CLINICAL STUDY PROTOCOL

Title:	A Phase 2a, Multicenter, Open-Label Study of RVT-1401 for the Treatment of Patients with Moderate to Severe Active 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-1401-1002
Indication	Graves' Ophthalmopathy
Development Phase	2a
Version/ **Effective Date:**	Amendment 03: Version 4.0 07-FEB-2019 Amendment 02: Version 3.0 10-JAN-2019 Amendment 01: Version 2.0 17-DEC-2018 Original: Version 1.0 7-DEC-2018
Immunovant, Inc. **Study Director**	[redacted], [redacted] Telephone: [redacted] Email: [redacted]

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SPONSOR SIGNATURE PAGE:

Study title: A Phase 2a, Multicenter, Open-Label Study of RVT-1401 for the Treatment of Patients with Moderate to Severe Active Graves' Ophthalmopathy

Protocol Number: RVT-1401-1002

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

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Date

[redacted]

Immunovant, Inc.

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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

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2. PROTOCOL SUMMARY FOR STUDY RVT-1401-1002

Study Title	A Phase 2a, Multicenter, Open-Label Study of RVT-1401 for the Treatment of Patients with Moderate to Severe Active Graves' Ophthalmopathy
Objectives	**Primary** To assess the safety and tolerability of RVT-1401 in patients with moderate to severe active GO over a 6-week treatment period To assess the change in serum levels of anti-TSHR antibodies and total IgG & IgG subclasses (1-4) **Secondary** To examine the effect of RVT-1401 on mean change in proptosis To examine the effect of RVT-1401 on proptosis responder rate To examine RVT-1401 PK following repeat doses in patients with moderate to severe active GO To measure anti-RVT-1401 antibodies following repeat doses in patients with moderate to severe active GO
Study Phase	Phase 2a
Target Population	Graves' Ophthalmopathy
Number of Participants Planned	Approximately 8 participants
Number of Study Centers Planned	Approximately 4
Study Design	Phase 2a, Multicenter, Open-Label Study to investigate the safety, tolerability, PK, PD, and efficacy of RVT-1401
Duration of Treatment	6 weeks
Criteria for Evaluation (Endpoints)	**Primary** Assessment of safety and tolerability by analysis of AE data and changes from baseline in vital signs, clinical

	laboratory values, and electrocardiograms Change from baseline in levels of anti-TSHR antibodies Change from baseline in levels of total IgG and IgG subclasses (1-4) **Secondary** Change from baseline in proptosis Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye). PK Parameters of AUC (0-168 h) and Cmax after first and last dose Concentration of RVT-1401 pre-dose (Ctrough) Immunogenicity determined by number of participants with positive anti-RVT-1401 antibodies and characterization of any anti-RVT-1401 to confirm neutralization potential

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 (pIgG), 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 patient-friendly subcutaneous (SC) mode of administration.

3.2. Rationale

3.2.1. Study Rationale

The purpose of the current study is to confirm safety/tolerability and key pharmacodynamic (PD) effects that are considered to drive clinical benefit (reduction of total IgG, anti-TSHR-IgG and anti-IGF-1R-IgG) in GO patients. Results from this trial will be used to support progression into a larger and longer study designed to confirm clinical efficacy.

3.2.2. Dose rationale

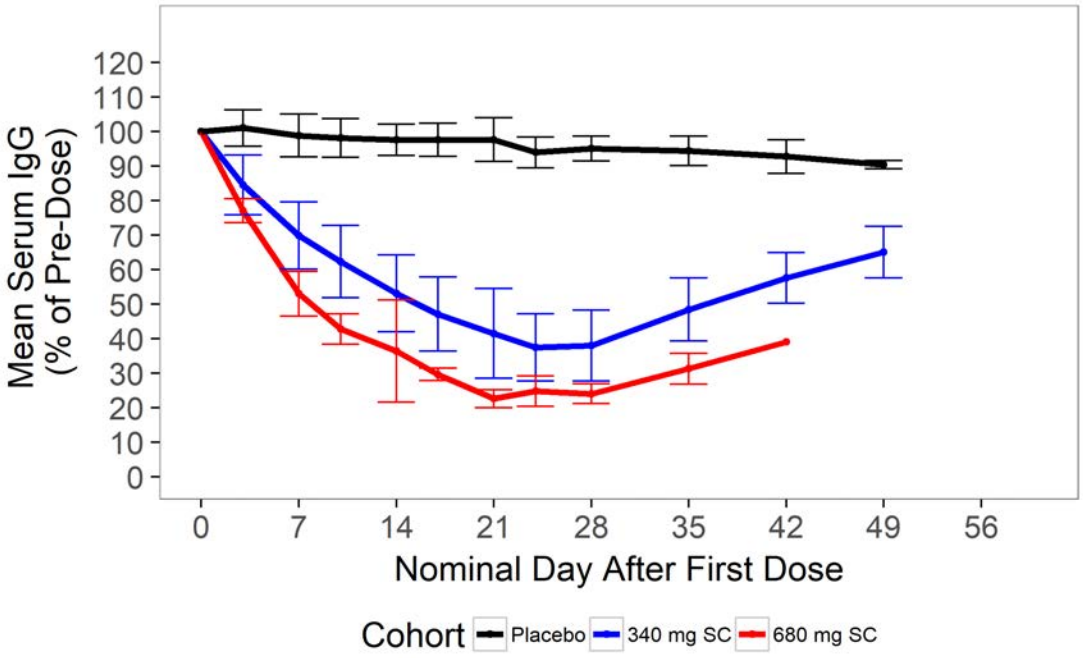
Autoimmunity against the TSHR plays a major role in the development of GO. This is supported by studies that have shown elevated TSHR expression in the orbital tissues from patients with GO as well as the fact that anti-TSHR IgG antibodies are detectable in virtually all patients with GO [Starkey, 2003; 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 has been evaluated in healthy participants using single and repeat SC doses (Section 3.2.3). Changes in serum IgG concentrations were used as a biomarker to assess the effects of repeat administration of RVT-1401 (340 mg and 680 mg). Following weekly administration of 340 mg and 680 mg SC for 4 weeks, serum IgG was reduced from baseline an average of 62.7% and 78.4% respectively, compared to 9.05% for placebo. Serum IgG levels began to return to baseline approximately 7 days after the last dose in both 340 and 680 mg cohorts. In the 340 mg cohort, IgG values returned to within 70% of their baseline value by 4 weeks post last dose and preliminary data also shows that rate of return to baseline for 680 mg cohort follows a similar trajectory, thus indicating the effect is reversible for both doses (consistent with other anti-FcRN's that are currently in development for other indications).

RVT-1401 will be administered as a weekly 680 mg SC injection for two weeks followed by weekly 340 mg SC injection for four weeks. These doses represent the upper limit of RVT-1401 which can be administered as two SC injections (680 mg) and one SC injection (340 mg) per week. In the proposed study, the first two weekly SC administrations of 680 mg is predicted to quickly reduce IgG to ~64% below baseline and the following four weekly doses of 340 mg would maintain this level of IgG reduction before recovering back to baseline over the next 6 to 8 weeks. This regimen would also be expected to maintain serum albumin levels within normal limits for most participants.

This dosing regimen of RVT-1401 produces a significant reduction in total serum IgG within two weeks, which in GO patients would also include anti-TSHR IgG. Thus, 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 reduce serum IgG quickly with induction dosing and then maintain that reduction over the next 5 weeks. The doses used in this regimen have been well-tolerated while producing robust reductions in total IgG in healthy participants.

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



Note: On Day 42 in 680 mg Cohort, only 1 subject had Serum IgG data at the time of data cut off therefore no error bars are presented.

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 (intravenous [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 intravenous (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 have been no Grade 3 or 4 adverse events (AEs) and no withdrawals due to AEs. An SAE (Malpighian carcinoma 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

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 [redacted] 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.

[redacted]. Weekly albumin levels will be reviewed throughout the current trial; specific stopping criteria are described in Section 6.8.4.

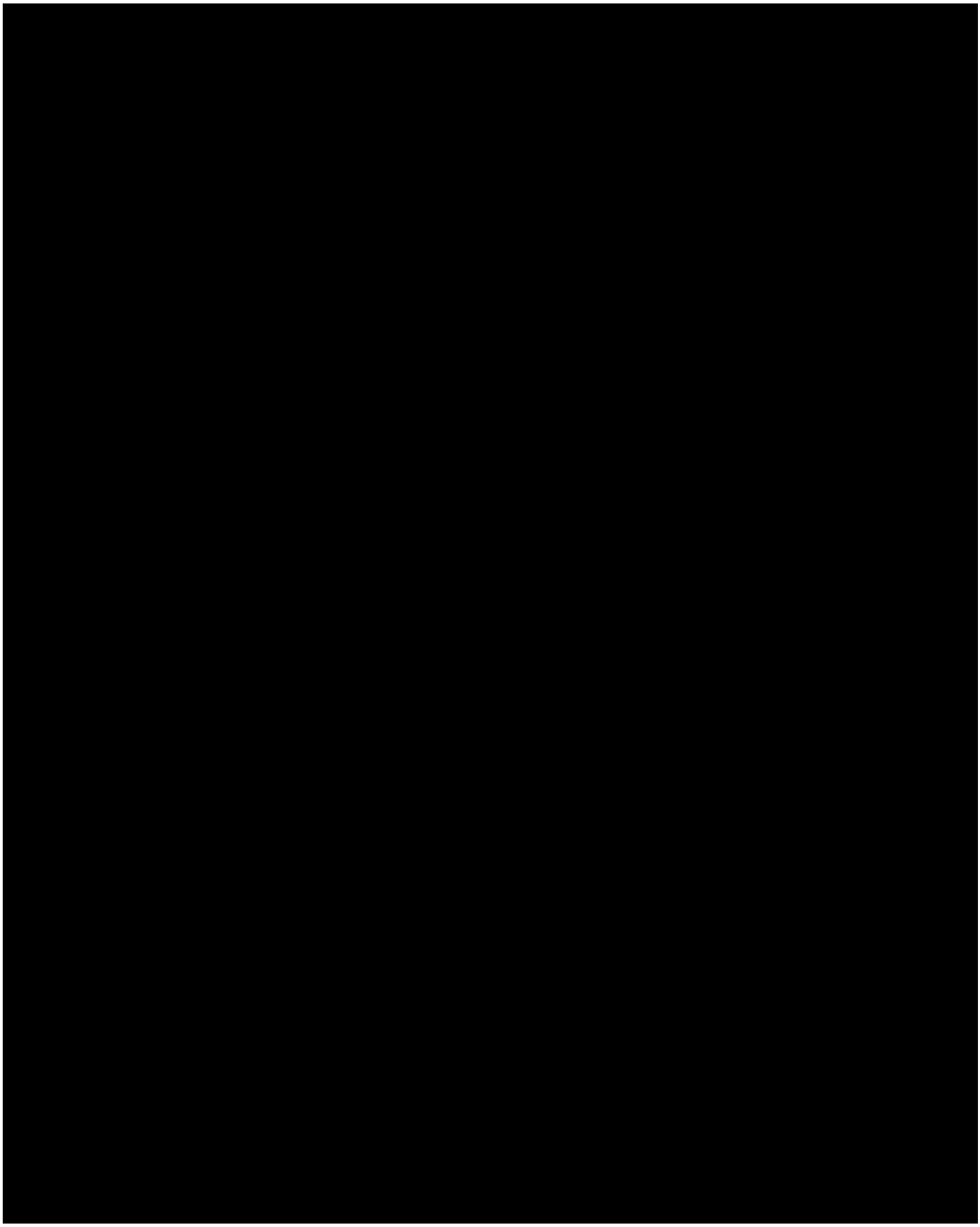


Table 4: Summary of Total IgG PD Parameters [Mean (SD)] following multiple dose administration of RVT-1401

Dose (mg)	N	Weight[2] (kg)	Baseline (g/L)	Nadir IgG Concentration (g/L)	Maximum IgG Reduction from Baseline (%)	Time to Nadir IgG Concentration[2,3] (Days)
340	7[1]	80.6 (66.8, 84.4)	11.4 (2.68)	4.43 (2.19)	62.7 (10.7)	24 (21, 28)
680	8	70.9 (59.2, 90.3)	12.5 (2.91)	2.75 (0.872)	78.4 (2.39)	21 (21, 24)
Placebo[4]	4	76.1 (75.4, 106)	10.5 (2.29)	9.57 (2.13)	9.05 (3.11)	24 (21, 28)

1. N=7 for PD as 1 subject dropped out prior to 4th and final dose
2. Median (Min, Max)
3. Time to nadir is relative to administration of first dose
4. Placebo Group is pooled from subjects receiving placebo from both treatment groups

[redacted]

Additional information is available in the current Investigator's Brochure (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 1 hr post-dose before they leave the clinic. 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), 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	Total IgG levels will be monitored throughout the study (Section 8.1). 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-1401-1002.

	will be excluded. -Absolute neutrophil count <1500 cells/mm^3	
Sustained hypoalbuminemia	Investigator discretion	Serum albumin levels will be monitored throughout the study (Section 8.1). 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).

4. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To assess the safety and tolerability of RVT-1401 in patients with moderate to severe active GO over a 6-week treatment period	Assessment of safety and tolerability by analysis of AE data and changes from baseline in vital signs, clinical laboratory values, and electrocardiograms
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)
Secondary	
To examine the effect of RVT-1401 on mean change in proptosis	Change from baseline in proptosis
To examine the effect of RVT-1401 on proptosis responder rate	Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye).
To examine RVT-1401 PK following repeat doses in patients with moderate to severe active GO	PK Parameters of AUC (0-168 h) and Cmax after first and last dose Concentration of RVT-1401 pre-dose (Ctrough)
To measure anti-RVT-1401 antibodies following repeat doses in patients with moderate to severe active GO	Immunogenicity determined by number of participants positive for anti-RVT-1401 antibodies and characterization of any anti-RVT-1401 to confirm neutralization potential
Exploratory	
To assess the change in serum levels of anti-IGF-1R antibodies	Change from baseline in levels of anti-IGF-1R antibodies
To examine the effect of RVT-1401 on the pro-inflammatory and FcRn gene expression in peripheral blood mononuclear cells.	Change from baseline in the level of gene expression
To examine the effect of RVT-1401 on the level of circulating pro-inflammatory cytokines/chemokines	Change from baseline in the circulating level of pro-inflammatory cytokines/chemokines

To assess FcRn receptor occupancy following RVT-1401 administration in whole blood	FcRn receptor occupancy following RVT-1401 administration
To assess the change in the ratio of stimulatory to total serum levels of anti-TSHR and anti-IGF-1R antibodies	Change from baseline in ratios of stimulatory to total anti-TSHR and anti-IGF-1R antibodies
To examine the effect of RVT-1401 on levels of anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin antibodies	Change from baseline in the levels of anti-TPO and anti-thyroglobulin antibodies
To assess the change in levels of TSH, free T3, and free T4	Change from baseline in levels of TSH, free T3, and free T4
To examine the effect of RVT-1401 on overall responder rate	Proportion of subjects with ≥2-point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis
To examine the effect of RVT-1401 on mean change in Clinical Activity Score (CAS)	Change from baseline in CAS
To examine the effect of RVT-1401 on CAS responder rate	Proportion of subjects with CAS of 0 or 1
To examine the effect of RVT-1401 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 on subjective diplopia	Change from baseline in the Gorman Score for diplopia
To examine the effect of RVT-1401 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 examine the effect of RVT-1401 on methimazole (or other anti-thyroid treatment)	Change from baseline in methimazole (or other anti-thyroid treatment) dose

dosage requirements to achieve/maintain euthyroid state	
To examine the effect of RVT-1401 on Computed Tomography (CT) measured muscle volume, fat volume, total orbital volume, and proptosis	Change from baseline in CT-measured muscle volume, fat volume, total orbital volume, and proptosis

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2a, open label study to investigate the safety, tolerability, PK, PD, and efficacy 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.

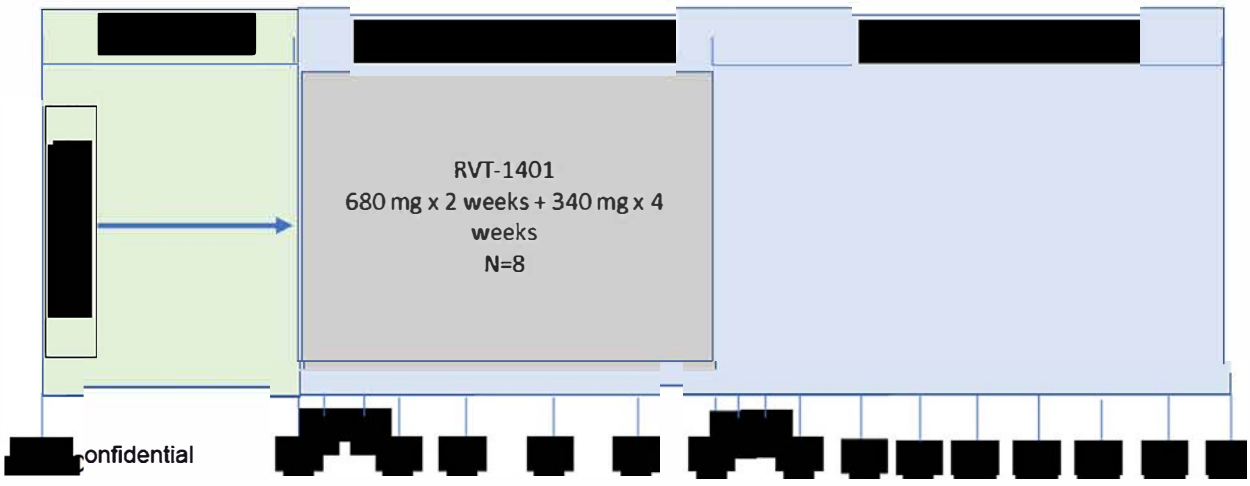
Following the initial dose at the Baseline Visit (Day 1), study visits will occur at Days 3 and 5 and then weekly throughout the treatment period. Following the final dose at Week 6, two study visits will occur at Days 38 and 40, and then weekly through Week 10 and then every 2 weeks until Week 18. Safety, PK, PD, and clinical assessments will be collected throughout the study. 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.

5.2. Study Schematic

Figure 3 Study Design



5.3. Treatment Arms and Duration

Participants will receive RVT-1401 for 6 weeks (680 mg/weekly for 2 weeks followed by 340 mg/weekly for 4 weeks).

6. PARTICIPANT POPULATION

6.1. Type and Number of Participants

A sufficient number of participants will be enrolled to achieve approximately 8 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 (on the 7-item scale) and Baseline (on the 10-item scale).
5. Onset of active GO within 9 months of screening.
6. Documented evidence at Screening of detectable autoantibodies (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 SRM), and/or inconstant or constant diplopia.
9. Stable medical regimen; unlikely to require adjustment of thyroid medications during the 6-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 (methimazole + adding levothyroxine) when FT4 and T3 have become normal are allowed.
13. 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 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 (intravenous [IV] or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED 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 TED and previous use of steroid eye drops is allowed if the corticosteroid was discontinued at least 3 weeks prior to Screening.
4. Use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation within the past 9 months prior to Baseline.
5. Use of selenium 3 weeks prior to Baseline and use during the clinical trial (multivitamins that include selenium are allowed).
6. Use of biotin within 48 hours prior to any laboratory collection (this includes multivitamins that include biotin).
7. Participants with ≥ 2 pts (CAS) or 2 mm (proptosis) decrease between screen & baseline.
8. Total IgG level < 6g/L at Screening.
9. Absolute neutrophil count <1500 cells/mm^3 at Screening.
10. 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.
11. Previous orbital irradiation or surgery for GO.
12. 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.
13. Have known autoimmune disease other than GO that would interfere with the course and conduct of the study.
14. Medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.
15. Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening.
16. 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.
17. 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.
18. 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

19. Body Mass Index (BMI) at Screening ≥ 35 kg/m^2.
20. Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
21. Currently participating or has participated in another GO clinical study within 28 days prior to signing the informed consent form.
22. 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.
23. Participant has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to baseline.
24. 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.
25. Pregnant or lactating females as determined by positive serum or urine human chorionic gonadotropin test at screening or baseline.
26. Participant has had their spleen removed.
27. 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 Clinical 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 at least 4 weeks before Screening.
- 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 a 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
- 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

In addition to lowering IgG, treatment with RVT-1401 is also expected to reduce albumin levels (Section 3.2.3.3). The site will utilize the following criteria to inform study drug discontinuation:

- Grade 3-4 (albumin levels are <2 g/dL): discontinue study drug
- Grade 2 (albumin levels <3-2 g/dL): study drug should be interrupted or discontinued if there are accompanying clinical signs and/or symptoms (edema, hypotension, etc) attributable to decreased albumin.

6.9. Toxicity Management Criteria

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

The severity of each AE will be graded and managed according to the criteria in Table 6.

Table 6 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 RVT-1401 as described below. Additional details related to the specific injection site location will be included within the 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 7.

Table 7: 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
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death

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.

Study Treatment Name:	**RVT-1401**
Supplier:	[redacted]
Dosage formulation:	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: 1 mL RVT-1401 in one syringe for a total of 2 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 1 hr 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

All participants will receive open label RVT-1401 for 6 weeks (680 mg/weekly for 2 weeks followed by 340 mg/weekly for 4 weeks).
.

7.3. Blinding

This will be an open-label study.

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.

Doses will be prepared by the 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 clinic staff.

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 SRM.

- 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.
- The Pharmacist or designee is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- 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 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 delivered to the Principal Investigator or designee to administer the dose, under medical supervision. The date and time of each dose administered along with the location of each injection will be recorded in the source documents. The location and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

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 Week 1 (Days)**			**Treatment Period Weekly Visit (Weeks)**				**Treatment Period Week 6 (Days)**			**Follow-up Period Weekly Visit (Weeks)**								**Early Withdrawal Visit**
Study Timepoint (Weeks)	Within 3-6 weeks	Day 1 (Baseline)	Day 3	Day 5	2 (Day 8)	3 (Day 15)	4 (Day 22)	5 (Day 29)	6 (Day 36)	Day 38	Day 40	7	8	9	10	12	14	16	18	
Time Window (days)			+1 day	+1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+1 day	+1 day	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Demographics, medical history, and smoking status	X																			
Height	X																			
Body weight	X	X																		
Complete physical examination	X	X																		
Brief physical examination																			X	X
Ophthalmic examination	X	X			X		X		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	X	X
12-lead Electrocardiogram[2]	X	X			X		X		X										X	X
Pregnancy test[3] (females)	X	X			X	X	X	X	X										X	X
Viral Serology	X																			
QuantiFERON® – TB GOLD	X																			
Urinalysis[2]	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

	Screening[1]	**Treatment Period Week 1 (Days)**			**Treatment Period Weekly Visit (Weeks)**				**Treatment Period Week 6 (Days)**			**Follow-up Period Weekly Visit (Weeks)**								**Early Withdrawal Visit**
Study Timepoint (Weeks)	Within 3-6 weeks	Day 1 (Baseline)	Day 3	Day 5	2 (Day 8)	3 (Day 15)	4 (Day 22)	5 (Day 29)	6 (Day 36)	Day 38	Day 40	7	8	9	10	12	14	16	18	
Time Window (days)			+1 day	+1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+1 day	+1 day	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	
Serum complement (CH50, C3)[2]		X			X	X	X	X	X			X							X	X
Immunoglobulins (IgM, IgA)[2]		X				X			X			X	X	X					X	X
Anti-TPO and anti-thyroglobulin antibodies[2]		X				X						X							X	X
TSH, Free T3, Free T4[2]	X	X			X	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	X	X	X	X
Anti-TSHR (Cell based)[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-IGF-1R[2]	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RVT-1401 PK sampling[2]		X	X	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	X	X	X	X
Immunoglobins (IgG subclasses)[2]		X	X	X	X	X	X		X	X	X	X				X			X	X
Gene Expression Analysis[2]		X				X			X						X				X	X
Pro-Inflammatory Biomarker Multiplex[2]		X				X			X						X				X	X

	Screening[1]	**Treatment Period Week 1 (Days)**			**Treatment Period Weekly Visit (Weeks)**				**Treatment Period Week 6 (Days)**			**Follow-up Period Weekly Visit (Weeks)**								**Early Withdrawal Visit**
Study Timepoint (Weeks)	Within 3-6 weeks	Day 1 (Baseline)	Day 3	Day 5	2 (Day 8)	3 (Day 15)	4 (Day 22)	5 (Day 29)	6 (Day 36)	Day 38	Day 40	7	8	9	10	12	14	16	18	
Time Window (days)			+1 day	+1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+1 day	+1 day	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	
Receptor Occupancy[2]		X	X	X					X	X	X	X	X		X				X	X
Anti- RVT-1401antibody[2,4]		X				X						X				X			X	X
Nab Assessment[2]		X				X						X				X			X	X
Drug administration		X			X	X	X	X	X											
Injection site reactions[5]		X			X	X	X	X	X											
Clinical Activity Score (CAS) [6]	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
Motility[6]		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
GO-QOL[6]		X			X		X		X			X			X				X	X
External Photographs[7]		X			X	X	X	X	X			X	X		X	X			X	X
Orbital CT Scan[8]		X											X						X	X
Lid retraction		X			X	X	X	X	X			X	X		X	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
Satisfaction Questionnaire												X								X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening[1]	**Treatment Period Week 1 (Days)**			**Treatment Period Weekly Visit (Weeks)**				**Treatment Period Week 6 (Days)**			**Follow-up Period Weekly Visit (Weeks)**								**Early Withdrawal Visit**
Study Timepoint (Weeks)	Within 3-6 weeks	Day 1 (Baseline)	Day 3	Day 5	2 (Day 8)	3 (Day 15)	4 (Day 22)	5 (Day 29)	6 (Day 36)	Day 38	Day 40	7	8	9	10	12	14	16	18	
Time Window (days)			+1 day	+1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+1 day	+1 day	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/- 2 days	
Concomitant medication	X	X	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 and blood draws for safety, PK, and PD assessment will be collected pre-dose on dosing days where specified.
3. Pregnancy tests will be collected pre-dose (via urine dipstick) on dosing days where specified. Serum pregnancy tests should be collected at screening follow up, and Early Withdrawal.
4. Participants positive for anti- RVT-1401 antibody at Week 18 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 18 visit.
5. Local injection site reactions will be assessed at approximately 10 minutes post dose and participants will be monitored for up to 1 hour post dose.
6. GO assessments will be assessed pre-dose when collected on dosing days.
7. Photographs will be assessed post each dose.
8. The baseline orbital scan should be scheduled once all entry criteria haven been met. Scans can be performed within +/- 7 days of the scheduled visit.

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 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.

8.3.3. Vital Signs

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

8.3.4. Electrocardiogram (ECG)

ECGs will be measured in semi-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

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose fasting [on Day 1 (baseline) and Week 7 only]	Total carbon dioxide (CO_2)	Gamma glutamyltransferase (GGT)	Albumin
Sodium	Calcium (corrected)	Alkaline phosphatase	Total Protein

Serum complement (CH50, C3)	Immunoglobulin M (IgM)	Immunoglobulin A (IgA)	TSH, Free T3, Free T4
Immunoglobulin G (IgG)			

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 protein is abnormal)

Other tests

Viral Serology [HIV1/HIV2, Hepatitis B (HBsAg), Hepatitis B (Core antibody), Hepatitis C (Hep C antibody]
FSH (as needed for confirmation of postmenopausal status)
Pregnancy Tests: serum test at screening and follow up and urine dipstick pre-dose and 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 site (detailed in the SRM).

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 (detailed in the SRM). If Anti-RVT-1401 antibody titers are detected, they will be further characterized using a validated cell based 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

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

Exploratory Biomarkers
Gene Expression Analysis
Pro-inflammatory Biomarker Multiplex
Receptor Occupancy
Anti-TPO
Anti-thyroglobulin
Anti-IGF-1R
Anti-TSHR (ratio of total to Activating – cell based)
Anti-IGF-1R (ratio of total to Activating – cell based)

The actual date and time of each blood sample collection will be recorded. The timing of samples may be altered and/or samples may be obtained at additional time points to ensure thorough biomarker assessment. These samples may be used for the analysis of additional exploratory biomarkers. Samples will be collected, labelled, stored, and shipped as detailed in the SRM or lab manual.

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 Screening, the 7-item scale and at all other visits the 10-item scale will be utilized. Specific details on scoring the CAS can be found within the SRM.

8.4.2. Proptosis

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).

8.4.3. 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).

8.4.4. 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).

8.4.5. 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.

8.4.6. External Photographs

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

8.4.7. Orbital CT Scan

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. Details can be found within the SRM.

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 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.

Specific details can be found within the SRM.

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

The sample size for this study was not determined using statistical methods. The sample size was chosen based on clinical and recruitment considerations.

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.

This will be the population for all PD parameters.

Safety Population

All participants who enroll 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

10.2.2. Interim Analysis

An interim analysis will occur after the last subject 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 a second analysis will occur, summarizing the endpoints after the treatment-free phase.

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 Endpoint

The primary endpoints will be defined as follows:

1.) the percentage change from Baseline in total IgG and IgG subclasses (1-4) at Week 7.

2.) change from baseline in levels of anti-TSHR antibodies at Week 7

Each of the endpoints will be summarized at Week 7 using a 6-number summary including the sample size, mean, standard deviation, median, minimum and maximum values

10.3.2. Secondary Endpoints

Analysis of the secondary endpoints for efficacy:

- Change from baseline in proptosis will include the actual value, change from baseline and percentage change from baseline summarized by visit using the n, mean, SD, median, first and third quartiles, minimum, and maximum values.

- The number of proptosis responders and the percentage will be summarized using those participants who had a value at each time point.

- Immunogenicity determined by number of participants with positive anti-RVT-1401 antibodies and characterization of any anti-RVT-1401 antibodies to confirm neutralization potential at Week 7.

10.3.3. Exploratory Endpoints

For each of the continuous exploratory endpoints, the actual value, change from baseline and percentage change from baseline for all exploratory endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values.

For categorical exploratory 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.

10.3.4. 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.

10.3.5. 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):

AUC(0-t), Cmax, tmax, t1/2

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

10.3.6. 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), and anti-TSHR and anti-IGF-1R 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.

10.3.7. Other Analyses

The analysis of the exploratory endpoints will include all participants in the ITT population.

Gene expression data will be analyzed using NanoString nSolver software or other appropriate method. Gene expression data will be presented in graphical and tabular form and summarized descriptively. Serum cytokine and chemokine concentrations will be analyzed with High Sensitivity Bead-Based Multiplex Assays using the Luminex technology. Cytokine/chemokine data will be presented in graphical and tabular form and will be summarized descriptively.

Receptor occupancy will be assessed by flow cytometry and analyzed using FlowJo v10 or higher. Receptor occupancy data will be presented as contour plots with 5% outliers, as well as graphical and tabular form and will be summarized descriptively.

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 a 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 a 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**.

A 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 subject 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 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 subjects 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 a 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 subject, or the partner of a subject, 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 subject 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.
- Notifying the IRB/IEC of SAEs or other significant safety findings as 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. 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.

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 before enrollment of participants begins. 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.

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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 a 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

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15.3. Appendix 3: Protocol Amendment Summary of Changes

Amendment 03 Changes

Rationale for the amendment:

This protocol has been amended to shift the assessment of anti-IGF-1R antibodies to an exploratory endpoint since the exact role of any antibodies against IGF-1R is still being investigated. Therefore, the presence of anti-IGF-1R antibodies was removed as an inclusion criterion and the change in levels of anti-IGF-1R antibodies moved to exploratory.

In addition, the definition for proptosis response was updated so that subjects with <2 mm of improvement will no longer be considered a responder, in line with the standardized definition used in the literature.

The Ophthalmic Exam was updated to allow the ophthalmologist to conduct additional investigations if needed, based on their judgement of whether significant negative changes are being observed in the study.

Measurements of proptosis and motility were added to the Graves' Ophthalmopathy Assessments.

A window of +/- 1 week was added to the collection of the CT orbital scan to allow flexibility for scheduling.

Other administrative changes were also made.

Change #1: Section 2 Protocol Summary for RVT-1401-1002, Section 4 Objectives and Endpoints, and Section 10.3.1 Primary Endpoint

Assessing the change in serum levels of anti-IGF-1R antibodies was moved from a primary objective and endpoint to an exploratory objective and endpoint

Change #2: Section 2 Protocol Summary for RVT-1401-1002, Section 4 Objectives and Endpoints

The following was removed from the secondary endpoint for proptosis:

For subjects with proptosis < 3 mm at baseline, response will be defined as returning to normal limits for race and gender.

Change #3: Section 6.2 Inclusion 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 autoantibodies (anti-TSHR-Ab).

Change #4: Section 6.3 Exclusion Criteria #5

Original text:

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

Revised text:

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

Change #5: Section 8.1 Time and Events Table

Added proptosis and motility assessments to the Time and Events Table

Change #6: Section 8.1 Time and Events Table, Footnote #8

Original text:

The baseline orbital scan should be scheduled once all entry criteria haven been met. This scan can be performed during the screening period or up to 2 days post the first dose.

Revised text:

The baseline orbital scan should be scheduled once all entry criteria haven been met. Scans can be performed within +/- 7 days of the scheduled visit.

Change #7: Section 8.3.2 Ophthalmic Exams

Original 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).

Revised 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.

Change #8: Section 8.3.8 Pharmacodynamics

Original text:

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

Revised text:

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

Change #9: Section 8.3.9 Exploratory Biomarkers

Original text:

Exploratory Biomarkers
Gene Expression Analysis
Pro-inflammatory Biomarker Multiplex
Receptor Occupancy
Anti-TPO
Anti-thyroglobulin

Revised text:

Exploratory Biomarkers
Gene Expression Analysis
Pro-inflammatory Biomarker Multiplex
Receptor Occupancy
Anti-TPO
Anti-thyroglobulin
Anti-IGF-1R
Anti-TSHR (ratio of total to Activating – cell based)
Anti-IGF-1R (ratio of total to Activating – cell based)

Change #10: Section 8.4 Graves' Ophthalmopathy Assessments- Added Proptosis and Motility Assessments

Added text:

Section 8.4.2 Proptosis

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).

Section 8.4.3 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).

Amendment 02 Changes

Rationale for the amendment:

This protocol has been amended based on Health Canada review and feedback. Additional administrative changes were also made as noted below.

Change #1: Section 3.3.1 Risk Assessment Table, First Potential Risk of Clinical Significance, Monitoring and Stopping Criteria or Management Criteria

Original text:

Participants will be closely monitored for reactions for up to 1 hr post-dose before they leave the clinic. If during the course of study administration, the participant experiences a drug related AE of Grade 3 (severe) or greater severity, study drug administration will be stopped.

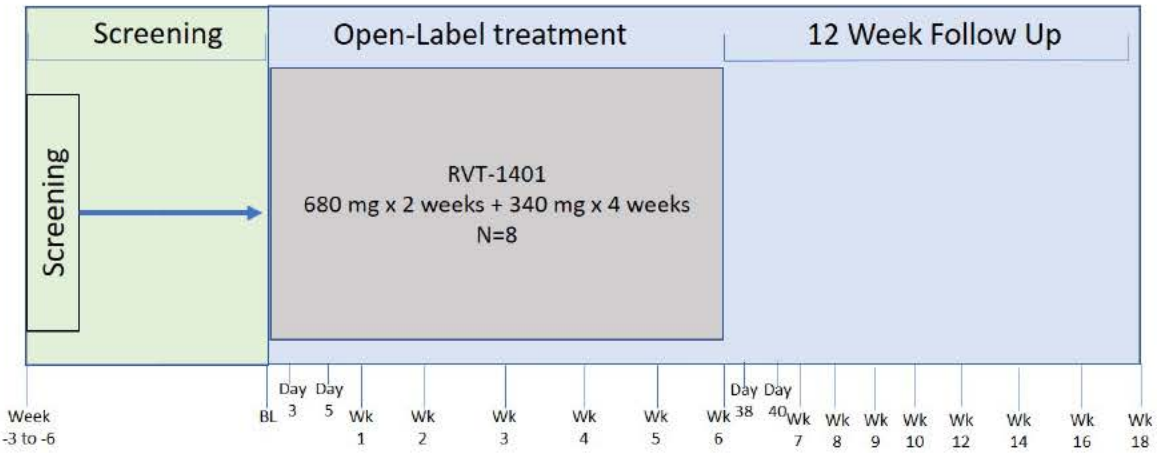
Revised text:

Participants will be closely monitored for reactions for up to 1 hr post-dose before they leave the clinic. 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.

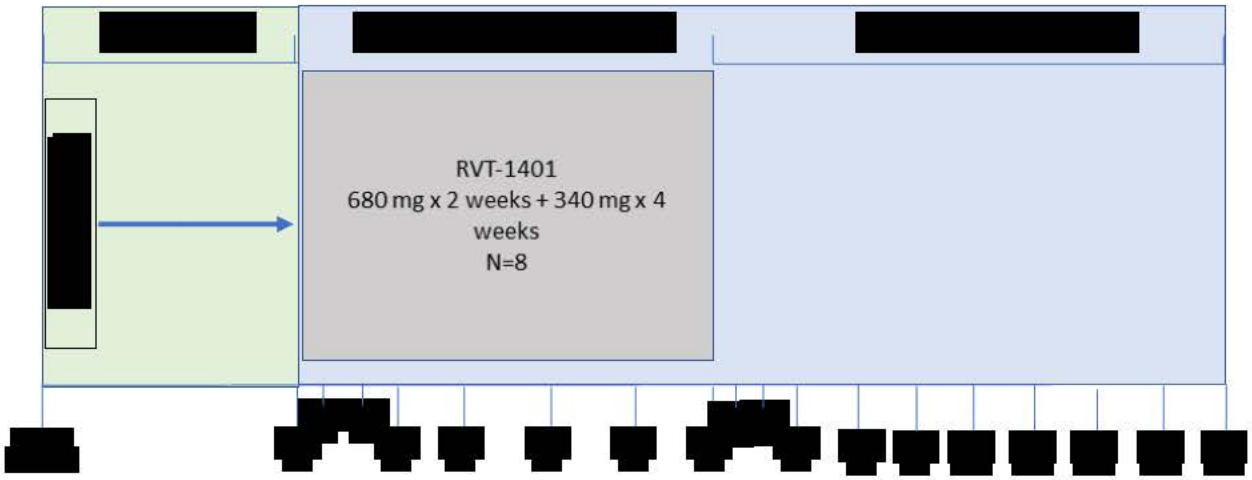
Change #2: Section 5.2 Study Schematic

Corrected an error noted within the schematic

Original schematic:



Revised schematic:



Change #3: Section 8.1 Time and Events Table

Added an ophthalmic exam at screening and corrected the spelling of methimazole.

Change #4: Section 8.3.5 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.

Amendment 01 Changes

Rationale for the amendment:

This protocol has been amended based on emerging data involving transient albumin reductions within healthy subjects at the 680 mg RVT-1401 dose. While the reductions were not considered clinically significant nor were they associated with any signs or symptoms, a decision was made to revise the dosing regimen to one that would maintain serum albumin levels within normal limits for most participants and still maintain IgG reduction at a potentially therapeutic level.

Due to the lack of placebo response on proptosis improvement that has been observed in previous clinical studies, the endpoints related to proptosis have been moved from exploratory to secondary objectives and the study has been updated from Phase 1b to Phase 2a.

Change #1: Title Page, Sponsor Signature Page, Section 2 Protocol Summary, Section 5.1 Overall Study Design

Updated the study phase from Phase 1b to Phase 2a

Change #2: Section 2 Protocol Summary and Section 4 Objectives and Endpoints

Moved exploratory objectives and endpoints related to proptosis to secondary objectives and endpoints

Previous Exploratory Objectives

To examine the effect of RVT-1401 on mean change in proptosis

To examine the effect of RVT-1401 on proptosis responder rate

Previous Exploratory Endpoints

Change from baseline in proptosis

Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye). For subjects with proptosis < 3 mm at baseline, response will be defined as returning to normal limits for race and gender.

Revised Secondary Objectives

To examine the effect of RVT-1401 on mean change in proptosis

To examine the effect of RVT-1401 on proptosis responder rate

Revised Secondary Endpoints

Change from baseline in proptosis

Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye). For subjects with proptosis < 3

mm at baseline, response will be defined as returning to normal limits for race and gender.

Change #3: Section 3.2.2 Dose Rationale, 3rd and 4th paragraphs

Original text:

RVT-1401 will be administered as a weekly 680 mg SC injection. This dose represents the upper limit of doses which can be administered as two SC injections (680 mg) per week. In the proposed study, weekly administration of 680 mg SC dose is predicted to result in a maximum IgG reduction of ~75-80% following the 3rd or 4th dose and would be maintained following the 6th dose before rising back to baseline over the next 6 to 8 weeks.

Since a weekly 680 mg dose of RVT-1401 produces 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 the highest dose that can be administered via 2 SC injections and which has shown to be well-tolerated while producing robust reductions in total IgG in healthy participants.

Revised text:

RVT-1401 will be administered as a weekly 680 mg SC injection for two weeks followed by weekly 340 mg SC injection for four weeks. These doses represent the upper limit of RVT-1401 which can be administered as two SC injections (680 mg) and one SC injection (340 mg) per week. In the proposed study, the first two weekly SC administrations of 680 mg is predicted to quickly reduce IgG to ~64% below baseline and the following four weekly doses of 340 mg would maintain this level of IgG reduction before recovering back to baseline over the next 6 to 8 weeks. This regimen would also be expected to maintain serum albumin levels within normal limits for most patients.

This dosing regimen of RVT-1401 produces a significant reduction in total serum IgG within two weeks, which in GO patients would also include anti-TSHR IgG. Thus, 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 reduce serum IgG quickly with induction dosing and then maintain that reduction over the next 5 weeks. The doses used in this regimen have been well-tolerated while producing robust reductions in total IgG in healthy participants.

Change #4: Section 3.2.3.1 Clinical Experience: Safety, 1st paragraph

Original text:

RVT-1401 has been well tolerated. As of the data cut-off of Nov 22, 2018, there were no serious adverse events (SAEs), no Grade 3 or 4 adverse events (AEs), and no withdrawals

due to AEs. An SAE (Malpighian carcinoma neck) considered unrelated to study drug was received by the sponsor following the data cut-off (see Investigator's Brochure for description).

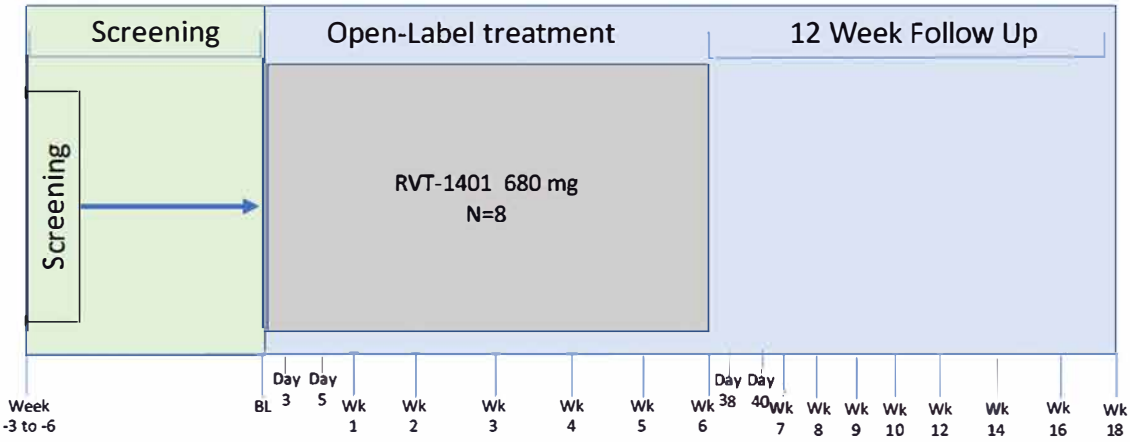
Revised text:

RVT-1401 has been well tolerated. There have been no Grade 3 or 4 adverse events (AEs) and no withdrawals due to AEs. An SAE (Malpighian carcinoma 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).

Change #5: Study Schematic, Figure 3

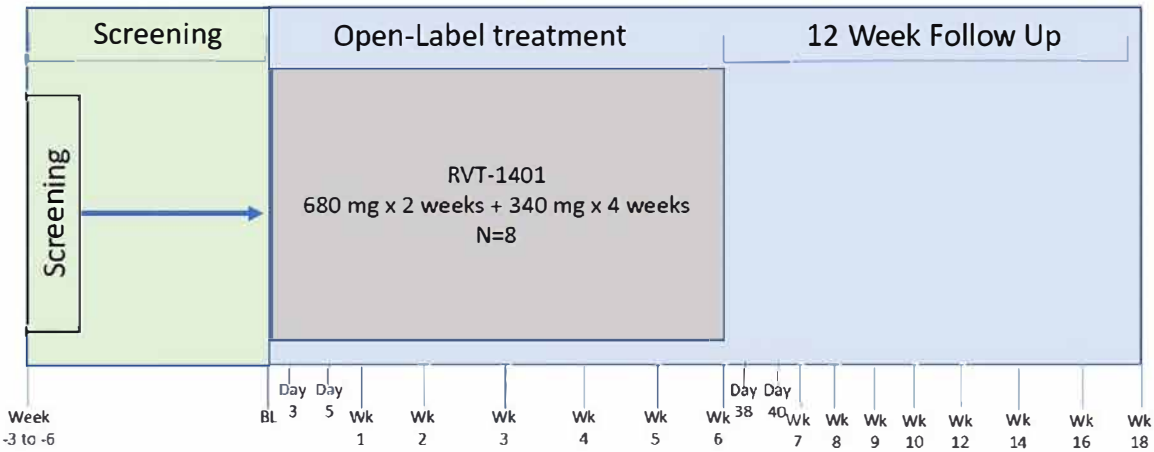
Original:

Figure 4 Study Design



Revised:

Figure 5 Study Design



Change #6: Section 5.3 Treatment Arms and Duration

Original text:

Participants will receive RVT-1401 (680 mg), as two SC injections for 6 weeks.

Revised text:

Participants will receive RVT-1401 for 6 weeks (680 mg/weekly for 2 weeks followed by 340 mg/weekly for 4 weeks).

Change #7: Section 6.8.4 Albumin Monitoring Criteria

Previous text:

In addition to lowering IgG, treatment with RVT-1401 is also expected to reduce albumin levels (Section 3.2.3.3). Since changes in albumin may potentially be unblinding, an unblinded medical monitor will review these laboratory data. The unblinded medical monitor will utilize the following criteria to inform study drug discontinuation:

- Grade 3-4 (albumin levels are <2 g/dL): discontinue study drug
- Grade 2 (albumin levels <3-2 g/dL): study drug should be interrupted or discontinued if there are accompanying clinical signs and/or symptoms (edema, hypotension, etc) attributable to decreased albumin.

Revised text:

In addition to lowering IgG, treatment with RVT-1401 is also expected to reduce albumin levels (Section 3.2.3.3). The site will utilize the following criteria to inform study drug discontinuation:

- Grade 3-4 (albumin levels are <2 g/dL): discontinue study drug
- Grade 2 (albumin levels <3-2 g/dL): study drug should be interrupted or discontinued if there are accompanying clinical signs and/or symptoms (edema, hypotension, etc) attributable to decreased albumin.

Change #8: Section 7.1 Investigational Product

Original text:

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

Study Treatment Name:	**RVT-1401**
Supplier:	[redacted]
Dosage formulation:	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
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 1 hr post-dose before they leave the clinic.
Dose Preparation	The preparation procedure and expiry details will be included in the Pharmacy manual/product label.

Revised text:

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

Study Treatment Name:	**RVT-1401**
Supplier:	[redacted]
Dosage formulation:	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: 1 mL RVT-1401 in one syringe for a total of 2 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 1 hr post-dose before they leave the clinic.
Dose Preparation	The preparation procedure and expiry details will be included in the Pharmacy manual/product label.

Change #9: Section 7.2 Treatment Assignment

Original text:

All participants will receive open label RVT-1401 (680 mg), as two SC injections for 6 weeks.

Revised text:

All participants will receive open label RVT-1401 for 6 weeks (680 mg/weekly for 2 weeks followed by 340 mg/weekly for 4 weeks).

Change #10: Section 8.3.10 Lid Retraction was moved to Section 8.4.2 with no revisions to the text

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).

Change #11: Section 10.3.2 Secondary Endpoints

Original text:

The secondary endpoints for efficacy are Immunogenicity determined by number of participants with positive anti-RVT-1401 antibodies and characterization of any anti-RVT-1401 antibodies to confirm neutralization potential at Week 7.

Revised text:

Analysis of the secondary endpoints for efficacy:

- Change from baseline in proptosis will include the actual value, change from baseline and percentage change from baseline summarized by visit using the n, mean, SD, median, first and third quartiles, minimum, and maximum values.
- The number of proptosis responders and the percentage will be summarized using those participants who had a value at each time point.
- Immunogenicity determined by number of participants with positive anti-RVT-1401 antibodies and characterization of any anti-RVT-1401 antibodies to confirm neutralization potential at Week 7.

Change #12: Section 10.3.3 Exploratory Endpoints

Original text:

For each of the continuous exploratory 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.

For categorical exploratory 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.

Revised text:

For each of the continuous exploratory endpoints, the actual value, change from baseline and percentage change from baseline for all exploratory endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values.

For categorical exploratory 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.