Statistical Analysis Plan

Immunovant

RVT-1401-1002

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

Protocol Version: 07 Feb 2019

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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
[redacted] I approve this document 16 Oct 2019 10:45:05 -05:00 cosign Synteract	16OCT2019
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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
ADA	anti-drug antibodies
AE	adverse event
ATC	anatomical therapeutic chemical
AUC_{0-t}	area under the concentration-time curve from zero to time t
BLQ	below the limit of quantitation
CAS	clinical activity score
C_{max}	maximum serum concentration
C_{trough}	concentration at end of dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
%CVb	between-participant coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FcRn	fully human anti-neonatal FC receptor
GO	Graves' ophthamalopathy
GO-QOL	Graves' ophthamalopathy quality of life
ICH	International Council for Harmonisation
IGF-1R	insulin-like growth receptor
IgG	immunoglobuin G
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKS	Phoenix Knowledgebase Server
Q1	first quartile
Q3	third quartile
QC	quality control
SAE	serious adverse event
SAP	statistical analysis plan
TSH	thyroid-stimulating hormone
TSHR	thyroid-stimulating hormone receptor
TLFs	tables, listings, and figures
t_{max}	time to maximum serum concentration

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Immunovant protocol RVT-1401-1002, A Phase 2a, Multicenter, Open-Label Study of RVT-1401 for the Treatment of Patients with Moderate to Severe Active Graves' Ophthalmopathy (GO). The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report.

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol Amendment 3: Version 4.0, 07 FEB 2019
- Annotated electronic case report form (eCRF), Version 3, 26 AUG 2019

3. STUDY OBJECTIVES

3.1 Primary Objectives

- To assess the safety and tolerability of RVT-1401 in subjects with moderate to severe active GO over a 6-week treatment period
- To assess the change in serum levels of anti-thyroid stimulating hormone receptor (anti-TSHR) antibodies, total immunoglobulin G (IgG), and IgG subclasses (1-4).

3.2 Secondary Objectives

- To examine the effect of RVT-1401 on mean change in proptosis
- To examine the effect of RVT-1401 on proptosis responder rate
- To examine RVT-1401 pharmacokinetics (PK) following repeat doses in subjects with moderate to severe active GO
- To measure anti-RVT-1401 antibodies following repeat doses in subjects with moderate to severe active GO

3.3 Exploratory Objectives

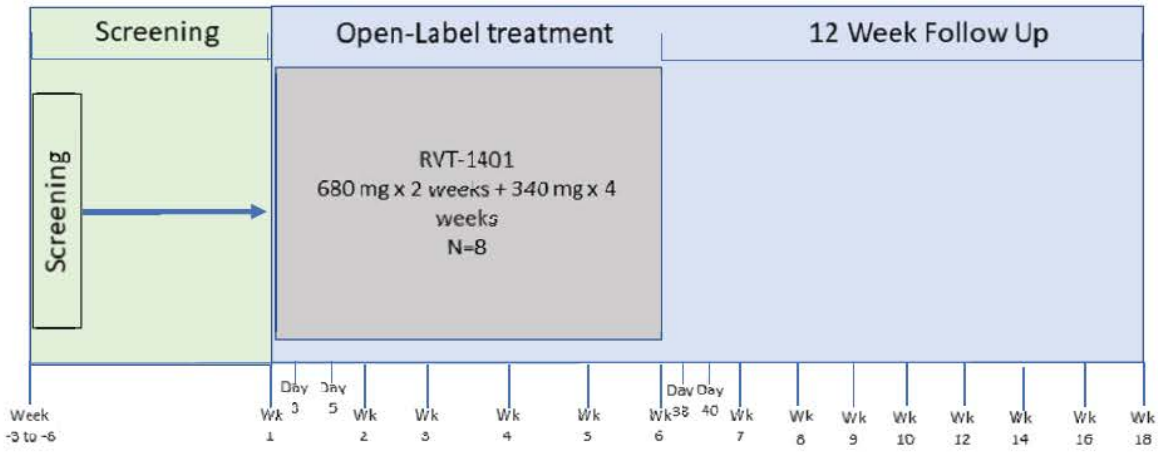
- To assess the change in serum levels of anti-insulin-like growth receptor (anti-IGF-1R) antibodies
- To examine the effect of RVT-1401 on the pro-inflammatory and fully human anti-neonatal FC receptor (FcRn) gene expression in peripheral blood mononuclear cells
- To examine the effect of RVT-1401 on the level of circulating pro-inflammatory cytokines/chemokines
- To assess FcRn receptor occupancy following RVT-1401 administration in whole blood
- To assess the change in the ratio of stimulatory to total serum levels of anti-TSHR and anti-IGF-1R antibodies

- To examine the effect of RVT-1401 on levels of anti-thyroperoxidase and anti-thyroglobulin antibodies
- To assess the change in levels of thyroid-stimulating hormone (TSH), free T3, and free T4
- To examine the effect of RVT-1401 on overall responder rate
- To examine the effect of RVT-1401 on mean change in clinical activity score (CAS)
- To examine the effect of RVT-1401 on CAS responder rate
- To examine the effect of RVT-1401 on overall ophthalmic improvement
- To examine the effect of RVT-1401 on subjective diplopia
- To examine the effect of RVT-1401 on the GO quality-of-life (GO-QOL) score in the visual functioning and appearance subscales
- To examine the effect of RVT-1401 on methimazole(or other anti-thyroid treatment) dosage requirements to achieve/maintain euthyroid state
- To examine the effect of RVT-1401 on computed tomography measured muscle volume, fat volume, total orbital volume, and proptosis

4. STUDY DESIGN AND PLAN

This is a Phase 2a, open-label study to investigate the safety, tolerability, PK, pharmacodynamics (PD), and efficacy of RVT-1401 in GO subjects.

Study Design



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

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

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

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

Table 1 Schedule of Assessments

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

	Screening[1]	Treatment Period Week 1 (Days)			Treatment Period Weekly Visit (Weeks)				Treatment Period Week 6 (Days)			Follow-up Period Weekly Visit (Weeks)								Early With-drawal Visit
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Time Window (days)			+1 day	+1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+/-1 day	+1 day	+1 day	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/- 2 days	
Serum complement (CH50, C3)[2]		X			X	X	X	X	X			X							X	X
Immunoglobulins (IgM, IgA)[2]		X				X			X			X	X	X					X	X
Anti-TPO and anti-thyroglobulin antibodies[2]		X				X						X							X	X
TSH, Free T3, Free T4[2]	X	X			X	X	X	X	X			X	X	X	X	X	X	X	X	X
Anti-TSHR[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-TSHR (Cell based)[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-IGF-1R[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-IGF-1R (Cell based)[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RVT-1401 PK sampling[2]		X	X	X	X	X	X	X	X	X	X	X	X							X
Total IgG[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobins (IgG subclasses)[2]		X	X	X	X	X	X		X	X	X	X				X			X	X
Gene Expression Analysis[2]		X				X			X						X				X	X
Pro-Inflammatory Biomarker Multiplex[2]		X				X			X						X				X	X
Receptor Occupancy[2]		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 With-drawal Visit
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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	
Anti- RVT-1401antibody[2,4]		X				X						X				X			X	X
Nab Assessment[2]		X				X						X				X			X	X
Drug administration		X			X	X	X	X	X											
Injection site reactions[5]		X			X	X	X	X	X											
Clinical Activity Score (CAS)[6]	X	X			X	X	X	X	X			X	X		X	X			X	X
Proptosis[6]	X	X			X	X	X	X	X			X	X		X	X			X	X
Motility[6]		X			X	X	X	X	X			X	X		X	X			X	X
Gorman Score for Diplopia[6]		X			X	X	X	X	X			X	X		X	X			X	X
GO-QOL[6]		X			X		X		X			X			X				X	X
External Photographs[7]		X			X	X	X	X	X			X	X		X	X			X	X
Orbital CT Scan[8]		X											X						X	X
Lid retraction		X			X	X	X	X	X			X	X		X	X			X	X
Collect Methimazole (or other anti-thyroid medication) dose	X	X			X	X	X	X	X			X	X	X	X	X	X	X	X	X
Satisfaction Questionnaire												X								X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Screening can take place over multiple days.
2. Vitals, ECG, and blood draws for safety, PK, and PD assessment will be collected predose on dosing days where specified.
3. Pregnancy tests will be collected predose (via urine dipstick) on dosing days where specified. Serum pregnancy tests should be collected at screening, follow-up, and Early Withdrawal.

4. Participants positive for anti-RVT-1401 antibody at Week 18 will be requested to return at approximately 6, 9, and 12 months postdose 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 postdose, and participants will be monitored for up to 1 hour postdose.
6. GO assessments will be assessed predose when collected on dosing days.
7. Photographs will be assessed after each dose.
8. The baseline orbital scan should be scheduled once all entry criteria haven been met. Scans can be performed within +/- 7days of the scheduled visit.

5. DETERMINATION OF SAMPLE SIZE

A sufficient number of subjects will be enrolled to achieve approximately 8 evaluable subjects. The sample size for this study was not determined using statistical methods. The sample size was chosen based on clinical and recruitment considerations.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs.

Continuous variables will be summarized with n, means, standard deviations, medians, first quartile (Q1) and third quartile (Q3), minimums, and maximums. The geometric mean with associated 95% confidence interval and the between-participant coefficient of variation (%CVb) for PK parameters only will also be included.

In general, summary statistics for raw variables will be displayed as follows: minimums and maximums 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, and standard deviations will be presented to 2 more decimal places than the raw data.

Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. Percentages will be routinely based on the population count if not otherwise mentioned.

Individual subject data obtained from the eCRFs, external vendors, central clinical laboratory, PK data, and any derived data will generally be presented by subject, date and day, and time in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock.

Post hoc analyses will be labeled as such on the output and identified in the clinical study report.

All analyses and tabulations will be performed using SAS® software Version 9.4 or higher (SAS Institute Inc, Cary, NC). Pharmacokinetic analyses will be performed using Phoenix® WinNonlin® Version 8.1 or higher (Certara USA, Inc, Princeton, NJ). Tables, listings, and figures will be presented in RTF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction “SAS programming quality control.” Study-specific QC requirements can be found in Appendix B: SAS programming QC requirements.

7. ANALYSIS POPULATIONS

The following subject population will be used for disposition analysis:

- Enrolled population will include all subjects who signed informed consent.

The following subject population will be used for all analyses except PK:

- Safety population will include all subjects who received at least 1 dose of study drug.

The following populations will be used for PK and PK/PD analyses:

- PK population will include all subjects who undergo serum PK sampling and have evaluable concentration-time data for analysis.
- PD population will include all subjects who have baseline measure, along with a postbaseline measure and receive at least 1 dose of study treatment. PD populations will be defined for each efficacy parameter.

8. STUDY POPULATION

8.1 Subject Disposition

Subject disposition information will be summarized for all enrolled subjects. Summaries will include the number of subjects screened, the number of subjects in each analysis population, the number of subjects completing the 6-week treatment period, the number of subjects completing the 12-week posttreatment follow-up period, and the primary reason for discontinuation.

8.2 Protocol Deviations

Protocol deviations will be listed.

8.3 Eligibility

A listing of subjects not fullfilling any eligibility criteria will be created.

8.4 Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, and race. Age will be calculated in years relative to the informed consent date.

Other baseline characteristics include height, weight, body mass index, and smoking status. Descriptive statistics will be presented for age, height, weight, body mass index, CAS, GO-QOL subscales, and proptosis. Frequency counts and percentages will be presented for sex, ethnicity, race, smoking status, and Gorman score for diplopia. GO status at baseline will be summarized.

8.5 Medical History

Medical history data verbatim terms in the eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 21.1). The data will be listed.

8.6 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to anatomical therapeutic chemical (ATC) class level 3 and preferred names using the WHODrug Global (version September 2018).

Prior medications are defined with a start date prior to screening and stop date before the date of the start of study medication. Concomitant medications are defined as any medication used prior to screening and with a stop date at/or after date of first study medication, or which are ongoing from baseline, or which are taken at/after date of first study medication intake. If it cannot be determined whether the medication was a prior (or concomitant) medication due to a partial start or stop date, then it will be counted as concomitant; see Appendix A for the imputation of missing dates algorithm.

Concomitant medications will be summarized by ATC class and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered alphabetically by ATC class and descending order of incidence of preferred name within each ATC class. A summary of steroid or other GO treatments during follow-up will be provided. These treatments will include the following:

- Preferred Name contains “TEARS”
- Preferred Name equals “BOTULINUM TOXIN TYPE A”
- Preferred Name contains “SELENIUM”
- Preferred Name contains “PREDNISONE” or “PREDNISOLONE”
- Preferred Name equals “METHYLPREDNISOLONE” and route is Intravenous
- Preferred Name equals “CYCLOSPORINE”
- Preferred Name contains “AZATHIOPRINE”
- Preferred Name contains “MYCOPHENOLATE MOFETIL”
- Preferred Name contains “RITUXIMAB”
- Preferred Name equals “TOCILIZUMAB”
- Preferred Name equals “RADIOTHERAPY”

All medications will be listed along with a flag to indicate whether the medication is a prior medication or a concomitant medication.

9. EFFICACY ANALYSES

The primary efficacy analysis will be based on the PD population.

9.1 Efficacy Variables

The primary efficacy variables are:

- Percentage change from baseline in total IgG at Week 7
- 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
- Change from baseline in anti-TSHR antibodies at Week 7

Percentage change from baseline will be calculated as:

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

Secondary efficacy variables include the following:

- Change from baseline in proptosis
- Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye from baseline at the same visit), including time to first proptosis response.

The study eye is defined as the most severely affected eye at the baseline visit. In the event that both eyes are affected the same, the right eye will be deemed the study eye. Time to first proptosis response is defined as the (date of first proptosis response – date of first dose + 1)/7. Subjects who do not achieve a proptosis response will be censored at the date of their last proptosis measurement which occurred in both eyes.

Exploratory efficacy variables include the following:

- Change from baseline in anti-IGF-1R antibodies
- Change from baseline in the level of gene expression
- Change from baseline in the circulating level of pro-inflammatory cytokines/chemokines
- FcRn receptor occupancy
- Change from baseline in ratios of stimulatory to total anti-TSHR and anti-IGF-1R antibodies
- Change from baseline in anti-thyroperoxidase and anti-thyroglobulin antibodies
- Proportion of subjects with ≥2-point reduction in CAS (using a 7-point scale) and ≥2 mm reduction in proptosis in the study eye
- Change from baseline in CAS
- Proportion of subjects with CAS of 0 or 1, including time to first CAS response
- Proportion of patients with overall ophthalmic improvement defined as when at least 2 of the following outcome measures improves in 1 eye, without worsening in any of these measures in either eye:
    a. Reduction in proptosis by at least 2 mm

b. Improvement of ≥8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree)
c. Improvement in CAS by at least 2 points

- Change from baseline in the Gorman Score for diplopia
- Change from baseline in the GO-QOL visual functioning and appearance subscale scores
- Change from baseline in methimazole (or other anti-thyroid treatment) dose
- Change from baseline in computed tomography-measured muscle volume, fat volume, total orbital volume, and proptosis
- Proportion of subjects with diplopia improvement ≥1 grade
- Change from baseline in proptosis

The analysis of the gene expression data will be handled in a separate plan.

The ratios of stimulatory to total anti-TSHR and anti-IGF-1R antibodies are defined as the following:

- Stimulatory anti-TSHR antibody level/total anti-TSHR antibody level
- Stimulatory anti-IGF-1R antibody level/total anti-IGF-1R antibody level

The GO-QOL questions 1 through 8 make up the visual functioning subscale and questions 9 through 16 make up the appearance subscale. The raw score is the sum of the responses in each subscale. In each subscale the score will be calculated in the following manner (Terwee et al):

- Score = 100 × (raw score – 8)/16, if no missing responses
- Score = 100 × (raw score – Number of Completed Items)/(2 × Number of Completed Items), if there are ≤ 4 missing responses, and
- Score will be missing if there are greater than 4 missing responses.

Time to first proptosis response is defined as the date of first proptosis response – date of first dose + 1. Subjects who do not achieve a proptosis response will be censored at the date of their last proptosis measurement. Time to first CAS response is defined as the date of first postbaseline CAS score of 0 or 1 – date of first dose + 1. Subjects who do not achieve a CAS of 0 or 1 will be censored at the date of their last CAS measurement.

9.2 Baseline Values

Unless otherwise noted, baseline is defined as the last nonmissing value recorded prior to the first dose of study drug. Unscheduled visits will be used in the determination of baseline values when applicable.

9.3 Handling of Dropouts or Missing Data

No imputations will be made for missing values. Summaries will be based on observed data only.

9.4 Interim Analysis and Data Monitoring

A readout of the topline results may occur at the end of 2019 depending on enrollment.

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 and the database is locked.

9.5 Examination of Subgroups

No subgroup analysis is planned.

9.6 Multiple Comparison/Multiplicity

No adjustments for multiplicity will be made in this study.

10. METHODS OF EFFICACY ANALYSIS

10.1 Primary Efficacy Analyses

The primary efficacy variables will be summarized descriptively (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by visit. Line graphs over time of percentage/change from baseline for each of the primary endpoints will be provided.

10.2 Secondary Efficacy Analyses

Continuous efficacy variables will be summarized by visit descriptively (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) and categorical variables will be summarized by visit using frequency counts and percentages. Additionally, the number of low responders, defined as having a proptosis measurement >1 mm and <2 mm, and the number of high responders, defined as having a proptosis measurement ≥3 mm, will be summarized. Line graphs over time of the change from baseline for proptosis will be provided.

10.3 Exploratory Analyses

Continuous exploratory efficacy variables will be summarized by visit descriptively (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum). Categorical exploratory efficacy endpoints will be summarized descriptively by visit (number and percent of subjects). A shift from baseline table will be provided to assess change in Gorman Score for diplopia from baseline to each scheduled postbaseline visit. Time to first proptosis response and time to first CAS response will be analyzed using Kaplan-Meier methods. The number and percentage of subjects achieving the event, number and percentage of censored subjects, and Kaplan-Meier estimates of Q1, median, and Q3. Line graphs over time of the change from

baseline for anti-IGF-1R antibody level, pro-inflammatory cytokines/chemokines, CAS, and GO-QOL subscales will be provided.

Responses to the treatment satisfaction questionnaire will be listed.

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. 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, using actual sampling times recorded during study. The PK analysis and generation of TLFs will be performed using a validated installation of Phoenix WinNonlin version 8.1 and above as part of a database system (Phoenix Knowledgebase Server [PKS]) compliant with United States Title 21 Code of Federal Regulations Part 11, 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 TLFs.

The primary analysis of PK will be conducted on the PK population, which includes all patients who undergo serum PK sampling and have evaluable concentration-time data for analysis. The primary PK parameters to be calculated are area under the concentration-time curve from time zero to time t (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 (eg, accumulation ratio for both C_{max} and/or $AUC_{(0-t)}$ between Week 1 and Week 6) may be calculated if data permits.

Pharmacokinetic 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, coefficient of variation (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. Individual PK parameter and serum concentration data will also be listed for all subjects.

12. SAFETY ANALYSES

All safety analyses will be based on the safety population.

12.1 Extent of Exposure

Duration of exposure to study drug will be defined as (last dose date – first dose date + 1), regardless of temporary interrruptions in study drug administration, and will be expressed in days. Duration of exposure to study drug will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and as the number and percentage of subjects weeks of exposure.

Study drug compliance will be defined as the number of doses received divided by the number of doses planned.

Study drug compliance will be summarized using counts and percentages as categorized in the following categories:

- >100%
- >90%-100%
- >80%-90%
- <80%

12.2 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. Verbatim terms in the eCRFs will be mapped to preferred terms and system organ classes using MedDRA Version 21.1.

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.

The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings.

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.

Adverse events will be classified according to the following:

- Pretreatment: 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 the last dose of study drug + 42 days, or had no recorded start date and the stop date is in between date of first dose and the last dose of study drug + 42 days.
- Posttreatment: AEs that started after the date of the last dose of study drug + 42 days.

If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such; see Appendix A for the imputation of missing dates algorithm.

Overall summaries of AEs will be provided to include the number and percentage of subjects who:

- Had any AE,
- Had any Grade 3 or higher AE,
- Had any treatment-related AE,
- Had any Grade 3 or higher treatment-related AE,
- Had a serious AE (SAE),
- Had any treatment-related SAE,
- Permanently discontinued from study drug due to an AE, and
- Died.

Summaries (number and percent of subjects) of treatment-emergent AEs (by system orgran class and preferred term) will be provided for the following:

- All AEs
- All Grade 3 or higher AEs
- All treatment-related AEs
- All Grade 3 or higher treatment-related AEs
- All serious adverse events (SAEs)
- All treatment-related SAEs.

Summaries that are displayed by system organ class and preferred terms will be ordered alphabetically by system organ class and descending order of incidence of preferred term within each system organ class.

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

- Pretreatment AEs
- Treatment-emergent AEs

- Posttreatment AEs
- SAEs
- Liver events
- AEs leading to discontinuation or interruption of study drug
- Deaths

12.3 Injection Site Reactions

Injection site reactions will be summarized (number and percentage of subjects) by maximum observed on treatment and visit, symptom, and toxicity grade. Multiple events will be counted only once per subject at the maximum toxicity grade 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.

12.4 Clinical Laboratory Evaluation

Hematology, clinical chemistry, thyroid functuion, and urinalysis parameters to be tested by central laboratory are as follows:

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	Potassium	Aspertate aminotransferase	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase	Uric acid
Glucose fasting [on Day 1 (baseline) and Week 7 only]	Total carbon dioxide	γ-Glutamyltransferase	Albumin*
Sodium	Calcium (corrected)	Alkaline phosphatase	Total Protein

Serum complement (CH50, C3)	Immunoglobulin M	Immunoglobulin A	

* Albumin collected from central lab will be graded to Grade 1 to 3 by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Thyroid Function Tests

TSH, Free T3, Free T4

Routine Urinalysis

Specific gravity, pH
Glucose, protein, blood, and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Laboratory parameters (serum chemistry, hematology, thyroid function, and urinalysis) will be summarized using descriptive statistics at baseline and at each postbaseline time point. Changes from baseline will also be summarized. Only results from the central laboratory will be summarized.

In addition, shift from baseline tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to each scheduled postbaseline visit for all continuous parameters.

Only results from the central laboratory will be summarized. All 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.

12.5 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and weight) will be summarized using descriptive statistics at baseline and at each postbaseline time point. Changes from baseline will also be summarized.

12.6 Physical Examination

Physical examination results will be included in data listings only.

12.7 Electrocardiogram

Electrocardiogram (ECG) results (heart rate, PR, QRS, QT, and corrected QT interval by Fredericia) will be summarized descriptively including baseline, postbaseline, and change from baseline values for each parameter and will be provided for all scheduled time points.

Overall interpretation results for ECGs will be summarized using shift tables (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) comparing baseline with each

scheduled postbaseline visit. Descriptive statistics at baseline and at each postbaseline time point as well as changes from baseline will be summarized for each ECG parameter.

13. IMMUNOGENICITY ANALYSIS

Immunogenicity analysis will be based on the safety population. The presence of anti-drug antibodies (ADA) will be determined using a 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 annalyzed in the tier 2 confirmation assay where presence of anti-RVT-1401 will be confirmed. The therapeutic antibody will be used to compare 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 characterize 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. The neutralizing potential of ADA may be evaluated.

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

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Note the following modifications and/or clarifications to the methodology specified in the protocol:

- The intention-to-treat population was removed as there was no difference between it and the safety population. The PD population will be used instead for the efficacy endpoints.
- Time to first CAS response, CAS response, and change from baseline in proptosis were added as exploratory endpoints.

15. REFERENCES

Terwee CB, Dekker FW, Mourits MP, et al. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. Clin Endcrinol. 2001 Mar;54(3):391-8.

US Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry ICH E9 Statistical principles for clinical trials. September 1998 [cited 2018 Aug 03]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

16. APPENDICES

Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, superscripted, and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard or Greek characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming, if appropriate, eg, tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.
- Means and medians 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. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be rounded and presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the patients discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0 and no percentage.
- Percentiles (eg, 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source **table number**(s) if applicable (in case aggregated results like mean or median are plotted) or the source listing(s) (in case individual responses are plotted) and/or source datatset(s) (eg, AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".
    where extract date is the datestamp of the data snapshot used.

Figures

- Legends will be used for all figures with more than 1 variable or item displayed.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source datatset(s) (eg, AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".
    where extract date is the datestamp of the data snapshot used.
- Line graphs over time of change from baseline results will include a horizontal dashed reference line at zero.

Listings

- Formal organization of the listing may be changed during programming, if appropriate, eg, additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, patient number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (eg, 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (eg, 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".
    where extract date is the datestamp of the data snapshot used.

Missing or incomplete dates (ie, AEs and concomitant medications)
The most conservative approach will be systematically considered. If the AE onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (ie, considered a treatment-emergent AE) except if the partial onset date or other data, such as the stop date, indicates differently.

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 (eg, ??-???-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. All other non-AE and nonconcomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last of the month (eg, ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (eg, ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug and will be imputed using the last known date on the study.

Appendix B: SAS programming QC requirements

Derived datasets are independently programmed by two programmers. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study analysis dataset specifications provided to the client at study conclusion.

Tables are independently reprogrammed by a second programmer for numeric results.
Listings are checked for consistency against corresponding tables, figures, and derived datasets.
Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.

Appendix C: List of Tables, Figures, and Listings

The following proposal for section 14 and 16.2 is completed according to ICH E3 guidelines. The ICH heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming, if appropriate, eg, tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.

TABLES, FIGURES AND GRAPHS

Output Number	Output Title
14	**TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**
	DEMOGRAPHIC DATA
14.1.1	Disposition (Enrolled Population)
14.1.2	Demographic and Baseline Characteristics (Safety Population)
14.1.3	Graves' Orbitopathy Status at Baseline (Safety Population)
14.1.4.1	Concomitant Medications (Safety Population)
14.1.4.2	Steroid or Other GO Treatment During Follow-up (Safety Population)
14.1.5	Exposure (Safety Population)
	EFFICACY DATA
14.2.1.1	Percentage Change from Baseline in Total IgG by Visit (PD Population)
14.2.1.2	Percentage Change from Baseline in IgG1 by Visit (PD Population)
14.2.1.3	Percentage Change from Baseline in IgG2 at by Visit (PD Population)
14.2.1.4	Percentage Change from Baseline in IgG3 at by Visit (PD Population)
14.2.1.5	Percentage Change from Baseline in IgG4 at by Visit (PD Population)
14.2.1.6	Change from Baseline in anti-TSHR antibody level by Visit (PD Population)
14.2.2.1.1	Proptosis by Visit (PD Population)
14.2.2.1.2	Proptosis Responder Rate (PD Population)
14.2.3.1	Anti-TSHR Antibody Level by Visit (PD Population)
14.2.3.2	Pro-inflammatory Cytokines/Chemokines by Visit (PD Population)
14.2.3.3	FcRn Receptor Occupancy by Visit (PD Population)
14.2.3.4	Ratio of Stimulatory to Total Anti-TSHR and Anti-IGF-1R Antibodies by Visit (PD Population)
14.2.3.5	Anti-Thyroperoxidase (TPO) and Anti-thyroglobulin Antibodies by Visit (PD Population)
14.2.3.6	Clinical Activity Score (CAS) and Proptosis Responder Analysis by Visit (PD Population)
14.2.3.7.1	Clinical Activity Score (CAS) by Visit (PD Population)

Output Number	Output Title
14.2.3.7.2	Proportion of Subjects with Clinical Activity Score (CAS) of 0 or 1 by Visit (PD Population)
14.2.3.8	Proportion of Subjects with Overall Ophthalmic Improvement by Visit (PD Population)
14.2.3.9.1	Gorman Score for Diplopia Shift from Baseline (PD Population)
14.2.3.9.2	Proportion of Subjects with Diplopia Improvement of at Least One Grade (PD Population)
14.2.3.10	GO-QOL and Subscales by Visit (PD Population)
14.2.3.11	Motility by Visit (PD Population)
14.2.3.12	Methimazole (or Other Anti-thyroid Treatment) Dose by Visit (PD Population)
14.2.3.13	Computed Tomography Measurements by Visit (PD Population)
14.2.4.1	Serum Concentrations (PK Population)
14.2.4.2	Pharmacokinetic Parameters (PK Population)
	SAFETY DATA
	Displays of Adverse Events
14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events (Safety Population)
14.3.1.1.2	Overall Summary of Adverse Events - Follow-up Period (Safety Population)
14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
14.3.1.2.2	Adverse Events by System Organ Class and Preferred Term – Follow-up Period (Safety Population)
14.3.1.3.1	Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
14.3.1.3.2	Grade 3 or Higher Adverse Events by System Organ Class and Preferred Term – Follow-up Period (Safety Population)
14.3.1.4.1	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Treatment Period (Safety Population)
14.3.1.4.2	Treatment-Related Adverse Events by System Organ Class and Preferred Term – Follow-up Period (Safety Population)
14.3.1.5.1	Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
14.3.1.5.2	Grade 3 or Higher Treatment-Related Adverse Events by System Organ Class and Preferred Term – Follow-up Period (Safety Population)
	Serious and Significant Adverse Events
14.3.2.1.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
14.3.2.1.2	Serious Adverse Events by System Organ Class and Preferred Term – Follow-up Period (Safety Population)
14.3.2.2.1	Treatment-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

Output Number	Output Title
14.3.2.2.2	Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term – Follow-up Period (Safety Population)
14.3.2.3.1	Injection Site Reactions by Symptom and Toxicity Grade (Safety Population)
14.3.2.3.2	Injection Site Reactions by Visit (Safety Population)
	Laboratory
14.3.4.1.1	Hematology (Safety Population)
14.3.4.1.2	Hematology Shift from Baseline (Safety Population)
14.3.4.2.1	Chemistry (Safety Population)
14.3.4.2.2	Chemistry Shift from Baseline (Safety Population)
14.3.4.3	Thyroid Function Tests (Safety Population)
14.3.4.4	Serum Complement (Safety Population)
14.3.4.5	Immunoglobulins (Safety Population)
	Other Safety Data
14.3.6.1	Vital Signs (Safety Population)
14.3.6.2.1	Electrocardiogram (Safety Population)
14.3.6.2.2	Electrocardiogram – Overall Interpretation Shift from Baseline (Safety Population)
14.3.6.3	Immunogenicity Analysis (Safety Population)
FIGURES	**EFFICACY DATA**
14.2.1.1	Mean Percentage Change Total IgG by Visit (PD Population)
14.2.1.2	Mean Percentage Change IgG1 by Visit (PD Population)
14.2.1.3	Mean Percentage Change IgG2 by Visit (PD Population)
14.2.1.4	Mean Percentage Change IgG3 by Visit (PD Population)
14.2.1.5	Mean Percentage Change IgG4 by Visit (PD Population)
14.2.1.6	Mean Change Anti-TSHR Antibody Level by Visit (PD Population)
14.2.2.1	Mean Change Proptosis by Visit (PD Population)
14.2.3.1	Mean Change Anti-IGF-1R Antibody Level by Visit (PD Population)
14.2.3.2	Mean Pro-inflammatory Cytokines/Chemokines Level by Visit (PD Population)
14.2.3.3	Mean Change Clinical Activity Score (CAS) by Visit (PD Population)
14.2.3.4.1	Mean Change GO-QOL Visual-Functioning Subscale by Visit (PD Population)
14.2.3.4.2	Mean Change GO-QOL Appearance Subscale by Visit (PD Population)
14.2.4.1.1	Mean Serum Concentration Over Time – Linear (PK Population)
14.2.4.1.2	Mean Serum Concentration Over Time – Log-linear (PK Population)
14.2.4.2.1	Individual Serum Concentrations Over Time – Linear (PK Population)
14.2.4.2.2	Individual Serum Concentrations Over Time – Log-linear (PK Population)
14.3.3.1	Mean Albumin by Visit (Safety Population)
14.3.3.2	Mean Triiodothyronine (FT3) by Visit (Safety Population)
14.3.3.3	Mean Thyroxine Free (FT4) by Visit (Safety Population)

Section 16.2: **List of Data Listings**

ICH Listing Number	Listing Title
16.2	**PATIENT DATA LISTINGS**
16.2.1	**Discontinued patients**
16.2.1	Disposition (Enrolled Population)
16.2.2	**Protocol Deviations**
16.2.2	Protocol Deviations (Safety Population)
16.2.3	**Subjects Excluded from the Safety Analysis**
16.2.3	Eligibility Criteria (Enrolled Population)
16.2.4	**Demographic and Baseline Data**
16.2.4.1	Demographic and Baseline Characteristics (Safety Population)
16.2.4.2	Graves' Orbitopathy Status at Baseline (Safety Population)
16.2.4.3	Tobacco Use (Safety Population)
16.2.4.4	Medical History (Safety Population)
16.2.4.5	Thyroid History (Safety Population)
16.2.4.6	Graves' Orbitopathy History (Safety Population)
16.2.4.7	Concomitant Medications (Safety Population)
16.2.4.8	Steroids or Graves' Orbitopathy Treatments During Follow-up (Safety Population)
16.2.4.9	Previous Thyroid Treatments (Safety Population)
16.2.4.10	Current Thyroid Status (Safety Population)
16.2.4.11	Procedures (Safety Population)
16.2.5	Compliance and/or Drug Concentration Data
16.2.5.1	Exposure (Safety Population)
16.2.5.2	Treatment Satisfaction Questionnaire (Safety Population)
16.2.6	**Individual Efficacy Response Data**
16.2.6.1	Total IgG and Subclasses (Safety Population)
15.2.6.2	Anti-TSHR Antibody Levels (Safety Population)
16.2.6.3	Proptosis (Safety Population)
16.2.6.4	Serum RVT-1401 Concentrations (PK Population)
16.2.6.5	Pharmacokinetic Parameters (PK Population)
16.2.6.6	Anti-IGF-1R Antibody Levels (Safety Population)
16.2.6.7	Pro-Inflammatory Cytokines/Chemokines (Safety Population)
16.2.6.8	Receptor Occupancy (Safety Population)
16.2.6.9	Anti-TPO and Anti-thyroglobulin Antibodies (Safety Population)
16.2.6.10	Motility (Safety Population)
16.2.6.11	Clinical Activity Score (Safety Population)
16.2.6.12	Gorman Score for Diplopia (Safety Population)
16.2.6.13	GO-QOL (Safety Population)

ICH Listing Number	Listing Title
16.2.6.14	Computed Tomography (CT) Results (Safety Population)
16.2.6.15	Lid Retraction (Safety Population)
16.2.7	**Adverse Events Listings**
16.2.7.1	Pre-treatment Adverse Events (Safety Population)
16.2.7.2	Treatment-Emergent Adverse Events (Safety Population)
16.2.7.3	Follow-up Period Adverse Events (Safety Population)
16.2.7.4	Serious Adverse Events (Safety Population)
16.2.7.5	Adverse Events Leading to Discontinuation or Interruption of Study Drug (Safety Population)
16.2.7.6	Deaths (Safety Population)
16.2.7.7	Injection Site Reactions (Safety Population)
16.2.7.8	Liver Events (Safety Population)
16.2.7.9	Liver Imaging (Safety Population)
16.2.7.10	Liver Biopsy (Safety Population)
16.2.8	**Laboratory and Other Data**
16.2.8.1	Hematology (Safety Population)
16.2.8.2	Chemistry (Safety Population)
16.2.8.3	Urinalysis (Safety Population)
16.2.8.4	Thyroid Function Tests (Safety Population)
16.2.8.5	Serum Complement (Safety Population)
16.2.8.6	Immunoglobulins (Safety Population)
16.2.8.7	Pregnancy Test (Safety Population)
16.2.8.8	Viral Serology (Safety Population)
16.2.8.9	QuantiFERON-TB Gold (Safety Population)
16.2.9	**Other Safety Data**
16.2.9.1	Vital Signs (Safety Population)
16.2.9.2	Electrocardiogram (Safety Population)
16.2.9.3	Physical Examination (Safety Population)
16.2.9.4	Ophthalmic Examination (Safety Population)
16.2.9.5	RVT-1401 Immunogenicity