individuals had nadir albumin concentration prior to last dose, indicating that maximum albumin reduction had been achieved. In all individuals, albumin levels were within normal limits (>3.5 g/dL) within 3-4 weeks of the last dose for the 680 mg cohort. Across both cohorts, on average, individuals were within 95% of their baseline concentration 5 weeks after the last dose, indicating the reversibility of the effect of RVT-1401 on albumin. There were no clinical signs or symptoms reported with these transient albumin reductions.

Additional information is available in the current Investigator's Brochure (IB).

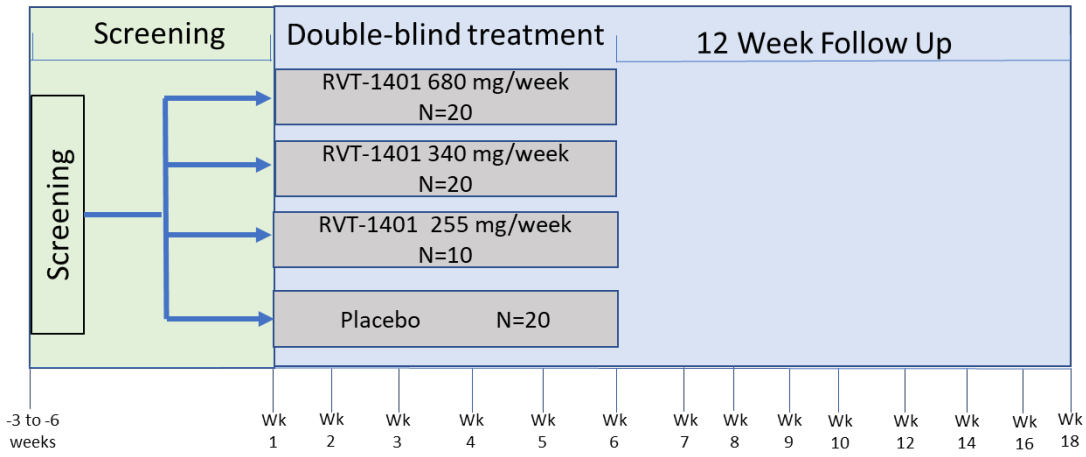
Change #4: Section 5.2 Study Schematic

Original text:



Regimen A= RVT-1401 680 mg weekly for 6 weeks
Regimen B= RVT-1401 340 mg weekly for 6 weeks
Regimen C= RVT-1401 255 mg weekly for 6 weeks

Revised text:



Change #5: Treatment Arms and Duration-added smoking stratification

Original text:

Participants will receive RVT-1401 or placebo as two SC injections for 6 weeks. Refer to Figure 3 for dosing regimen details.

Revised text:

Participants will be randomized 2:2:1:2 to RVT-1401 or placebo. Randomization will be stratified based on smoking status at the screening visit. Refer to Figure 2 for dosing regimen details.

Change #6: Section 6.2 Inclusion Criteria, Criteria # 4

Original text:

Clinical diagnosis of Graves' disease with hyperthyroidism associated with active, moderate to severe GO with a CAS ≥ 4 for the most severely affected eye at Screening. (on the 7-item scale) and Baseline (on the 10-item scale).

Revised text:

Clinical diagnosis of Graves' disease with hyperthyroidism associated with active, moderate to severe GO with a CAS ≥ 4 for the most severely affected eye at Screening.

Change #7: Section 6.2 Inclusion Criteria, Criteria #6

Original text:

Documented evidence at Screening of detectable autoantibodies (anti-TSHR-Ab, anti-IGF-1R-Ab, or both).

Revised text:

Documented evidence at Screening of detectable anti-TSHR-Ab.

Change #8 Section Exclusion Criteria, Criteria #4

Original text:

Use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation within the past 9 months prior to Baseline.

Revised text:

Use of rituximab, tocilizumab, or any monoclonal antibody/Fc-fusion biologic for immunomodulation within the past 9 months prior to Baseline.

Change #9: Section 6.3 Exclusion Criteria, Criteria # 5

Original text:

Use of selenium 3 months prior to Baseline and use during the clinical trial (multivitamins that include selenium are allowed).

Revised text:

Use of selenium within 3 weeks prior to Baseline and use during the clinical trial (this includes multivitamins that include selenium).

Change #10: Section 7.3 Blinding, Section 8.3.4 Clinical Safety Laboratory Assessments

Added alkaline phosphatase (ALP) to a blinded safety laboratory assessment

Change #11: Section 8.1 Time and Events Table,

Added/updated text:

Added collection of thyroid history to medical history at baseline

Added Ophthalmic exam at Screening

Added Proptosis and Motility assessments

Updated timepoints for the Anti IGF-1R and Anti-TSHR samples

Added a footnote to clarify the ophthalmic exam

Change #12: Section 8.1 Time and Events Table, Section 8.3.4 Clinical Safety Laboratory Assessments

Clarified that serum pregnancy tests are required at screening, Week 18, and Early Withdrawal. At other timepoints urine dipstick tests are acceptable.

Change #13: Section 8.3.2 Ophthalmic Exams

Added text:

If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities, rise in intraocular pressure, or other abnormalities of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.

Change #14: Section 8.3.4 Clinical Safety Laboratory Assessments

Changed glucose fasting lab test to Day 1 (baseline) and Week 7 only. Added Immunoglobulin G (IgG) to the chemistry lab panel to be analysed at the central lab.

Change #15: Section 8.3.8 Pharmacodynamics

Updated table to remove total and activating as follows:

Pharmacodynamic Markers

Total IgG, and differentiation by class: IgG subclasses (IgG1, 2, 3, and 4)
Anti-TSHR ~~(Total & Activating)~~
Anti-IGF-1R ~~(Total & Activating)~~

Change #16: Section 8.3.9 Exploratory Biomarkers

[redacted]

Change #17: Section 8.4 Graves Ophthalmopathy Assessments

In Section 8.4.1 Clinical Activity Score (CAS), removed the 10-point scale and changed the scoring to a 7-point scale at all visits.

Added Section 8.4.3 Proptosis and Section 8.4.4 Motility to the assessments

Proptosis will be assessed using the same Hertel instrument (provided by sponsor) and ideally with the same examiner for each participant. The same intercanthal distance should be used on each occasion. Proptosis will be assessed at the times indicated in the Time and Events Table (Section 8.1).

Motility will be assessed by the examiner by estimating the degrees of restriction in eye movements. Ideally, the same examiner should be used for each participant. Motility will be assessed at the times indicated in the Time and Events Table (Section 8.1).

Change #18: Section 10.1 Sample Size Considerations

Original text:

For the primary endpoint, proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye. For participants with proptosis that is < 3 mm at baseline, response will be defined as returning to normal limits for race and gender. It will be assumed that the placebo arm will have a 5% response rate and the highest dosing arm (680 mg) will have a 50% response rate. Using these assumptions, 19 participants per arm will be sufficient to

detect this treatment group difference with at least 80% power using a two-sided Fisher's Exact Test assuming an alpha of 0.05.

Revised text:

For the primary endpoint, proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye. It will be assumed that the placebo arm will have a 5% response rate and the highest dosing arm (680 mg) will have a 50% response rate. Using these assumptions, 19 participants per arm will be sufficient to detect this treatment group difference with at least 80% power using a two-sided Fisher's Exact Test assuming an alpha of 0.05.

Change #19: Section 10.2.2 Interim Analysis

Original text:

Two interim analyses will be performed:

The first interim analysis will be a performed when 50% of the participants complete the Week 7 visit. This interim will be performed on the primary endpoint only, for the purpose of increasing the sample size as needed. Since there is no plan to stop the study early based on these results, alpha spending should not be necessary.

The second interim analysis will occur after the last participant completes the Week 7 visit of the study. All endpoints will be evaluated for this analysis. Since this analysis is occurring at the end of the treatment phase, no adjustments of the alpha level are necessary. This analysis will serve as the primary analysis and an additional analysis will occur, summarizing the endpoints after the treatment-free phase.

Revised text:

Two interim analyses will be performed:

The first interim analysis will be a blinded review performed when 50% of the participants complete the Week 7 visit. This interim will be performed on the primary endpoint only, for the purpose of increasing the sample size as needed. Since there is no plan to stop the study early based on these results, alpha spending should not be necessary.

The second interim analysis will occur after the last participant completes the Week 7 visit of the study. All endpoints will be evaluated for this analysis. Since this analysis is occurring at the end of the treatment phase, no adjustments of the alpha level are necessary. This analysis will serve as the primary analysis and an additional analysis will occur, summarizing the endpoints after the treatment-free phase.

Change #20: Section 10.3.1 Primary Efficacy Endpoint

Original text:

The primary endpoint is defined as the Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye For participants with proptosis that is < 3 mm at baseline, response will be defined as returning to normal limits for race and gender.) at the end of treatment (Week 7). The proportion of responders will be summarized for all participants in the ITT population by treatment group at each visit.

Revised text:

The primary endpoint is defined as the Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye at the end of treatment (Week 7). The proportion of responders will be summarized for all participants in the ITT population by treatment group at each visit. A closed, sequential testing procedure will be used to test the three active treatment groups vs placebo. The highest dose will be tested vs placebo at a significance level =0.05. If that test is significant, then the middle dose will be tested against placebo at a significance level of 0.05. If this test is significant, the smallest dose level will be tested against placebo at a significance level =0.05. Testing will stop when a non-significant test occurs.

Change #21: Section 10.3.2 Secondary Efficacy Endpoints

Original text:

All secondary endpoints will be evaluated with the end of the treatment period (Week 7), unless otherwise specified.

The following secondary endpoints will be evaluated:

- Proportion of participants with ≥2-point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis (or return to normal limits for race and gender if proptosis baseline <3 mm)
- Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye). For participants with proptosis but < 3 mm at baseline, response will be defined as returning to normal limits for race and gender.
- Proportion of participants with CAS of 0 or 1
- Change from baseline in proptosis
- Change from baseline in CAS
- Proportion of participants with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye:
    - Reduction in proptosis by at least 2 mm;
    - Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree);
    - Improvement in CAS by at least 2 points
- Change from baseline in the Gorman Score for diplopia
- Change from baseline in the GO-QOL visual and appearance subscale scores

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Treatment group differences will be evaluated using ANCOVA techniques with terms in the model for baseline and treatment. Pairwise differences comparing both active arms to placebo will be performed assuming an alpha of 0.05.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Treatment group differences will be evaluated using a two-sided Fisher's Exact test assuming an alpha of 0.05.

Revised text:

All secondary endpoints will be evaluated with the end of the treatment period (Week 7), unless otherwise specified.

The following secondary endpoints will be evaluated:

Proportion of participants with ≥2-point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis (Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, and 18) **[Not Week 7]**

- Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye).
    - (Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, and 18) **[Not Week 7]**

- Proportion of participants with CAS of 0 or 1
- Change from baseline in proptosis
- Change from baseline in CAS
- Proportion of participants with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye:
    - Reduction in proptosis by at least 2 mm;
    - Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree);
    - Improvement in CAS by at least 2 points
- Change from baseline in the Gorman Score for diplopia
- Change from baseline in the GO-QOL visual and appearance subscale scores

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. Treatment group differences will be evaluated using ANCOVA techniques with terms in the model for baseline and treatment. Pairwise

differences comparing both active arms to placebo will be performed assuming an alpha of 0.05.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Treatment group differences will be evaluated using a two-sided Fisher's Exact test assuming an alpha of 0.05.