CLINICAL STUDY PROTOCOL

Title:	A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Extension of RVT-1401 in Myasthenia Gravis Patients
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-1401-2002
Indication	Myasthenia Gravis
Development Phase	2a
IND #	141885
Version/ **Effective Date:**	Amendment 2: Version 3.0 10-APR-2019 Amendment 1: Version 2.0 18-JAN-2019 Original: Version 1.0 04-DEC-2018
Immunovant, Inc. **Study Director**	[redacted] Telephone: [redacted] Email: [redacted]

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SPONSOR SIGNATURE PAGE:

Study title: A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Extension of RVT-1401 in Myasthenia Gravis Patients

Protocol Number: RVT-1401-2002

This protocol has been approved by Sponsor's representative. The following signature documents this approval.

[redacted] _____ [redacted] _____

Date

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

1. TABLE OF CONTENTS

PAGE

2. PROTOCOL SUMMARY FOR STUDY RVT-1401-2002

Study Title	A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Extension of RVT-1401 in Myasthenia Gravis Patients
Objectives	**Primary** To assess the safety and tolerability of RVT-1401 in AChR antibody positive MG patients over a 6-week treatment period To examine the effects of RVT-1401 on total IgG, IgG subclasses (1-4) and anti-AChR-IgG levels **Secondary** To examine RVT-1401 PK following repeat doses in patients with Myasthenia Gravis (MG) To measure anti-RVT-1401 antibodies following repeat doses in patients with MG and assess any potential impact on PK or PD To examine the effects of RVT-1401 on the Quantitative Myasthenia Gravis (QMG) score To examine the effects of RVT-1401 on the proportion of patients with improvement on the QMG score by ≥ 3 points from baseline To examine the effects of RVT-1401 on Myasthenia Gravis-Activities of Daily Living score (MG-ADL) To examine the effects of RVT-1401 on the proportion of participants with an improvement on the MG-ADL Score by ≥2 points To examine the effects of RVT-1401 on the Myasthenia Gravis Composite (MGC) score To examine the effects of RVT-1401 on the proportion of participants with an improvement on the MGC Score by ≥3 To examine the effects of RVT-1401 on the Myasthenia Gravis Quality of Life (MG-QOL15r) score **Open-Label Extension Objective:** The objective of the OLE is to evaluate the effect of switching to every 2-week dosing regimen of 340 mg RVT-1401 on all study endpoints.

Study Phase	Phase 2a
Target Population	Myasthenia Gravis
Number of Participants Planned	Approximately 21
Number of Study Centers Planned	Approximately 10-15
Study Design	Phase 2a, randomized, double-blind, placebo-controlled study, with an open-label extension (OLE) to investigate the safety, tolerability, PK, PD, and efficacy of two dosing regimens of RVT-1401
Duration of Treatment	6 weeks or 12 weeks (3 additional doses for the OLE)
Criteria for Evaluation (Endpoints)	**Primary** Assessment of safety and tolerability by analysis of adverse events (AEs) data and changes from baseline in vital signs, clinical laboratory values, and electrocardiograms Change from baseline in levels of total IgG and IgG subclasses (1-4) Change from baseline in levels of anti-AChR-IgG **Secondary** PK Parameters of AUC (0-168 h) and maximum concentration (Cmax) after first and last dose Concentration of RVT-1401 pre-dose (Ctrough) Immunogenicity determined by change from pre-dose in anti-RVT-1401 antibodies, characterization of any anti-RVT-1401 to confirm neutralization potential Change from baseline in the QMG Score Proportion of participants with an improvement on the QMG score by ≥ 3 points from baseline Change from baseline in the MG-ADL score Proportion of participants with an improvement on the MG-ADL Score by ≥2 points Change from baseline in the MGC score Proportion of participants with an improvement on the MGC

	Score by ≥3 points Change from baseline in the MG-QOL15r score

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.

3.1.1. Myasthenia Gravis

Myasthenia Gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness and fatigue. The muscles that control eye and eyelid movement are particularly susceptible to weakness, but other muscles for chewing, talking, and swallowing are frequently involved. Patients with ocular MG often progress to more severe, generalized disease with involvement of bulbar, axial, limb, and/or respiratory muscles.

MG is part of a spectrum of autoimmune diseases in which pathogenic IgG (pIgG) is thought to directly cause and/or exacerbate the condition. MG results from binding of autoantibodies to proteins that lead to impaired transmission at the neuromuscular junction. Most commonly, in approximately 80% of MG patients, anti-acetylcholine receptor (AChR) IgG is detected, and in a smaller subset (approximately 40-50% of patients who are seronegative for anti-AChR IgG), anti-muscle-specific kinase receptor (MuSK) IgG is detected [Gilhus, 2015]. Recently, autoantibodies against low-density lipoprotein related receptor protein 4 (Lrp4) have been described in seronegative MG patients with varying frequencies ranging from 2 to 50% [Higuchi, 2011; Zisimopoulou, 2014; Zhang, 2012; Pevzne, 2012]. The clinical characteristics of Lrp4-MG have yet to be fully characterized [Evoli, 2015].

The chronic nature of MG requires patients to cope with fluctuating symptoms and often maintain treatment with acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, plasmapheresis, and/or intravenous immunoglobulin [Sanders, 2016; Nowak, 2018]. Despite chronic treatment, up to 20% of MG patients can progress into myasthenic crisis [Utsugisawa, 2014]. MG has widespread and significant negative effects on quality of life including daily activities such as eating, walking, and speaking [Nowak, 2018]. Overall, the persistent muscle weakness associated with MG often negatively interferes with patients' ability to engage in daily activities, including demands of work, family, social functions, and physical activities [Paul, 2001].

Current treatment guidelines recommend pyridostigmine as first line therapy with or without concomitant corticosteroids for patients who are anti-AChR-IgG-positive [Sanders, 2016]. If corticosteroids are contraindicated, nonsteroidal immunosuppressive (IS) agents are used, including azathioprine (AZA), cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. Despite existing treatment regimens, current methods provide variable efficacy. Failure rates for current treatments range from 15–53%

depending upon the presentation and diagnosis, and up to 20% of patients treated with IS agents experience severe side effects [Sanders, 2010]. Thus, there is a need for more efficacious and safer therapies.

3.2. Rationale

3.2.1. Study Rationale

RVT-1401 functions by inhibiting the binding of IgG to FcRn. This results in the rapid catabolism of IgG via lysosomal degradation. In MG, RVT-1401 treatment is expected to lead to a significant reduction in the levels of pIgG such as anti-AChR-IgG, anti-MuSK-IgG, and anti-Lrp4-IgG that have been identified to drive disease pathology. While this initial Ph2a study will focus on anti-AChR IgG positive patients to reduce heterogeneity, future studies may also assess the efficacy of anti-FcRn blockade in seronegative patients.

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 and anti-AChR-IgG) in MG patients. A positive correlation between total and pIgG reduction and clinical improvement in MG patients has been previously observed with another anti-FcRn treatment (ARGX-113). A 6-week open-label extension (OLE) has been included to assess transition from weekly dosing regimens for RVT-1401 and placebo to a every 2-week dosing regimen (3 additional doses of 340 mg). 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

In MG, RVT-1401 treatment is expected to lead to a significant reduction in the levels of pIgG such as anti-AChR-IgG and anti-MuSK-IgG that are considered to be a primary driver of disease pathology. Available evidence suggests that reducing the levels of pIgG in MG is associated with clinical benefit. For example, the use of IVIG treatment has been shown to reduce AChR autoantibodies by ~30% from baseline and this is associated with clinical improvement [Liu, 2010]. Recently, data with another anti-FcRn compound (ARGX-113, efgartigimod), reported clinical improvement on the Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis-Activities of Daily Living (MG-ADL) scores with an approximate 80% reduction in total IgG and 50% reduction in AChR-IgG after once weekly administration for 4 weeks [Howard, 2018]. These data provide a target range for potentially therapeutic PD effects; however it is unknown whether there is a minimum threshold for pIgG reduction that translates into clinical efficacy.

RVT-1401 is designed to provide patients with a treatment option that allows home administration via subcutaneous (SC) injection. This significantly reduces the burden that an IV infusion treatment (e.g., IVIG, Soliris® and other anti-FcRn treatments in development) places on patients who will be required to go to an infusion center to receive their treatment.

Two dosing regimens of RVT-1401 will be assessed in double-blind phase of this study. Both will involve once weekly SC injections:

- Dosing Regimen A -680 mg weekly for 6 weeks, and
- Dosing Regimen B - 340 mg weekly for 6 weeks

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

The OLE will involve 1 dosing regimen as a single SC injection:

- 340 mg every 2 weeks for 6 weeks

The OLE dose of 340 mg every 2 weeks will allow for the exploration of the effect of less frequent dosing of RVT-1401. This dose comprises a less frequent regimen with a convenient single SC injection. Since the frequency of dosing will decrease, the drug exposure over the dosing interval for subjects who were on active drug will decrease by approximately 8- 10 -fold for Regimen A and by 1-2 fold for Regimen B.

Expected Treatment Effect

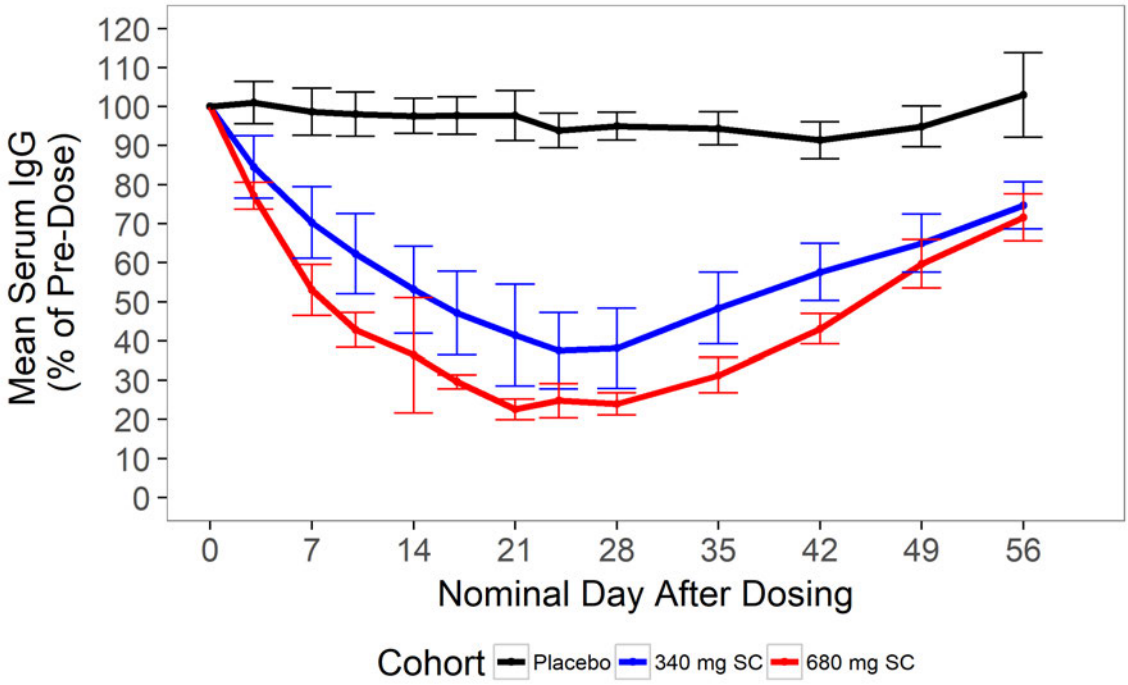
The proposed dosing regimens are expected to provide a sustained total IgG reduction of approximately 75-80% and 65-70% for Regimen A and B respectively, following the fourth or fifth dose. It is expected that the nadir IgG reduction will occur by the 5th dose and be maintained following the sixth dose before rising back to baseline over the next 6 to 8 weeks. These assumptions are supported by preliminary PD results, shown in Figure 1, from the ongoing Phase 1 clinical study RVT-1401-1001 (Section 3.2.3). In healthy participants, 4 weekly SC injections of 680 mg of RVT-1401 produced an average total IgG percent reduction from baseline of 78%.

For participants that enter into the OLE, IgG levels will rise over the 2-week interval between week 6 and the start of OLE dosing at week 8. The IgG levels are expected to oscillate between decreasing and increasing over the next 3 doses, with trough IgG levels expected to rise by 15-25% above the nadir levels achieved during the treatment phase in the double-blind part of the study. Subjects who switch to 340 mg every 2 weeks from the placebo treatment are expected to achieve an IgG reduction of approximately 35-45% after the last OLE dose. Upon completion of OLE dosing, all subject IgG levels are expected to return to baseline over the next 6-8 weeks.

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

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

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



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 December 14, 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

See Investigator's Brochure for Details.

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

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

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

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

3.2.3.2. Pharmacokinetics

RVT-1401 exhibited non-linear pharmacokinetics (PK) following single SC administration across doses ranging from 0.5 mg/kg to 765 mg. The non-linearity is consistent with RVT-1401 exhibiting target mediated disposition PK. In addition to single dose administration, RVT-1401 has also been administered weekly SC for 4 weeks at doses of 340 and 680 mg. The observed mean concentration-time profile following the first and last dose were generally similar, rising to peak concentration between 2 and 3 days after the dose and then declining beginning 4 days after administration up until the next dose. The rate of elimination was more rapid following administration of 340 mg compared to 680 mg, indicative of target mediated drug disposition. Across both dosing cohorts there was accumulation in the exposure measures of Cmax and $AUC_{(0\text{-}168)}$. The accumulation in Cmax and $AUC_{(0\text{-}168)}$ in the 340 mg cohort was 7 and 8.7-fold respectively between the first and last dose, and 2.23 and 2.64, respectively in the 680 mg cohort. There was large variability in Cmax and $AUC_{(0\text{-}168)}$ after the first dose of 340 mg, whereas there was less variability following first SC dose of 680 mg, consistent with what was observed in single dose data. Overall there was reduction in the inter-individual variability around Cmax and $AUC_{(0\text{-}168)}$ after subsequent doses. Following the last dose in the 680 mg cohort, the profile shows characteristics of target mediated drug disposition, with a linear elimination phase from ~96 hours to 168 hours after the last dose, at which time the elimination was very rapid from 168 hours to 336 hours post dose. Exposures increased more than dose proportionally when comparing week four of the 340 mg dose to exposures following the 680 mg SC dose.

3.2.3.3. Pharmacodynamic

Following the administration of single SC doses of RVT-1401, total IgG reduction increased with increasing dose, with a maximum reduction of 47% observed after a fixed dose of 765 mg. The nadir for IgG reduction following single SC dosing occurred between days 8-15 in most individuals. IgG serum levels on average returned to within 90% of baseline by 43 days after drug administration. Albumin levels were also reduced from baseline when compared to placebo showing a similar dose related trend. The highest reduction occurring following the 765 mg SC dose (average ~14.5%) but were not considered to be clinically significant reductions as all patients remained within normal limits (3.5 g/dL to 5.5 g/dL) and levels recovered quickly, returning to baseline ~ 2 weeks after nadir.

The amount of IgG reduction has also been assessed following weekly SC administration of 340 and 680 mg of RVT-1401 or placebo for 4 weeks. There were 8 subjects with data out to day 35, that were included in a preliminary PD analysis for the 680 mg cohort and 7 subjects with data out to day 49 that were included in the analysis for the 340 mg cohort. One subject only received 2 doses of 340 mg prior to withdrawing due to personal reasons, their data was not included in the preliminary PD analysis. There were 4 placebo subjects with data out to day 35 pooled across two cohorts for analysis of PD endpoints. Figure 1 presents the mean IgG concentration-time profiles for both weekly SC administration of 340 mg and 680 mg doses. Figure 1 shows a reduction in serum IgG as a percent of pre-dose across both 340 mg and 680 mg cohorts. In contrast, the placebo group demonstrated minimal changes in serum IgG as a percent of pre-dose. The reduction in serum IgG was more rapid following the 680 mg SC compared vs 340 mg SC. The median IgG nadir concentration occurred prior to the last dose in the 680 mg cohort whereas for 340 mg, it occurred approximately 3 days after the last dose. The finding that the 680 mg cohort achieved nadir concentration following the 3rd dose and maintained serum IgG reduction after the 4th dose, indicates a maximum response has likely been achieved, and that higher doses or more frequent dosing would yield little additional benefit. This is consistent with data from other anti-FcRn agents in development that have observed a maximum percent reduction in serum IgG from baseline of ~ 75-80%.

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

The change in serum albumin was also assessed following repeat SC administration of 340 and 680 mg of RVT-1401 as compared to pooled placebo. Following both single and repeat dosing RVT-1401 serum albumin concentrations were reduced in a dose dependent fashion, whereas placebo subjects showed little to no change in albumin concentrations. While there was a reduction in albumin concentrations following weekly dosing of 340 mg of RVT-1401, individual concentrations remained within normal limits (>3.5 g/dL) for serum albumin. Following weekly administration of 680 mg of RVT-1401, all but 1 individual remained above 3.0 g/dL for the duration of dosing and most

individuals had nadir albumin concentration prior to last dose, indicating that maximum albumin reduction had been achieved. In all individuals, albumin levels were within normal limits (>3.5 g/dL) within 3-4 weeks of the last dose for the 680 mg cohort. Across both cohorts, on average, individuals were within 95% of their baseline concentration 5 weeks after the last dose, indicating the reversibility of the effect of RVT-1401 on albumin. There were no clinical signs or symptoms reported with these transient albumin reductions.

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

3.3. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with RVT-1401 can be found in the current 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	Total IgG levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Transient depletion of IgG following administration of certain drugs (e.g., corticosteroids) are not generally associated with an increased risk of infections [Furst, 2008]. Furthermore, available data from other FcRn antagonists in development have not reported an increased risk of infection in short-term trials similar to RVT-1401-

	immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Mycobacterium tuberculosis. Participants must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®- tuberculin (TB) Gold test at Screening. Participants with an indeterminate QuantiFERON®-TB Gold test result will be allowed one retest; if not negative on retesting, the participant will be excluded. -Absolute neutrophil count <1500 cells/mm3	2002.
Sustained hypoalbuminemia	Investigator discretion	Serum albumin levels will be monitored throughout the study (Section 8.1) by an unblinded Medical Monitor. Treatment of hypoalbuminemia will be left to the discretion of the investigator and decision on dosing discussed with the study medical monitor.

4. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To assess the safety and tolerability of RVT-1401 in AChR antibody positive MG patients 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 examine the effects of RVT-1401 on total IgG, IgG subclasses (1-4) and anti-AChR-IgG levels	Change from baseline in levels of total IgG and IgG subclasses (1-4) Change from baseline in levels of anti-AChR-IgG
Secondary	
To examine RVT-1401 PK following repeat doses in patients with Myasthenia Gravis (MG)	PK Parameters of AUC (0-168 h) and maximum concentration (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 MG and assess any potential impact on PK or PD	Immunogenicity determined by change from pre-dose in anti-RVT-1401 antibodies, characterization of any anti-RVT-1401 to confirm neutralization potential
To examine the effects of RVT-1401 on the Quantitative Myasthenia Gravis (QMG) score	Change from baseline in the QMG Score
To examine the effects of RVT-1401 on the proportion of patients with improvement on the QMG score by ≥ 3 points from baseline	Proportion of participants with an improvement on the QMG score by ≥ 3 points from baseline
To examine the effects of RVT-1401 on Myasthenia Gravis-Activities of Daily Living score (MG-ADL)	Change from baseline in the MG-ADL score
To examine the effects of RVT-1401 on the proportion of participants with an improvement on the MG-ADL Score by ≥2 points	Proportion of participants with an improvement on the MG-ADL Score by ≥2 points

To examine the effects of RVT-1401 on the Myasthenia Gravis Composite (MGC) score	Change from baseline in the MGC score
To examine the effects of RVT-1401 on the proportion of participants with an improvement on the MGC Score by ≥3	Proportion of participants with an improvement on the MGC Score by ≥3 points
To examine the effects of RVT-1401 on the Myasthenia Gravis Quality of Life (MG-QOL15r) score	Change from baseline in the MG-QOL15r score
[redacted]	

Open-Label Extension Objective:

The objective of the OLE is to evaluate the effect of switching to a every 2-week dosing regimen of 340 mg RVT-1401 on all study endpoints.

5. STUDY DESIGN

5.1. Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled study with an OLE designed to investigate the safety, tolerability, PK, PD, and efficacy of RVT-1401 (340 mg/weekly and 680 mg/weekly) vs placebo in AChR antibody positive MG patients. Following a 6-week double-blind, placebo-controlled phase, all participants will have the option to enter an OLE where they will receive an additional 3 doses of 340 mg RVT-1401 every 2 weeks for 6 weeks. The study designs are illustrated in Section 5.2**.**

Safety, PK, PD, and clinical assessments will be collected throughout the study. Refer to Section 8.1 and 8.2, Time and Events Tables.

Optional home visits will be offered to collect (at a minimum) blood samples, vital signs, and review adverse events and concomitant medications.

Each participant will participate in the study for up to approximately 21 weeks: a 3-week screening period, and a 6-week double-blind, placebo-controlled treatment period. Participants who choose not to enroll into the OLE will continue into a 12-week follow-up period. Those who choose to enroll into the OLE will receive treatment in a 6-week OLE period (3 additional doses, every 2 weeks), and a 6-week follow up period. The study duration is the same whether a participant continues directly into the 12-week follow-up period or enrolls into the OLE.

Randomized, Double-Blind, Placebo-Controlled Phase

Participants will screen to determine eligibility up to 21 days prior to first dose/baseline visit. Once eligibility is confirmed, participants will be randomized on Day 1 to receive one of two dose regimens or placebo for weekly SC injections in addition to their standard of care therapy for 6 weeks. No dose adjustments of RVT-1401 are allowed during the study. See Section 6.9 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.

After Week 6, if the participant chooses not to enroll into the OLE, they will continue with the 12-week follow up period.

Transition Phase: Option to Enroll into OLE

Participants will have the option to continue with the follow up period or enroll into the OLE (described below) upon completion of the randomized, double-blind, placebo-controlled phase of the study (Week 6). To enroll into the OLE, consent must be obtained prior to the Week 8 visit.

The visit schedule will be the same for either option as outlined in Section 5.2; two study visits will occur at Days 38 and 40, and then weekly through Week 10 and then every 2 weeks until Week 18.

Open-Label Extension

If the participant is eligible and consents to enroll into the OLE, starting at Week 8 an additional 3 doses of 340 mg RVT-1401 will be administered over a 6-week period (every 2 weeks) followed by a 6-week follow up period.

5.2. Study Schematics

Figure 2 Study Design without OLE

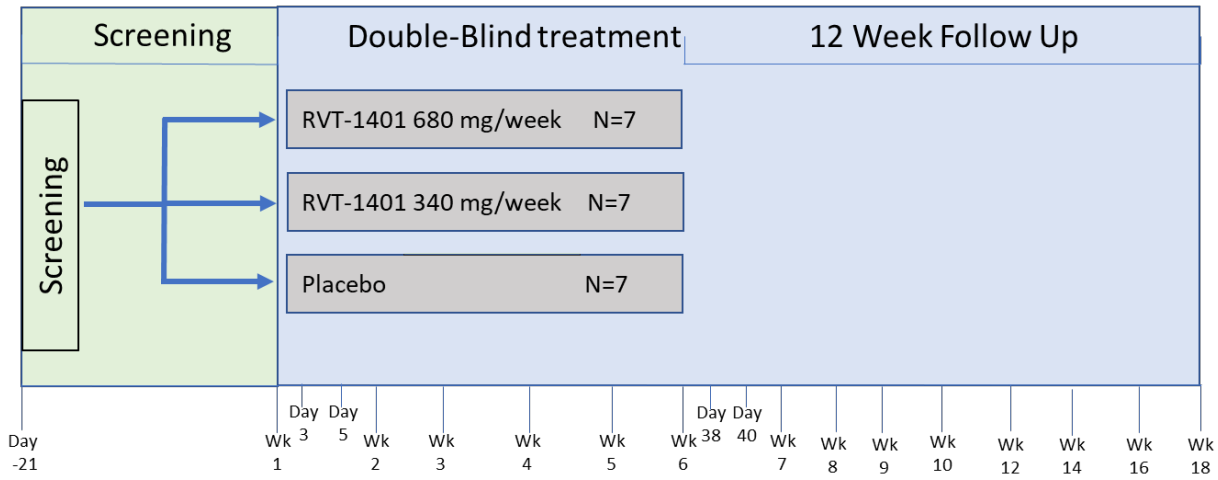


Figure 3 Study Design with OLE

5.3. Treatment Arms and Duration

In the double-blind phase of the study, participants will be randomized 1:1:1 to one of the three blinded treatments illustrated in Figure 2.

In the OLE an additional 3 doses over a 6-week period (every 2 weeks) will be administered, illustrated in Figure 3.

6. PARTICIPANT POPULATION

6.1. Type and Number of Participants

A sufficient number of participants will be enrolled to achieve approximately 21 evaluable participants. Enrollment is competitive.

In order to manage the total study enrollment, the Sponsor may suspend screening and/or enrolment 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. Myasthenia Gravis Foundation of America (MGFA) Class II-IVa and likely not in need of a respirator for the duration of the study as judged by the Investigator.
3. Positive serologic test for anti-AChR antibodies at the screening visit and at least 1 of the following:
    a. History of abnormal neuromuscular transmission test demonstrated by single-fiber-electromyography or repetitive nerve stimulation OR
    b. History of positive edrophonium chloride test OR
    c. Participant has demonstrated improvement in MG signs on oral cholinesterase inhibitors as assessed by the treating physician.
4. QMG score ≥12 at Screening and Baseline.
5. Stable dose of MG treatment prior to randomization. For participants receiving AZA, other non-steroidal immunosuppressive agents, steroids, and/or cholinesterase inhibitors as concomitant medications the following conditions will apply:
    a. AZA: treatment initiated at least 12 months ago and no dose changes in the last 6 months before Screening.

b. Other immunosuppressive treatment (e.g., methotrexate, cyclosporine, mycophenolate mofetil, and cyclophosphamide) initiated at least 6 months ago and no dose changes in the last 3 months before Screening.

c. Stable dose of steroid treatment at least 6 weeks before Baseline.

d. Cholinesterase inhibitors: stable dose for >1 week before Screening. Note: cholinesterase inhibitors must be held for at least 12 hours consistent with the revised manual for the QMG test as recommended by the MGFA, before the QMG and MGC assessments.

6. 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.

7. 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.

8. 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 rituximab, belimumab, eculizumab or any monoclonal antibody/Fc-fusion biologic for immunomodulation within 6 months prior to first dosing.
2. Use of tacrolimus within 1 week of first dose and throughout the treatment period.
3. Immunoglobulins given by SC, IV (IVIG), or intramuscular route, or plasmapheresis/plasma exchange (PE) within 4 weeks before Screening.
4. Thymectomy performed < 12 months prior to screening.
5. Total IgG level <6 g/L (at screening).
6. Absolute neutrophil count <1500 cells/mm^3(at screening).

7. 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.
8. Have known autoimmune disease other than MG that would interfere with the course and conduct of the study (such as uncontrolled thyroid disease).
9. Medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.
10. Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening.
11. 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.
12. 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.
13. 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
14. Body Mass Index (BMI) at Screening $\geq$ 35 kg/m^2.
15. Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
16. Currently participating or has participated in another MG clinical study within 28 days prior to signing the informed consent form.
17. 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.
18. Participant has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to Day baseline.
19. 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.
20. Pregnant or lactating females as determined by positive serum or urine human chorionic gonadotropin test at screening or baseline.
21. Participant has had their spleen removed.
22. 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. Eligibility for the OLE

Participants who complete the 6-week, randomized, double-blind treatment phase are eligible to participate in the OLE.

6.5. Other Eligibility Criteria Considerations

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

RVT-1401 Investigator's Brochure

6.6. Screening/Baseline Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomized. 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).

6.7. Lifestyle Restrictions

6.7.1. 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.

6.8. Withdrawal Criteria

6.8.1. 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 6.9

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

6.8.2. Participant Withdrawal Procedures

If a participant is prematurely discontinued from the study, the Principal Investigator must make every effort to perform an Early Termination Visit per Section 8.1 and Section 8.2, Time and Events Tables 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".

6.9. Stopping Criteria for Individual Participants

6.9.1. 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%).

Rechallenge 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 rechallenge.

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

6.9.2. 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.

6.9.3. 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

6.9.4. Albumin Monitoring Criteria

6.10. Toxicity Management Criteria

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

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

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

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

Injection Site Reactions

Injection site evaluations will be made by clinical staff following administration of RVT-1401 and placebo as described below. Additional details related to the specific injection site location will be included within a study specific manual. If an injection site reaction is observed, a physician will characterize and document the reaction as an AE. Review of the injection site will continue until the AE is resolved. Symptomatic treatment (e.g. antihistamines, NSAIDs, IV fluids) may be provided for any injection site reactions based on the discretion of the Investigator.

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

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

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

6.10.2. 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.

6.11. 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 and Other Study Treatment

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

To maintain the study blind within the double-blind phase of the study, all participants will receive two injections (2 ml volume each) by an unblinded designee (Section 7.6); participants receiving the 680 mg dose will receive two injections of RVT-1401, while participants receiving the 340 mg dose will receive one injection with RVT-1401 and one

placebo injection. Participants receiving placebo will receive two injections of placebo. The blinded syringes will be numbered so that any injection site reaction can be assigned to a specific syringe number and medication #.

The OLE is open-label. Each participant will receive 3 additional doses of RVT-1401, once every 2 weeks, as a single 340 mg injection over a 6-week period.

Double-Blind: Investigational Product

Study Treatment Name:	**RVT-1401**	**Placebo**
Supplier:	[redacted]	
Dosage formulation:	Sterile solution for injection.	Sterile solution for injection.
Unit dose strength(s)/Dosage level(s):	340 mg: 2mL RVT-1401 in one syringe and 2mLs placebo in the second syringe for a total of 4 mL 680 mg: 2 mL RVT-1401 in two syringes for a total of 4 mL	2 mL placebo in two syringes for a total of 4 mL
Route of Administration	SC injection	
Dosing instructions:	The detailed methods are indicated in the Pharmacy Manual. Participants will be closely monitored for reactions for up to 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.	

OLE: Investigational Product

Study Treatment Name:	**RVT-1401**
Supplier:	[redacted]
Dosage formulation:	Sterile solution for injection.
Unit dose strength(s)/Dosage level(s):	340 mg: 2mL RVT-1401 in one syringe
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

Randomization within the double-blind phase will occur centrally using an interactive web response system (IWRS) using central randomization. Participants will be assigned in accordance with the randomization schedule, prepared prior to the start of the study. The OLE is open-label.

7.3. Blinding

This will be a double-blind study. The investigator and study site will also remain blinded to the IgG, albumin, total protein, alkaline phosphatase (ALP), and anti-AChR antibody data post screening as this could potentially unblind them. An unblinded Medical Monitor will review this lab data on an ongoing basis for safety. In order to maintain the blind of which treatment subjects received during the double-blind phase of the study, these labs will continue to be blinded to the investigator and study site in the OLE.

The following will apply throughout the study:

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

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

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

7.4. Packaging and Labeling

RVT-1401 will be supplied to the study site as a sterile liquid formulation with a nominal fill of at least 1 mL in Nuova Ompi 2R clear glass vials with a flip-off cap. The solution is clear to slightly yellow, essentially free of visible particles, for SC administration. [redacted]

[redacted]

Placebo will be provided as a sterile liquid formulation with at least a 1 mL fill in Nuova Ompi 2R clear glass vials with a flip-off cap. The solution is clear, essentially free of visible particles, for SC administration. [redacted]

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

See Pharmacy Manual for exact instructions on dose preparation.

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

7.5. Preparation/Handling/Storage/Accountability

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

- Only participants enrolled in the study may receive study treatment and only authorized site staff may prepare, handle, supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- For the double-blind phase of the study, the Unblinded 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 unblinded 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

For the double-blind phase of the study only, the individual dose for a participant is prepared by an unblinded Pharmacist, licensed Pharmacy Technician, or designee. The

preparation of the dose will be reviewed and confirmed by a second unblinded member of the study site staff.

For the double-blind phase of the study only, the IP will be administered by an unblinded designee. For the double-blind phase and the OLE, the date and time of each dose administered along with the location of each injection identified by syringe number, will be recorded in the source documents. The location/syringe number and study participant identification will be confirmed at the time of dosing by a member of the study site staff (blinded to study treatment) other than the person administering the study drug.

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 MG 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 Tables, 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 Tables, Section 8.1 and Section 8.2.

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 (12-week follow-up without OLE)

	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 21 Days	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 and medical history	X																			
Height	X																			
Body weight	X	X																		
Complete physical examination	X	X																		
Brief physical examination																			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
QuantiFERON®-TB Gold	X																			
Viral Serology	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
Serum complement (CH50, C3)[2]		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 21 Days	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	
Immunoglobulins (IgM, IgA)[2]		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				
[redacted]																				
Anti- RVT-1401antibody[2, 4]		X				X						X				X			X	X
Nab Assessment[2]		X				X						X				X			X	X
anti-AChR antibody[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration		X			X	X	X	X	X											
Injection site reactions[5]		X			X	X	X	X	X											
MG-ADL[6, 7]		X			X	X	X	X	X			X	X		X	X			X	X
Quantitative Myasthenia Gravis (QMG) Score[6, 7]	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 21 Days	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	
Myasthenia Gravis Composite (MGC) Score[6, 7]		X			X	X	X	X	X			X	X		X	X			X	X
Myasthenia Gravis Quality of Life (MG-QOL15r) Score[6, 7]		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
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 to ensure participants withhold cholinesterase inhibitors for at least 12 hours prior to the QMG and MGC assessments.
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, week 18, 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.
6. MG assessments will be assessed pre-dose when collected on dosing days
7. Subjects should be instructed to withhold cholinesterase inhibitors for at least 12 hours prior to the QMG and MGC assessments.

8.2. Time and Events Table (With OLE and 6-week follow-up)

	Screening[1]	Treatment Period Week 1 (Days)			Treatment Period Weekly Visit (Weeks)				Treatment Period Week 6 (Days)			OLE and Follow-up Period Weekly Visit (Weeks)								Early Withdrawal Visit
Study Timepoint (Weeks)	Within 21 Days	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[2]→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→																			
Inclusion/exclusion criteria	X	X											X[3]							
Demographics and medical history	X																			
Height	X																			
Body weight	X	X																		
Complete physical examination	X	X																		
Brief physical examination																			X	X
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram[4]	X	X			X		X		X										X	X
Pregnancy test[4, 5] (females)	X	X			X	X	X	X	X				X		X	X			X	X
QuantiFERON®-TB Gold	X																			
Viral Serology	X																			
Urinalysis[4]	X	X			X	X	X	X	X			X							X	X
Blood chemistry and hematology[4]	X	X			X	X	X	X	X			X							X	X
Serum complement (CH50, C3)[4]		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)			OLE and Follow-up Period Weekly Visit (Weeks)								Early Withdrawal Visit
Study Timepoint (Weeks)	Within 21 Days	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	
Immunoglobulins (IgM, IgA)[4]		X				X			X			X	X	X					X	X
RVT-1401 PK sampling[4]		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			X
Total IgG[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobins (IgG subclasses)[4]		X	X	X	X	X	X		X	X	X	X				X				
[redacted]																				
Anti- RVT-1401antibody[4, 6]		X				X						X				X			X	X
Nab Assessment[4]		X				X						X				X			X	X
anti-AChR antibody[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration		X			X	X	X	X	X				X		X	X				
Injection site reactions[7]		X			X	X	X	X	X				X		X	X				
MG-ADL [8,9]		X			X	X	X	X	X			X	X		X	X			X	X
Quantitative Myasthenia Gravis (QMG) Score[8, 9]	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)**			**OLE and Follow-up Period Weekly Visit (Weeks)**								**Early Withdrawal Visit**
Study Timepoint (Weeks)	Within 21 Days	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	
Myasthenia Gravis Composite (MGC) Score [8,9]		X			X	X	X	X	X			X	X		X	X			X	X
Myasthenia Gravis Quality of Life (MG-QOL15r) Score [8,9]		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
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 to ensure participants withhold cholinesterase inhibitors for at least 12 hours prior to the QMG and MGC assessments.
2. Consent for enrollment into the OLE must occur prior to Week 8.
3. Participants who complete the 6- week, randomized, double-blind treatment phase are eligible to participate in the OLE
4. Vitals, ECG and blood draws for safety, PK, and PD assessment will be collected pre-dose on dosing days where specified.
5. Pregnancy tests will be collected pre-dose (via urine dipstick) on dosing days where specified. Serum pregnancy tests should be collected at screening, week 18, and early withdrawal.
6. 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.
7. Local injection site reactions will be assessed at approximately 10 minutes post dose.
8. MG assessments will be assessed pre-dose when collected on dosing days.
9. Subjects should be instructed to withhold cholinesterase inhibitors for at least 12 hours prior to the QMG and MGC assessments.

8.3. 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.

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. In particular, the protocol requirement to withhold cholinesterase inhibitors for at least 12 hours prior to the QMG and MGC assessments may require participants to return on a separate day during the screening period to ensure they sign an informed consent form prior to withholding this treatment.

8.4. Study Assessments and Procedures

8.4.1. 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).

8.4.2. Vital Signs

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

8.4.3. 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.

8.4.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments must be conducted in accordance with the SRM or Laboratory Manual, and Protocol Time and Events Tables (Section 8.1 and

Section 8.2). 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 (ALP)	Total Protein
Serum complement (CH50, C3)	Immunoglobulin M (IgM)	Immunoglobulin A (IgA)	
Immunoglobulin G (IgG)			

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

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

QuantiFERON®-TB Gold
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, Week 18, and early withdrawal and urine dipstick pre-dose at other timepoints. Positive urine tests should be confirmed with a serum test.

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

8.4.5. Pharmacokinetics

Blood samples for PK analysis of RVT-1401 will be collected at the time points indicated in Section 8.1 and 8.2, Time and Events Tables. 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.

8.4.6. 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 and 8.2, Time and Events Tables. The actual date and time of each blood sample collection will be recorded.

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

ADA analysis will be performed under the control of the Sponsor. Anti-RVT-1401 antibody titers will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. If Anti-

RVT-1401 antibody titers are detected, they will be further characterized using a validated cell based Nab assay

8.4.7. Pharmacodynamics

Blood samples for PD analysis will be collected at times indicated in the Time and Events Tables (Section 8.1 and 8.2).

Pharmacodynamic Markers

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

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.

8.4.8. Exploratory Biomarkers

[redacted]

8.5. Myasthenia Gravis Assessments

8.5.1. Myasthenia Gravis Activities of Daily Living (MG-ADL)

The MG-ADL is an 8-item, patient reported questionnaire that assesses MG symptoms and their effects on activities of daily living. The scale has been validated and shown to correlate with the QMG scale and newer MG outcome scales such as the MGC and MG-QOL15r [Wolfe, 1999, Muppidi, 2011].

Participants are asked to rate each item on a scale of 0-3. The MG-ADL score is calculated by totalling the rating for each of the 8 items. The scale takes approximately 2-3 min to complete and can be administered by the physician or trained clinic personnel or study coordinator. Details can be found within the SRM or study specific manual.

8.5.2. Quantitative Myasthenia Gravis Score (QMG)

The QMG score was developed as a tool to assess MG disease severity and the pattern of deficits based on quantitative testing of affected muscle groups [Barohn, 1998]. The scale is comprised of 13 test items that are graded on a scale of 0-3. The total sum across all 13 items represents the QMG Score. The test takes approximately 30 minutes to perform and can be administered by a trained physician, research coordinator or clinical evaluator who has been trained for this study. Details can be found within the SRM or study specific manual.

8.5.3. Myasthenia Gravis Composite Score (MGC)

The MGC was developed by selecting the best performing items from 3 commonly used MG-specific scales (QMG, MG manual muscle test, and MG-ADL) and is comprised of 10 functional domains: 3 ocular, 3 bulbar, 1 respiratory, 1 neck, and two limb items [Burns, 2008]. The scale measures symptoms and signs of MG in these domains incorporating both physician and patient-reported test items. The MGC takes approximately 5 min to complete and can be administered by a trained physician, research coordinator or clinical evaluator. Details can be found within the SRM or study specific manual.

8.5.4. Myasthenia Gravis Quality of Life 15 revised Score (MG-QOL 15r)

The MG-QOL15r is a patient-reported scale designed to assess how their MG affects different aspects related to quality of life. There are 15 items that are graded on a scale of 0-2; the total across all 15 items represents the MG-QOL15r score. The survey takes approximately 2 minutes to complete by the participant. Details can be found within the SRM or study specific manual.

8.5.5. 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. However, the sample size of 14 active and 7 placebo participants will allow the study to show a 33% difference between either active arm and the placebo arm, assuming 90% power, equal standard deviations of 20 and an alpha of 0.05 using a two-sided z-test for the primary endpoint of percentage change from baseline in IgG at Week 7.

10.2. Data Analysis Considerations

10.2.1. Analysis Populations

Intention-To-Treat (ITT) Population

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

This will be the population for all PD parameters.

Safety Population

All participants 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.

Open-Label Extension Population

The OLE population will include all participants who enroll in the OLE and receive at least one dose of study treatment in the OLE.

12-Week Follow up Population

The 12-Week Follow up Population will include all participants who receive at least one dose of study treatment in Part 1 and decline participation in the OLE but continue with the 12-week follow up period.

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. A final analysis will occur when the last subject completes or discontinues the study. Since this analysis is occurring at the end of the double-blind 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), which will be signed off prior to the lock of the study database.

10.3.1. Primary Endpoint for Efficacy

The primary endpoint will be defined as the percentage change from Baseline in the IgG parameter at Week 7. The endpoint will be summarized using a 6-number summary including the sample size, mean, standard deviation, median, minimum and maximum values. Treatment group comparisons between the two active (separately) to the placebo arm will be performed using an Analysis of Covariance model with treatment and baseline value in the model. An alpha of 0.05 will be used to determine statistical significance.

10.3.2. Secondary Endpoints for Efficacy

The secondary endpoints for efficacy are Immunogenicity determined by percentage change from Baseline in anti-RVT-1401 antibodies and characterization of any anti-RVT-1401 antibodies to confirm neutralization potential at Week 7.

For each of the continuous secondary endpoints, the actual value, change from baseline and percentage change from baseline for all secondary endpoints will be summarized by visit and treatment group using the n, mean, SD, median, first and third quartiles, minimum, and maximum values. The comparison of the active arms (separately) to the placebo arm will be performed using an Analysis of Covariance model with treatment and baseline value in the model. An alpha of 0.05 will be used to determine statistical significance. If deemed appropriate, the two active arms may be combined and compared to placebo to evaluate any treatment effect.

For categorical secondary endpoints, the number of participants who meet the endpoint and the percentage will be summarized. The percentage will be calculated using those participants who had a value at the time point. Statistical testing may be performed between the two treatments using a Fishers Exact Test. If deemed appropriate, the two active arms may be combined and compared to placebo to evaluate any treatment effect.

10.3.3. Safety Analyses

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

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

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

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

10.3.4. Pharmacokinetic Analyses

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

AUC(0-t), Cmax, tmax, Ctrough

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

10.3.5. Pharmacodynamic Analyses

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

Serum IgG, IgG subclass (1-4), and anti-AChR 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.

The comparison of the active arms (separately) to the placebo arm will be performed using an Analysis of Covariance model with treatment and baseline value in the model. An alpha of 0.05 will be used to determine statistical significance.

10.3.6. Other Analyses

[redacted]

10.3.1. OLE and Follow up Analyses

Data listings and summaries will be provided separately for the OLE and 12-Week Follow up Populations. Descriptive Analyses will be presented by randomized treatment assignment from the double-blind treatment period and overall. Baseline will be specified in the Statistical Analysis Plan. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. Only the scheduled assessments will be included in the summary tables. All OLE and follow up analyses will be based on the OLE and 12-Week Follow up Populations, respectively. Ad hoc statistical analyses such as two sample t-test or Chi-Square test, may be performed for the changes or shifts at weeks 8, 10, and 12 separately. The significance will be evaluated at a 0.05 two-sided level for informational purposes only.

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 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 and 8.2, Time and Events Tables.
- Medical occurrences that begin prior to any study procedure but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to the Sponsor within 24 hours of site awareness.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to investigational

product will be recorded from the time a participant consents to participate in the study up to and including any follow-up contact.

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

11.4. Method of Detecting and Reporting AEs and SAEs

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

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?

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

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

11.5. Assessing Severity of AEs and SAEs

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

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

Criteria for Determining the Grade/Severity of Adverse Event Terms

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

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

11.6. Assessing Causality of AEs and SAEs

Regulatory authorities require that both investigator and sponsor assess whether there is a reasonable possibility that the study treatment caused each AE. This assessment requires careful medical consideration of each event in relationship to the timing of drug administration, the presence of other factors which may have caused the event (underlying illness, concomitant medication, complications, exposure to other toxins or allergens, environmental factors, etc.), and the effects of stopping and/or restarting the study treatment. The following definitions are to be used for the relationship of the AE to Study Treatment:

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

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

11.7. Follow-up of AEs and SAEs

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

11.8. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of SAEs/adverse event of special interest (AESIs) is essential so that legal obligations and ethical responsibilities towards the safety of 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 and query 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 AEs 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 including placebo. 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.

14. REFERENCES

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15. APPENDICES

15.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AChR	Anti-acetylcholine receptor
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
AZA	Azathioprine
BMI	Body mass index
BUN	Blood urea nitrogen
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
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
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
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL15r	Myasthenia Gravis Quality of Life
MedDRA	Medical dictionary for regulatory activities
MSDS	Material safety data sheet
MuSK	Muscle-specific kinase receptor
NAb	Neutralizing Antibody
NSAID	Non-steroidal anti-inflammatory agents
OLE	Open-label extension
PD	Pharmacodynamic
PE	Plasma exchange
pIgG	Pathogenic IgG
PIS	Post-Intervention Status
PK	Pharmacokinetic
QMG	Quantitative Myasthenia Gravis
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
ULN	Upper limit of normal
WBC	White blood cell
WHO-DDE	World health organization drug dictionary enhanced

Trademark Information

Trademarks of Immunovant Sciences GmbH

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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.

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