IMMUNOVANT

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Extension of RVT-1401 in Myasthenia Gravis Patients
Name of Test Drug:	RVT-1401
Study Number:	RVT-1401-2002
Protocol Version:	Amendment 2 (Version 3.0)
Protocol Date:	10-Apr-2019
CRF Version:	Version 5.0
CRF Date:	15-May-2020
Analysis Plan Version:	Version 2.0 (Final)
Analysis Plan Date:	28-Jul-2020
Analysis Plan History:	

Version	Date	
Final 1.0	20Aug2019	This original version was not used for analyses
Final 2.0 (Final)	28-Jul2020	This version was completed prior to any unblinding so it is considered the original version for analyses

APPROVAL

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
DocuSigned by: [redacted] BDA9EA1EA55A43B... [redacted]	[redacted]
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AChR	Anti-acetylcholine receptor
ADA	Anti-drug antibody
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	Area under the concentration-time curve from time zero to time
BLQ	Below the limit of quantitation
CI	Confidence interval
C_{max}	Maximum serum concentration
$C\tau$	Concentration at end of dosing interval
C_{trough}	Concentration at end of dosing interval
CV	Coefficient of variation
ECG	Electrocardiogram
FAS	Full analysis set
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITT	Intent to treat
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL	Myasthenia Gravis Quality of Life
MI	Multiple Imputation
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QMG	Quantitative Myasthenia Gravis
SAE	Serious adverse event

SAF	Safety
SOC	System organ class
TLFs	Tables, listings and figures
t_{max}	Time to maximum serum concentration
WHO	World Health Organization

1. INTRODUCTION

1.1. Study Objectives

Primary Study Objectives	• To assess the safety and tolerability of RVT-1401 in anti-acetylcholine receptor (AChR) antibody-positive myasthenia gravis (MG) patients over a 6-week treatment period • To examine the effects of RVT-1401 on total immunoglobulin G (IgG), IgG subclasses (1-4) and anti-AChR-IgG levels
Secondary Study Objectives	• To examine RVT-1401 pharmacokinetics (PK) following repeat doses in patients with MG • To measure anti-RVT-1401 antibodies following repeat doses in patients with MG and assess any potential impact on PK or pharmacodynamics (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 (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 • 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

Exploratory Study Objectives	[redacted]
Open-Label Extension Objective	• To evaluate the effect of switching to an every 2-week dosing regimen of 340 mg RVT-1401 on all study endpoints

1.2. Study Design

Design Configuration and Subject Population	This is a Phase 2a, randomized, double-blind, placebo-controlled study with an open-label extension (OLE) to investigate the safety, tolerability, PK, PD, and efficacy of 2 dosing regimens of RVT-1401 in AChR antibody-positive MG patients.
Treatment Groups	• RVT-1401 680 mg/week • RVT-1401 340 mg/week • Placebo
Key Eligibility Criteria	• 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 • 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. • QMG score ≥12 at Screening and Baseline • Stable dose of MG treatment prior to randomization. For participants receiving azathioprine, other non-

	steroidal immunosuppressive agents, steroids, and/or cholinesterase inhibitors as concomitant medications the following conditions will apply: a. Azathioprine: 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
Study Periods/Phases	• 3-week screening period • 6-week treatment period • 12-week follow-up period or 6-week OLE period and a 6-week follow-up period

Figure 1. Study Design for Subjects Who do not Participate in the Open-Label Extension

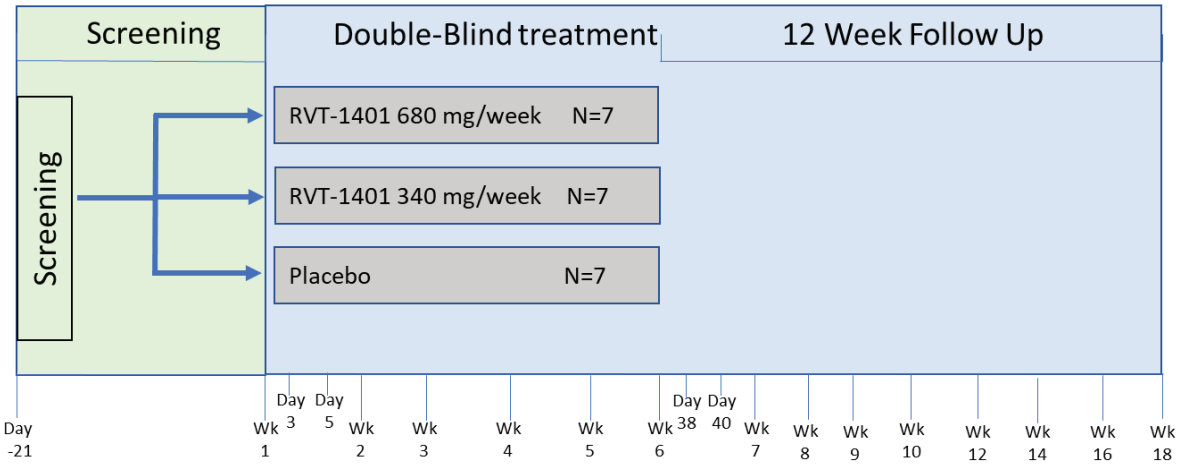
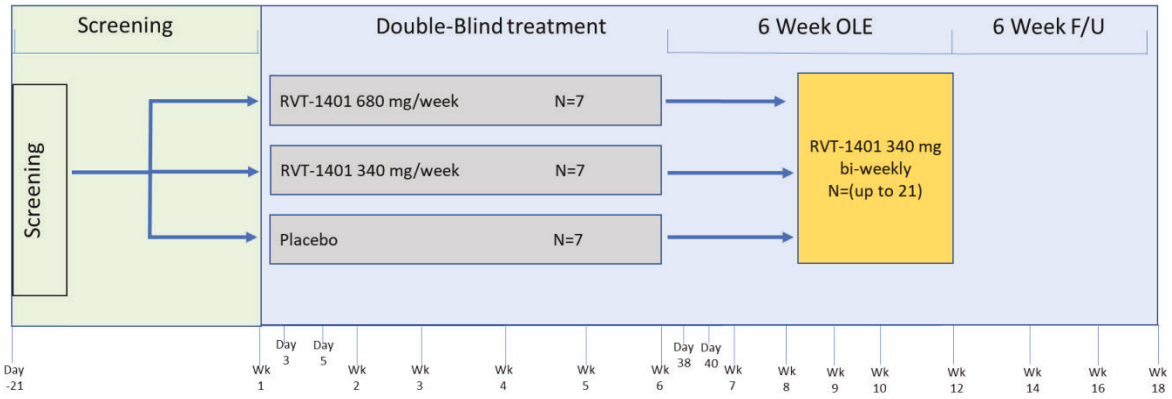


Figure 2. Study Design for Subjects Who Participate in the Open-Label Extension



Schedule of Assessments

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

Randomization	Participants will be randomized to RVT-1401 680 mg/week, RVT-1401 340 mg/week or placebo according to a 1:1:1 ratio.
Study Duration	Each participant will participate in the study for up to approximately 21 weeks, including a 3-week screening period, and a 6-week double-blind, placebo-controlled treatment period. Participants who choose not to enroll in the OLE will proceed to 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 of 340 mg RVT-1401, every 2 weeks), followed by a 6-week follow-up period.

Schedule of Assessments: 12-Week Follow-Up Without Open-Label Extension

	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
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

	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	
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
Myasthenia Gravis Composite (MGC) Score[6, 7]		X			X	X	X	X	X			X	X		X	X			X	X
Myasthenia Gravis Quality of Life		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	
(MG-QOL15r) Score[6, 7]																				
Participant 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.

Schedule of Assessments: Open-Label Extension 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[3]	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
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

	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	
Immunoglobins (IgG subclasses)[3]		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[3]	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
Myasthenia Gravis Composite (MGC) Score [7,8]		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
Participant Satisfaction Questionnaire												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	
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 enrolment into the OLE needs to 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.

1.3. Sample Size and Power

Planned Sample Size and Power Statement	A sufficient number of participants will be enrolled to achieve approximately 21 evaluable participants. 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 2-sided z-test for the primary endpoint of percentage change from baseline in IgG at Week 7.

2. IMPACT OF COVID-19

In accordance with FDA guidance, Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency: Guidance for Industry (CDER, CBER, June 2020), this SAP is updated to reflect the evaluation by the Immunovant team and agreements as to accommodation of issues related to COVID-19.

An interim analysis after 15 patients have completed Week 7 has been introduced, due to barriers to recruitment and data gathering following site closures. An IAP has been developed to support such an analysis, should it be done.

During blind data review meetings (BDRM), which are done consistent with ICH E9, it was discovered that one subject had a missing Week 7 visit, although there had been no study withdrawals. This subject could not attend the Week 7 visit due to the closure of the site due to COVID-19. Assessments that could be done remotely were done remotely.

The statistical impact was evaluated by the team with the following convention agreed:

1. This subject did not withdraw from the study, and the statistics will not represent this patient as a withdrawal.
2. This subject did not miss a visit. The missing data resulting from the site closure is not missing for reasons typical for clinical studies, and the missing data should be not handled in the typical way in the analysis.
3. The assessments that could be done remotely were done remotely, and those values will be used as the Week 7 assessment values. Other values used for analysis will be the latest values obtained prior to the first dose of open-label treatment.

In this case, hard-coding is permitted for programming.

3. TYPE OF PLANNED ANALYSIS AND ALPHA ALLOCATION

Per protocol, an interim analysis will occur after the last subject completes the Week 7 visit of the study. All efficacy endpoints will be evaluated for this analysis. It is noted that the planned interim/primary analysis is the final analysis of the complete dataset from the double-blind treatment period. The database is interim due to the follow-up period, in which safety data will continue to accrue and be updated.

Due to COVID-19 impact on the study, an interim analysis may be done after 15 subjects have completed Week 7, although the study is continuing. An interim analysis plan (IAP) will guide any interim analysis that is done. The IAP will document disclosure and safeguards to protect the integrity of the ongoing study.

A final analysis will occur when the last subject completes or discontinues the study and the database is locked.

An additional analysis of the anti-RVT-1401 antibody data will be performed if any subjects require follow-up testing. This analysis will focus solely on the antibody data and does not require any alpha correction. The CSR will be amended with this additional analysis if it is necessary.

Alpha is controlled through the conditional sequencing of hypotheses. No other adjustment for multiplicity is needed. The interim analysis, if done, will be executed for administrative purposes due to business needs in response to circumstances precipitated by COVID-19 issues. Alpha is allocated for the interim analysis of 0.0001, which is considered to be negligible; consequently, the final analysis has alpha = 0.05 preserved.

4. BLINDING

At the time of the finalization of this SAP, no unblinding of any kind has occurred. It is noted that the only unblinded personnel for the study are documented in planning documents. Immunovant supports strong process and has standard operating procedures (SOPs) consistent with written regulatory guidance and standard conventions to protect the blinding of this study.

Selected laboratory analytes that may reveal the treatment for individual subjects are conveyed and stored in protected spaces with controlled access to safeguard further the treatment given to specific subjects.

There are four sources of unblinding or potential unblinding for this study:

1. The randomization scheme, which was created by and is managed by contracted statisticians and personnel not otherwise involved in operational execution of the study and not involved with site activities.
2. The concentration values, which are conveyed and stored in controlled places, consistent with other companies.
3. The clinical trial material (CTM) to be assigned by computerized systems and dispensed by site personnel, which are managed by individuals not involved in operational execution of the study related to site activities,
4. Selected laboratory analytes, including IgG and albumin, which are known to be reduced with this compound, which are conveyed and stored in controlled-access space.

At the time of this SAP development, no one involved in the development of the SAP and no one involved in the query process is unblinded from any of these sources.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Data will be listed and summarized. Listings will be sorted by treatment, participant, day, and time and include both scheduled and unscheduled visits; table summaries will be presented by treatment include placebo, RVT-1401 340 mg, RVT-1401 680 mg, combined RVT-1401 group, and by scheduled visit.

Open label extension period will start from the date of the first OLE dose for each subject. Unless otherwise specified, data collected during OLE period will be included in the same listings, tables, and figures with data collected during double-blind period.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, and maximum. The geometric mean with associated 95% confidence interval (CI) and the between-participant coefficient of variation (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.

In general, summary statistics for raw variables will be displayed as follows: minimaand maxima will be displayed to the same number of decimal places as the raw data. Means, medians, and quartiles will be presented to 1 more decimal place than the raw data ; standard deviations will be presented to 2 more decimal places than the raw data.

The numbers of decimal places for summary statistics of derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be determined on a case by case basis.

5.1. Analysis Populations

In accordance with guidance from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *Statistical Principles for Clinical Trials E9* (1998), the following analysis populations will be used for all statistical analyses:

- The full analysis set (FAS) includes all randomized subjects who receive at least one dose of randomized study medication with at least one valid post-treatment value. The FAS is used for all efficacy analyses.
- The per-protocol set (PPS) includes all FAS subjects who do not have significant protocol violations, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blinded data review meeting in accordance with guidance from ICH E9 (Statistical Principles).
- The safety analysis set (SAF) includes all subjects who received at least one dose of study medication. The SAF is used for all safety analyses.

- The Pharmacokinetic (PK) analysis set includes all subjects who undergo PK sampling and have evaluable concentration-time data for analysis.
- The Pharmacodynamic (PD) analysis set includes all subjects who received at least 1 dose of study medication and have a baseline PD measurement and at least 1 post-baseline PD measurement.
- The Open-label Extension (OLE) analysis set includes all subjects who enroll in the OLE study phase and receive at least 1 dose of study medication in the OLE. The OLE subjects will be summarized by actual treatment in the double-blind treatment period for safety and PK analyses and by randomized treatment assigned in the double-blind treatment period for other analyses based on the OLE population.

Solely to understand the influence of dropouts on study conclusions, the FAS will be partitioned into completers and dropouts.

Efficacy analysis will be done as randomized. Safety analysis will be done as treated. In the event the administered dose level is not consistent throughout the double-blinded period, the as treated arm will be determined by the highest dose level received during the double-blinded treatment period.

A summary of the number and percent of subjects in each analysis set will be provided by treatment group and in total. Analysis based on a 12-week Follow-up analysis set may be provided depending on the number of subjects who choose not to enroll in the OLE study phase.

5.2. Baseline

Baseline is defined as the last non-missing value prior to the date (time) of first dose of study drug unless otherwise specified. If there are multiple assessments collected on the same scheduled date and time, the average of these values will be used.

For the OLE, baseline is defined as the last non-missing value prior to the date (time) of first dose of study drug in the OLE.

5.3. Subject Groups

For analyses based on the SAF analysis set or the PK analysis set, subjects will be grouped for analyses according to the actual treatment received. For all other analyses, subjects will be grouped for analyses according to randomized treatment assignment from the double-blind treatment period.

5.4. Multiple Comparisons

Adjustments for multiple comparisons for the primary efficacy endpoints list in Section 9.2 will be performed using a fixed, sequential testing procedure. The order of the testing sequence is specified in Section 9.2. The first test in the sequence will be performed at a significance level of 0.05. If that test is significant, then the second test in the sequence will be performed at a significance level of 0.05, and so on. Testing will stop when a non-significant test occurs in order to maintain a family-wise error rate of alpha=0.05.

There will be no adjustments for multiple comparisons for the secondary efficacy or OLE endpoints.

5.5. Missing Data

In general, values for missing data will not be imputed, except as noted.

If there are no missing data, other than COVID-19-related missing values (which are handled as described previously in this SAP), or if there is a single subject with missing data, the following missing data conventions are deemed unnecessary. For a single subject, the latest available value will be used as the response value of interest.

In the event that more than one subject has missing data, the following missing data methodologies will be followed:

For the primary endpoints, missing values for post-baseline assessments will be imputed using the method of multiple imputation (MI). As a sensitivity analysis, last observation after baseline carried forward (LOCF) will be used to impute the missing value.

Post-baseline values that are missing will be imputed for each primary efficacy endpoint using the Markov Chain Monte Carlo (MCMC) method. Ten copies of the dataset with a monotonic missing pattern will be generated using the monotone data augmentation method, to impute the amount of missing data that is required to make the missing data pattern monotone before applying the multiple imputation algorithm. This method uses a non-informative Jeffery's prior to derive the posterior mode from the expectation-maximization algorithm as starting values for the MCMC method. For each of the 10 monotonic missing pattern datasets, an additional 10 datasets will be imputed to replace missing values at scheduled visits for a total of 100 datasets. These datasets will be generated using a monotone regression-based multiple imputation model. For subjects with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits, treatment group, baseline age, gender, time from disease onset, concomitant medications and duration of use, and baseline outcome as independent variables. Using these regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), the treatment group, age, gender, time from disease onset, concomitant medications and duration of use, and the baseline value.

The SAS MI procedure (ie PROC MI) will be used. The ROUND option will be used to round the imputed values to the same precision as the observed values and the minimum value for imputed will be specified as zero to avoid negative values. The seed to be used for generating the monotonic missing pattern datasets will be 0518, the seed to be used for the regression-based MI will be 0519. The analysis of covariance (ANCOVA) or rank analysis, and the mixed model repeated measures (MMRM) will be performed separately for each of the 100 complete analysis data sets, and the results will be combined into one multiple

imputation inference (estimated treatment effect and associated confidence interval and p value), using PROC MIANLALYZE.

Missing individual items or questions from the QMG scale, MGC scale, the MG-ADL questionnaire, and the MG-QOL15r scale will be imputed using the method of LOCF if no more than 2 questions are missing for QMG scale, MGC scale and MG-QOL15r scale, or no more than 1 question in MG-ADL questionnaire is missing. Otherwise, the individual score and the corresponding total score will be treated as missing.

6. SUBJECT DISPOSITION

6.1. Disposition of Subjects

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, randomized, included in each analysis set, and the number and percent of subjects:

- Completing the 6-week double-blind treatment period,
- Completing the 12-week post-treatment follow-up period, and
- Not completing the study (with summary of reasons for not completing the study)

The denominator for the percentages of subjects in each category will be the number of subjects in the full analysis set.

Additionally, a summary of disposition will be provided for the OLE by randomized treatment assignment from the double-blind treatment period. This summary will present the number and percent of subjects:

- Completing the 6-week OLE treatment period,
- Completing the 6-week OLE follow-up period, and
- Not completing the OLE

The denominator for the percentages of subjects in each category will be the number of subjects in the OLE analysis set.

No inferential statistics will be generated. Data listings of reasons for study discontinuation and reasons for OLE discontinuation will be provided.

6.2. Extent of Exposure

6.2.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in days. Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) and as the number and percent of subjects exposed at each week.

Summaries will be provided separately for the 6-week double-blind treatment period and the 6-week OLE treatment period by treatment group for the SAF analysis set and the OLE analysis set, respectively. No inferential statistics will be generated.

6.2.2. Adherence with Study Drug Regimen

Adherence to study drug will be defined as the number of doses received divided by the number of doses planned. Adherence will be calculated separately for the 6-week double-blind treatment period and the 6-week OLE treatment period.

Descriptive statistics for adherence (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) along with the number and percent of subjects belonging to adherence categories (e.g., <80%, 80% - 90%) will be provided by treatment group for the SAF analysis population and the OLE analysis population, respectively. No inferential statistics will be provided.

6.2.3. Satisfaction with Study Drug Regimen

For each item listed in the first question ("In this study, how bothered have you been by the following:") of the treatment satisfaction questionnaire, the number and percentage of subjects who responded "quite a bit bothered" or "severely bothered" will be summarized. Likewise, for each item listed in the second question ("Regarding the weekly injections, please rate how satisfied you were with the following:"), the number and percentage of subjects who responded "not at all satisfied," "a little satisfied," or "moderately satisfied" will be summarized.

All responses to the treatment satisfaction questionnaire will be listed.

6.3. Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock and unblinding. Major protocol deviations may include, but are not limited to:

- Randomly assigned subjects who did not satisfy selected inclusion and exclusion criteria;
- Randomly assigned subjects who developed withdrawal criteria during the study but were not withdrawn;
- Subjects who received the wrong treatment or incorrect dose;
- Subjects who received an excluded concomitant treatment;

A listing of all protocol deviations including the deviation designation (major or minor), category, whether it is significant deviation led to an exclusion of a subject from the PP set will be presented in a data listing.

Major protocol deviations will be summarized by deviation category and treatment group. This ongoing clinical study coincides with the coronavirus disease 2019 (COVID-19) global pandemic. Any protocol deviations specifically due to COVID-19 will be summarized separately.

7. BASELINE DATA

7.1. Demographics and Baseline Characteristics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., QMG, MG-ADL, MGC, and MG-QOL15r scores, treatments for disease, time since thymectomy, and time from MG onset) will be summarized by treatment group and overall using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. The summaries of demographic and baseline characteristics data will be provided for the SAF analysis set. No inferential statistics will be generated. The time from MG onset will be calculated by using (The date of randomization – The start date of the MG collected in the CRF medical history form + 1) / 365. Refer Section 8.4 algorithms for the missing or incomplete MG start date.

Additionally, a summary of demographic and baseline characteristics data will be provided for subjects who enrolled in the OLE.

7.2. Medical History

Medical history will be listed.

8. ESTIMAND SPECIFICATION

This SAP is constructed to conform to regulatory guidance. In particular, this section is included as recommended by ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (30 August 2017) and the update November 2019. The scientific question of interest evaluates the potential superiority of RVT-1401 over placebo in the treatment of MG in subjects who meet protocol eligibility criteria.

In accordance with ICH E9 Addendum, the specification of the estimand is included in this SAP with the 4 attributes detailed in ICH E9 Addendum, Section A.3.1.

In accordance with guidance from the ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline to Statistical Principles tor Clinical Trials (2018), the characterization of the estimand includes the following attributes.

8.1. The Treatment Condition

Blind data review considerations of intercurrent events revealed the potential that infections experienced by some subjects could affect the efficacy scales in important ways, rendering the responses to questionnaire data uninterpretable for protocol purposes.

8.2. The Population of Interest

The population of interest includes qualified subjects who meet eligibility criteria specified in the protocol and who have at least one valid post-baseline measure of IgG.

8.3. The Variable of Interest

For this study, the primary endpoint is IgG level and anti-AChR-IgG with co-primary importance on treatment responsiveness (whether or not subjects are treatment responders) evaluated based on clinical endpoints.

8.4. The Population-level Summary

The population-level summary for this study includes the mean percent change in IgG of patients in the FAS who received RVT-1401 (combined) versus placebo followed by estimates of subjects receiving each dose. Response data from efficacy questionnaires will include mean changes, mean percent changes, and responder analysis as defined under variables of analysis.

9. EFFICACY ANALYSES

9.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoints include:

- Percentage change from baseline in total IgG at Week 7.

Supportive variables to the primary efficacy laboratory variable are:

- Percentage change from baseline in IgG1 at Week 7
- Percentage change from baseline in IgG2 at Week 7
- Percentage change from baseline in IgG3 at Week 7
- Percentage change from baseline in IgG4 at Week 7
- Percentage change from baseline in anti-AChR-IgG level at Week 7

Percentage change from baseline will be calculated as:

$$\%\Delta = \left[100 \text{ x } \left(\frac{\text{Week 7 - Baseline}}{\text{Baseline}}\right)\right]$$

9.2. Statistical Hypotheses for the Efficacy Endpoints

The efficacy endpoint hypotheses will be tested in the order below.

1. H_0: $\mu_{11} = \mu_{1p}$ vs. H_A: $\mu_{11} \neq \mu_{1p}$, where μ_{11} = LSmean of $\%\Delta_{\text{Total IgG}}$ for RVT-1401 680 mg/wk or RVT 340 mg/wk and μ_{1p} = LSmean of $\%\Delta_{\text{Total IgG}}$ for placebo

Supportive superiority on percent change in IgG is evaluated:

- H_{01}: The percent change from baseline in Total IgG after 6 weeks of treatment for the group treated with RVT-1401 680 mg/wk is equal to that of the placebo group.
- H_{11}: The percent change from baseline in IgG after 6 weeks of treatment for the group treated with RVT-1401 680 mg/wk is not equal to that of the placebo group.

Supportive superiority on percent change in IgG is evaluated:

- H_{02}: The percent change from baseline in IgG after 6 weeks of treatment for the group treated with RVT-1401 340 mg/wk is equal to that of the placebo group.
- H_{12}: The percent change from baseline in IgG after 6 weeks of treatment for the group treated with RVT-1401 340 mg/wk is not equal to that of the placebo group.

Superiority on percent change in anti-AChR-IgG level is evaluated:

- H_{03}: The percent change from baseline in *anti-AChR-IgG* after 6 weeks of treatment for the group treated with RVT-1401 680 mg/wk is equal to that of the placebo group.

- H_{13}: The percent change from baseline in *anti-AChR-IgG* after 6 weeks of treatment for the group treated with RVT-1401 680 mg/wk is not equal to that of the placebo group.

evaluation continues:

- H_{04}: The percent change from baseline in *anti-AChR-IgG* after 6 weeks of treatment for the group treated with RVT-1401 340 mg/wk is equal to that of the placebo group.

- H_{14}: The percent change from baseline in *anti-AChR-IgG* after 6 weeks of treatment for the group treated with RVT-1401 340 mg/wk is not equal to that of the placebo group.

Conditional on the p-value being less than alpha, testing continues:

Superiority on change in MG-ADL is evaluated:

- H_{05}: The percent change from baseline in *MG-ADL* after 6 weeks of treatment for the group treated with RVT-1401 680 mg/wk or RVT 340 mg//wk is equal to that of the placebo group.
- H_{15}: The percent change from baseline in *MG-ADL* after 6 weeks of treatment for the group treated with RVT-1401 680 mg/wk or RVT-1401 340 mg/wk is not equal to that of the placebo group.

Conditional on the p-value being less than alpha, testing continues:

- H_{06}: The proportion of responders on *MG-ADL* after 6 weeks of treatment for the group treated with RVT-1401 680 or 340 mg/wk is equal to that of the placebo group.
- H_{16}: The proportion of responders on *MG-ADL* after 6 weeks of treatment for the group treated with RVT-1401 680 or 340 mg/wk is not equal to that of the placebo group.

9.3. Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoints will be summarized descriptively (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum). Efficacy analysis will be done on the FAS subjects consistent with ICH E9 principles.

The primary hypothesis test analysis will use the intent-to-treat methodology and a main-effects model for ANCOVA, with adjustment for baseline levels. If 2 or more subjects have missing Week 7 data, missing data will be predicted using MI methodology.

For sensitivity analysis, interaction terms of site by treatment group will be examined. In the event of a significant interaction term, the impact on analysis conclusion will be examined. The primary analysis model will not include interaction terms. Assumptions underlying ANCOVA will be examined. If assumptions of ANCOVA are unwarranted and the validity of the ANCOVA becomes questionable, rank analogues will be advanced as the primary analysis. Missing data will be managed using MI methods.

The primary analysis on treatment responders will use Fisher's exact test supported by logistic regression with baseline measure as covariables.

The primary analysis will be conducted using the FAS following the intent-to-treat (ITT) principle.

Descriptive summaries will be produced for the actual values, change from baseline and percent change from baseline by treatment group and visit.

Longitudinal data analyses will be used to support the primary analysis utilizing a mixed model repeated measures (MMRM) methodology with treatment, baseline as covariate, time, treatment-by-time interaction as fixed effects, and subject as a random effect.

For completeness, an observed cases analysis will be done by visit in which no data are excluded, no data are imputed, and no data are represented at times other than when they were observed. As an alternative for handling missing data according to the rules of the primary analysis, a sensitivity analysis will be done using LOCF.

For statistical analyses, 95% confidence intervals will be produced for the least squares means (LSM) in each treatment group and combined treatment group, as well as the LSM differences as compared to placebo. For MMRM and ANCOVA, two-sided p-values will be displayed for the comparison against placebo.

To ensure robustness of analysis conclusions against parametric assumptions, rank analogues will be executed as sensitivity analysis. If the PPS differs from the FAS by more than 10%, the analyses will be replicated on the PPS. If the PPS and the FAS do not differ by more than 10%, analysis may not be done on the PPS. Final judgments will be made at the blinded data review meeting in accordance with ICH E9.

All analyses will be done using the intent-to-treat (ITT) principle.

9.4. Secondary Efficacy Endpoints

9.4.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change from baseline in the MG-ADL score by visit through Week 7

- Achievement of MG-ADL response of 2 points or more at Week 7
- Change from baseline in the QMG score by visit through Week 7
- Achievement of QMG improvement with an improvement from baseline on the QMG score by ≥3 points at Week 7
- Achievement of MGC improvement with an improvement from baseline on the MGC score by ≥3 points at Week 7
- Change from baseline in the MGC score by visit through Week 7
- Change from baseline in the MG-QOL15r score by visit through Week 7
- Durability of MG-ADL response as evaluated by proportion of assessments by Week 7 with change showing improvement of 2 or more points.
- Durability of QMG response as evaluated by proportion of assessments by Week 7 with change showing improvement of 3 or more points.
- Durability of MGC score as evaluated by proportion of assessments by Week 7 with change showing improvement of 3 or more points.
- Achievement of improvement by meeting at least one of the following criteria:
    - Achievement of improvement of at least 2 points on MG-ADL
    - Achievement of improvement of at least 3 points on QMG
    - Achievement of improvement of at least 3 points on MGC
- Achievement of improvement by meeting at least two of the following criteria:
    - Achievement of improvement of at least 2 points on MG-ADL
    - Achievement of improvement of at least 3 points on QMG
    - Achievement of improvement of at least 3 points on MGC
- Achievement of improvement by meeting all three of the following criteria:
    - Achievement of improvement of at least 2 points on MG-ADL
    - Achievement of improvement of at least 3 points on QMG
    - Achievement of improvement of at least 3 points on MGC

The QMG scale is comprised of 13 items that are graded on a scale of 0 to 3. The sum across all 13 items represents the QMG score which will range from 0 to 39.

The MGC scale is a patient reported scale comprised of 10 items that are rated on a scale ranging from 0 to 9 depending on the item. The sum across all 10 items represents the total MGC score which will range from 0 to 50.

The MG-ADL is a patient reported questionnaire comprised of 8 items that are rated on a scale of 0 to 3. The sum across all 8 items represents the MG-ADL score which will range from 0 to 24.

The MG-QOL15r is a patient-reported scale comprised of 15 items that are graded on a scale of 0 to 2. The sum across all 15 items represents the MG-QOL15r score which will range from 0 to 30.

Missing individual items or questions from the QMG scale, MGC scale, the MG-ADL questionnaire, and the MG-QOL15r scale will be imputed using the method of LOCF if no more than 2 questions are missing for QMG scale, MGC scale, and MG-QOL15r scale or no more than 1 question is missing for the MG-ADL questionnaire. Otherwise, will take the total score for the given scale as missing.

9.4.2. Analysis Methods for Secondary Efficacy Endpoints

Total MG-ADL, QMG, MGC, and MG-QoL15r score and each of the component scores will be summarized descriptively (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) by treatment group and analyzed using ANCOVA model with treatment as a fixed factor and baseline value as a covariate. Least-squares means and 95% CIs will be calculated and provided for each treatment group. The least-squares means will be compared using a t-test.

Number and proportion of subjects with a ≥2-, ≥3-, ≥4-, ≥5-, ≥6-, ≥7-, or ≥8-point improvement in total MG-ADL, QMG, and MGC score at all timepoints will be summarized descriptively by treatment group. The percentage will be calculated using those participants who had a value at the time point. Fisher's exact test will be used to compare each active dose regimen to placebo. A logistic regression with treatment as the main effect and the baseline value as a covariate will be used for comparing the proportion of responders between the treatment groups. The odds ratio and corresponding 2-sided 95% Wald confidence interval will be provided.

There will be no adjustments for multiple comparisons for secondary endpoints. An alpha level of 0.05 will determine statistical significance. Analyses of secondary efficacy endpoints will be provided for the FAS.

9.5. Exploratory Analyses

10. SAFETY ANALYSES

10.1. Adverse Events

An adverse event (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.

Adverse events summaries will be constructed displaying AEs in decreasing order of frequency under the combined RVT-1401 group according to the numbers of subjects reporting the AE (not the number of events).

A listing will be constructed that includes the subject identification, the dose group, TEAEs, MedDRA terms, seriousness, severity, causality related to study medication, elapsed time to onset, duration, and outcome.

10.1.1. Adverse Event Dictionary

AE verbatim text will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.1). System organ class (SOC), high level group term, high level term, preferred term (PT), and lower level term will be attached to the clinical database.

10.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening) or Grade 5 (death) according to toxicity criteria specified in the study protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings and will be considered the least severe for the purposes of sorting for data presentation.

10.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator answers “Probably Related” or “Possibly Related” to the question “Is there a reasonable possibility that the study treatment caused or contributed to the adverse event?” Adverse events for which the investigator did not record relationship to study drug will be considered related to study drug. Data listings will show relationship as missing.

10.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified in the clinical database as such. The clinical database will be reconciled with the SAE database before database lock.

10.1.5. Treatment-Emergent Adverse Events

10.1.5.1. Definition of Treatment-Emergent

Adverse events will be classified by study part according to the following:

- Pre-treatment: AEs that either started prior to the date of the first dose of study drug or had no recorded start date and the stop date is prior to the first dose of study drug.
- Treatment-emergent: AEs that either started on or after the date of the first dose of study drug and on or before the date of 6 weeks (42 days) post the last dose of study drug or had no recorded start date and the stop date is not before the first dose of study drug.
- Post-treatment: AEs that started after the date of 6 weeks (42 days) post the last dose of study drug.
- OLE treatment-emergent: AEs that either started on or after the date of the first dose of study drug in the OLE.

10.1.5.2. Incomplete Dates

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates:

If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."

If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).

If the start date is completely missing and the stop date is either after the first dose of study drug or completely missing, the start date will be estimated to be the first day of study drug dosing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date.

Stop Dates:

If only the day of the stop date is unknown, the day will be assumed to be the last of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).

If both the day and month of the stop date are unknown, the stop date will be assumed to be last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).

If the stop date is completely missing, and the stop date will be imputed using the last known date on the study.

10.1.6. Summaries of Adverse Events

All AE summaries will be provided separately for the double-blind treatment period and the follow-up period as well as the OLE treatment period and OLE follow-up period. Double-blind treatment period AE summaries will present treatment-emergent AEs which occurred before study drug administration during OLE study period or before the primary lock date, whichever comes first. Follow-up period AE summaries will present post-treatment AEs, OLE treatment period AE summaries will present OLE treatment-emergent AEs which occur before or on week 12 visit and OLE follow-up period AE summaries will present OLE post-treatment AEs. Pre-treatment AEs will be listed.

Overall summaries of treatment-emergent AEs by treatment group will be provided to include the number and percentage of subjects who:

1. Had any AE,
2. Had any Grade 3 or higher AE,
3. Had any treatment-related AE,
4. Had any Grade 3 or higher treatment-related AE,
5. Had any SAE,
6. Had any treatment-related SAE,
7. Permanently discontinued from study drug due to an AE, and
8. Died.

Summaries (number and percent of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by treatment group for the following:

- All AEs,
- All Grade 3 or higher AEs,
- All treatment-related AEs,
- All Grade 3 or higher treatment-related AEs,
- All SAEs,
- All treatment-related SAEs,
- All AEs that leading to permanently discontinued from study drug.

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing frequency in

the combined RVT-1401 column. Treatment period and follow-up period AE summaries will be provided for the SAF analysis population. Open-label extension AE summaries will be provided for the OLE analysis population. Whole study AE summaries include the double blinded period, OLE period and follow up will be provided for below 3 tables:

- Overall summaries of treatment-Emergent AEs
- Treatment-emergent AEs by SOC and PT
- Serious treatment-emergent AEs by SOC and PT

In addition to the by-treatment AE summaries, data listings will be provided for the following:

- Pre-treatment AEs
- Treatment-emergent AEs
- Post-treatment AEs
- OLE treatment-emergent AEs
- SAEs
- Liver events
- AEs leading to discontinuation or interruption of study drug
- Deaths
- Grades 2-4 albumin events

10.1.7. Injection Site Reactions

Injection site reactions will be summarized (number and percentage of subjects) by symptom and toxicity grade and provided by treatment group. Multiple events will be counted once only per subject in each summary. Additionally, a summary of the number of subjects who experienced at least 1 injection site reaction during the study and at each visit will be provided for the SAF analysis population. No inferential statistics will be generated. Injection site reactions will also be listed.

10.2. Laboratory Evaluations

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) of baseline, post-baseline, and change from baseline central laboratory values collected for each laboratory parameter will be provided by treatment group for all scheduled visits. If result contains '<', then the result for continuous summaries will be the value divided by 2, and if the result contains '>' then the result for continuous summaries will be the value plus 0.01 for analysis. The listings will display the value as collected.

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

Hematology

Platelet count	*Red Blood Cell Indices*:	*Automated White Blood Cell Differential:*
Red blood cell count	Mean corpuscular volume	Neutrophils
White blood cell count (absolute)	Mean corpuscular hemoglobin	Lymphocytes
Reticulocyte count	Mean corpuscular hemoglobin concentration	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 glutamyl transferase (GGT)	Albumin*
Sodium	Calcium (corrected)	Alkaline phosphatase (ALP)	Total Protein
Serum complement (CH50, C3)	Immunoglobulin M (IgM)	Immunoglobulin A (IgA)	Immunoglobulin G (IgG)

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]
Follicle-stimulating hormone (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 time points. Positive urine tests should be confirmed with a serum test.

* Albumin collected from central lab will be graded to Grade 1 to 3 by CTCAE version 5.0.

Additionally, summaries (number and percentage of subjects) of shifts from baseline central laboratory value (low, normal, or high) to post-baseline value (low, normal, or high) at each scheduled post-baseline visit for each parameter will be provided by treatment group.

Albumin from central laboratory will be graded according to CTCAE v5.0 as below. The highest CTCAE grade for each visit will be summarized using a shift table to assess changes from baseline. Grading of albumin will only be based on the following numeric values, (note this may lead to a discrepancy with the protocol-defined Grade 2 event since the protocol also involves signs/symptoms attributable to hypoalbuminemia and not just on the lab value):

Grade 1	**Grade 2**	**Grade 3**
<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L

Central and local laboratory clinical chemistry, hematology, and urinalysis values will be listed and flagged high or low relative to the normal range where appropriate. Summaries of laboratory data will be provided for the SAF analysis population. No inferential statistics will be generated.

Because "exacerbations" of pre-existing abnormalities in laboratory analytes are examined using clinical judgment and are reported as TEAEs, additional analysis on treatment-emergent abnormal values is limited to subjects with values that are normal prior to dosing and abnormal after dosing.

Adverse events of special interest also treatment-emergent abnormal values TEAVs in laboratory parameters related to liver function tests, specifically ALT, AST, bilirubin, and ALK.

Potentially clinically significant values in laboratory analytes will be examined in accordance with the table of values or changes of potential clinical significance in this SAP. Proportions of subjects in each treatment group who meet the criteria will be analyzed.

Laboratory data will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

Liver function tests have additional monitoring for this study.

To explore the potential for drug-induced liver injury consistent with *Guidance for Industry "Drug-induced liver injury: premarketing clinical evaluation"* (CDER, CBER, July 2009), subjects will be summarized and listed who meet the following criteria:

1. Elevations in either AST or ALT of at least 3-times the upper limit of normal, and
2. An accompanying abnormal bilirubin.

Additionally, a summary and listing will be examined for subjects with elevations in either AST or ALT of at least 3-times the upper limit of normal, regardless of bilirubin.

10.3. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature, weight, and height) will be summarized descriptively. Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) of baseline, post-baseline, and change from baseline values for each parameter will be provided by treatment group for all scheduled time points. Summaries of vital sign data will be provided for the SAF analysis set. No inferential statistics will be generated. Vital sign values will also be listed.

10.4. Concomitant Medications

Concomitant medication verbatim terms on case report forms will be mapped to Anatomical Therapeutic Chemical (ATC) Class and Preferred Names using the World Health Organization (WHO) Drug Dictionary version 01Sep2018. Concomitant medications will be summarized (number and percentage of subjects) by ATC class and preferred name and provided by treatment group. Multiple medications (by preferred name) will be counted once only per subject. The summary will be sorted alphabetically by ATC class and then by decreasing total frequency within preferred names. Additionally, a summary of the frequency of IVIG/PLEX rescue medications will be provided. Summaries of concomitant and rescue medications will be provided for the SAF analysis population. No inferential statistics will be generated.

Concomitant medications will be defined as medications that started or were ongoing on or after the date of the first dose of study drug. Prior medications will be defined as medications that stopped prior to the first dose of study drug. All medications will be listed along with a flag to indicate whether the medication was a prior medication or a concomitant medication.

Concomitant and rescue medications will be summarized separately for the OLE. Concomitant medications in the OLE will be defined as medications that started or were ongoing on or after the date of the first dose of study drug in the OLE. Summaries of concomitant and rescue medications in the OLE will be provided for the OLE analysis population.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates:

If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as “01.”

If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).

If the start date is completely missing and the stop date is either after the first dose of study drug or completely missing, the start date will be estimated to be the first day of study drug

dosing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date.

Stop Dates:

If only the day of the stop date is unknown, the day will be assumed to be the last of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).

If both the day and month of the stop date are unknown, the stop date will be assumed to be last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).

If the stop date is completely missing, and the stop date will be imputed using the last known date on the study.

10.5. Electrocardiogram Results

Electrocardiogram (ECG) results (heart rate, PR, QRS, QT, and corrected QT interval by Fredericia (QTcF) will be summarized descriptively. Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) of baseline, post-baseline, and change from baseline values for each parameter will be provided by treatment group for all scheduled time points.

Additionally, summaries (number and percentage of subjects) of shifts in the investigator's ECG assessment from baseline (normal, abnormal and clinically significant, or abnormal but not clinically significant) to post-baseline (normal, abnormal and clinically significant, or abnormal but not clinically significant) at each scheduled post-baseline visit will be provided by treatment group.

Summaries of ECG data will be provided for the SAF analysis set. No inferential statistics will be generated. ECG data will also be listed.

Corrections to QT intervals will be made by Fridercia's method. Categorical analysis will be done consistent with ICH E14, "Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs" (October 2005). Subjects will be categorized and summarized according to:

- Absolute QTc interval prolongation:
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from baseline in QTc interval:
  - QTc interval increases from baseline > 30
  - QTc interval increases from baseline > 60

10.6. Other Safety Data

Data listings will be provided for the following:

- Eligibility criteria
- Procedures
- Physical examination
- Pregnancy test
- Liver imaging
- Liver biopsy
- Receptor occupancy
- Pro-inflammatory biomarker multiplex
- Gene expression
- Immunoglobulins (IgM, IgA)
- Serum complement
- Viral serology
- QuantiFERON-TB Gold

11. PHARMACOKINETIC ANALYSES

Serum concentration data will be summarized descriptively for each nominal time point. Individual serum concentration-time plots will be presented on linear and semi-log scales. The PK analysis will be divided into 2 sections: primary analysis and OLE analysis, where the OLE analysis will contain individuals in the OLE population only. For descriptive statistics and mean figures, concentrations that are below the limit of quantitation (BLQ) will be treated as zero, except when an individual BLQ falls between 2 quantifiable values, in which case it will be treated as missing data and will be excluded from the mean profile.

Serum RVT-1401 concentration-time data will be analyzed by non-compartmental analysis (NCA), using actual sampling times recorded during study. The pharmacokinetic analysis and generation of tables, listings, and figures will be performed using a validated installation of Phoenix WinNonlin® version 8.1 and above (Certara, Princeton, NJ, USA) as part of a 21 CFR Part 11 compliant database system (Phoenix Knowledgebase Server "PKS") and all the analysis will be stored on the PKS, with an audit trail for all the steps capturing the changes needed for the completion of the analysis and generation of the tables, listings, and figures.

The primary analysis of PK will be conducted on the Pharmacokinetic (PK) population, which includes all subjects who had both a pre-dose and at least 1 analyzable post-dose PK sample. The primary pharmacokinetic parameters to be calculated are area under the concentration-time curve from time zero to time AUC_{0-t}, maximum serum concentration (C_{max}), concentration at end of dosing interval (C_{trough}), and time to maximum serum concentration (t_{max}) after the first and last dose on Week 1 and Week 6, respectively. The $C_{max,}$, t_{max}, AUC_{0-t} will be estimated using linear-up log-down method, as data permits. Additionally, C_{trough} will be determined for every dosing interval (Week 2, Week 3, Week 4, and Week 5), where PK samples taken within 8 hours before the next dose administration will be considered for reporting. Additional PK parameters (e.g. accumulation ratio for both C_{max} and/or $AUC_{(0-t)}$ between Week 1 and Week 6) may be calculated if data permits.

Pharmacokinetic (PK) parameters (AUC_{0-t}, C_{max}, C_{trough} and t_{max}) will be summarized descriptively as follows:

- Serum concentration data: sample size, number and percentage BLQ, mean, standard deviation, CV, median, minimum and maximum
- AUC_{0-t}, C_{trough} and C_{max}: sample size, mean, standard deviation, CV, geometric mean, geometric CV, median, minimum and maximum
- t_{max}: sample size, median, minimum and maximum

Summaries of PK parameters and serum concentration data will be provided for the PK analysis population. No inferential statistics will be generated. Individual and summary PK parameter and serum concentration data will also be listed.

For summary tables, the descriptive statistics will be rounded to 1 more digit than the individual values for the arithmetic mean, SD, median and geometric mean, and to the same number of digits for the minimum and maximum values. The t_{max} will be reported using the median and range up to 2 decimal points in listing and summary tables. The number of non-

missing observations (n) will be reported as an integer number. The CV% and geometric CV% will be reported as a percentage of the integer number.

For individual plots, the time course of RVT-1401 serum concentration profile will be presented as 1 plot per graph and as composite plots (consisting of overlaid profiles for all subjects with the same dose as connected lines). The graphical output will be presented in both linear and semi-log scales. Actual sampling times will be used for individual plots. For mean plots for each dose group, the arithmetic mean of RVT-1401 serum concentration time profiles will be presented in linear and semi-log graphs. Linear mean plots will be presented with their upper SD bars. Scheduled (nominal) sampling times will be used for mean plots.

12. PHARMACODYNAMIC ANALYSES

Pharmacodynamic endpoints (total IgG, IgG1, IgG2, IgG3, IgG4, and anti-AChR-IgG level) will be summarized descriptively and analyzed using an ANCOVA model. Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) of baseline, post-baseline, change from baseline, and percentage change from baseline values for each PD endpoint will be provided by treatment group for all scheduled visits.

The ANCOVA model with treatment as a fixed factor, and baseline value as covariate will be used to produce least-squares means and 95% CIs for each treatment group at each scheduled visit. For each scheduled visit, the least-squares means will be compared using a t-test. Line plots of the least squares means and 95% CIs by visit will also be provided.

There will be no adjustments for multiple comparisons of PD endpoints. An alpha level of 0.05 will determine statistical significance. Analyses of PD endpoints will be provided for the PD analysis population.

13. IMMUNOGENICITY ANALYSIS

Immunogenicity analysis will be based on the safety population and the presence of anti-drug antibodies (ADAs) will be determined using the 3-tiered approach: screening, confirmation, and titration. All samples will be brought through the tier 1 screening assay to determine the potential presence of anti RVT-1401 antibody. All samples determined potentially positive will be analyzed in the tier 2 confirmation assay where presence of anti-RVT-1401 will be confirmed – the therapeutic antibody will be used to compete with the analytical responses of ADA to assess specificity of screened positive samples. After ADA confirmation, all samples that were confirmed positive for ADA will be analyzed in the tier 3 assay in order to characterized and determine antibody titers. Titration results will characterize the magnitude of the ADA response during the confirmatory assay.

Interpretation of the result will first be performed with a descriptive count of the immunogenicity assessment with a summary of ADA titer confirmed positive and a summary of immunogenicity rate by anti-RVT-1401 from confirmatory assay across all doses. Comparison will be performed between active and placebo treatment descriptively.

Optional analysis on ADA incidence and PK parameter descriptive presentation in ADA negative and positive confirmed subjects might be performed.

14. CHANGES FROM ANALYSES AS DESCRIBED IN THE PROTOCOL

- The definition of PP population was not included in the protocol but was defined as follows:

The PP analysis population includes all subjects who were randomized and received at least one 1 dose of study medication and had no major protocol deviations. Subjects will be summarized by randomized treatment for analyses based on the PP population.

- Below definition of 12-Week Follow-up Population was defined in the protocol but was not included the SAP.

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

- The analysis populations defined in the SAP are not consistent with the protocol Section 10.2.1; the definitions in SAP were updated to comply with ICH E9.

15. REFERENCES

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16. SOFTWARE

SAS Software Version 9.4 or higher. SAS Institute Inc., Cary, NC, USA.

WinNonLin Version 6 or higher