Statistical Analysis Plan

Study Title	ASCEND GO2: A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Study of RVT-1401 for the Treatment of Patients with Active, Moderate to Severe Graves'
Study Protocol Number	RVT-1401-2001
Study Protocol Version / Date of Study Protocol	Amendment 2, Version 3.0 / 09-AUG-2019
Sponsor:	Immunovant Sciences GmbH
Document Version / Date	Amendment 1, Version 2.0 / 09-MAY-2022

Version History

Date	Version	Description of Change	Section Affected	Author
12-Mar-2021	1.0	Original version		[redacted]
09-May-2022	2.0	Moved secondary efficacy objectives and endpoints to exploratory and to analyze as exploratory analyses	Introduction 1.1.2 Secondary Objectives 1.1.3 Exploratory Objectives 5.2.2. Secondary Efficacy Endpoints (Included in Safety Analysis) 5.2.3 Exploratory Endpoints 5.2.4. Exploratory Efficacy Endpoints (Included in Safety Analysis) 9.3. Exploratory Efficacy Analyses	[redacted]
		Analyze clinical laboratory evaluations in safety population in addition to modified safety population	10.2 Clinical Laboratory Evaluations (Safety and Modified Safety Population)	
		Added Section 11: Change from protocol	11. Change from protocol	
		Added version history	Version history	

SIGNATURE PAGE

Author:	[redacted]
Title:	[redacted]
Signature:	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 20-May-22 | 09:36 PDT [redacted]
Date:	20-May-22 | 09:36 PDT
Approval:	[redacted]
Title:	[redacted]
Signature	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-May-22 | 09:03 PDT [redacted]
Date:	20-May-22 | 09:03 PDT
Approval:	[redacted]
Title:	[redacted]
Signature	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-May-22 | 11:54 PDT [redacted]
Date:	20-May-22 | 11:54 PDT

TABLE OF CONTENTS

LIST OF TABLES

[redacted]

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
anti-TPO	antithyroperoxidase
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	area under the concentration-time curve from zero to last time
BLQ	below limit of quantitation
CAS	clinical activity score
CI	confidence interval
C_{max}	maximum serum concentration
C_{trough}	concentration at end of dosing interval
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
GO	Graves' ophthalmopathy
GO-QOL	Graves' Ophthalmopathy Quality of Life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGF-1R	insulin-like growth factor receptor
IgG	Total immunoglobulin G
ITT	intent to treat
LOCF	Last observation carried forward
LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
PT	Preferred term
QC	quality control
QTcF	corrected QT interval according to Fridericia's formula
SAP	Statistical analysis plan
SD	standard deviation
SI	International System of Units
TEAE	treatment-emergent adverse event
TFLs	tables, listings, and figures
t_{max}	time to maximum serum concentration
TPO	Thyroperoxidase
TSH	thyroid-stimulating hormone
TSHR	Anti-thyroid stimulating receptors

1. INTRODUCTION

This document outlines the statistical methods to be implemented for the interim analysis of data collected within the scope of Immunovant protocol RVT-1401-2001 Amendment 02: Version 3.0 [ASCEND GO2: A Phase 2b, Multicenter, Randomized, Double-blind,

Placebo-controlled, Study of RVT-1401 for the Treatment of Patients with Active, Moderate to Severe Graves' Ophthalmopathy]. Based upon a composite review and data suggesting a drug-related effect of RVT-1401 on lipids, the study was paused, and an interim analysis is being conducted.

At the time of the pause, 65 subjects were enrolled, with 47 subjects completing 12 weeks on treatment or withdrawing early (1 pregnancy and 1 early termination at Week 5) and an additional 18 subjects were under treatment at the time of the pause.

[redacted] has prepared this SAP. On [redacted] received unblinded data from Immunovant that included subject IDs, treatment assignments, visit, albumin, creatinine, glucose, IgG, TSH, cholesterol/HDL cholesterol ratio, microalbumin/creatinine ratio, granular casts, hyaline casts, non-HDL cholesterol, HDL cholesterol, RBC casts, triglycerides, WBC casts, sex, age, race, ethnicity, and dose start date [redacted] provided Immunovant with listings and descriptive statistics by treatment group and visit, for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. A memorandum describing the unblinding that occurred when the safety signal was identified is filed in the RVT-1401-2001 Trial Master File.

The analyses outlined in this SAP will generally follow the conventions described in the protocol. In instances where the analyses outlined in the SAP differ from those in the protocol, a justification for the difference will be given. This SAP is an expansion of the Safety SAP dated [redacted] and includes all safety and efficacy endpoints and analyses from the Safety SAP. Due to the early termination of this study, efficacy information obtained from this study was limited, thus the SAP has been updated, keeping the primary outcomes related to efficacy and safety, and secondary outcomes related to safety, but analyzing other secondary endpoints as exploratory.

1.1. Study objectives

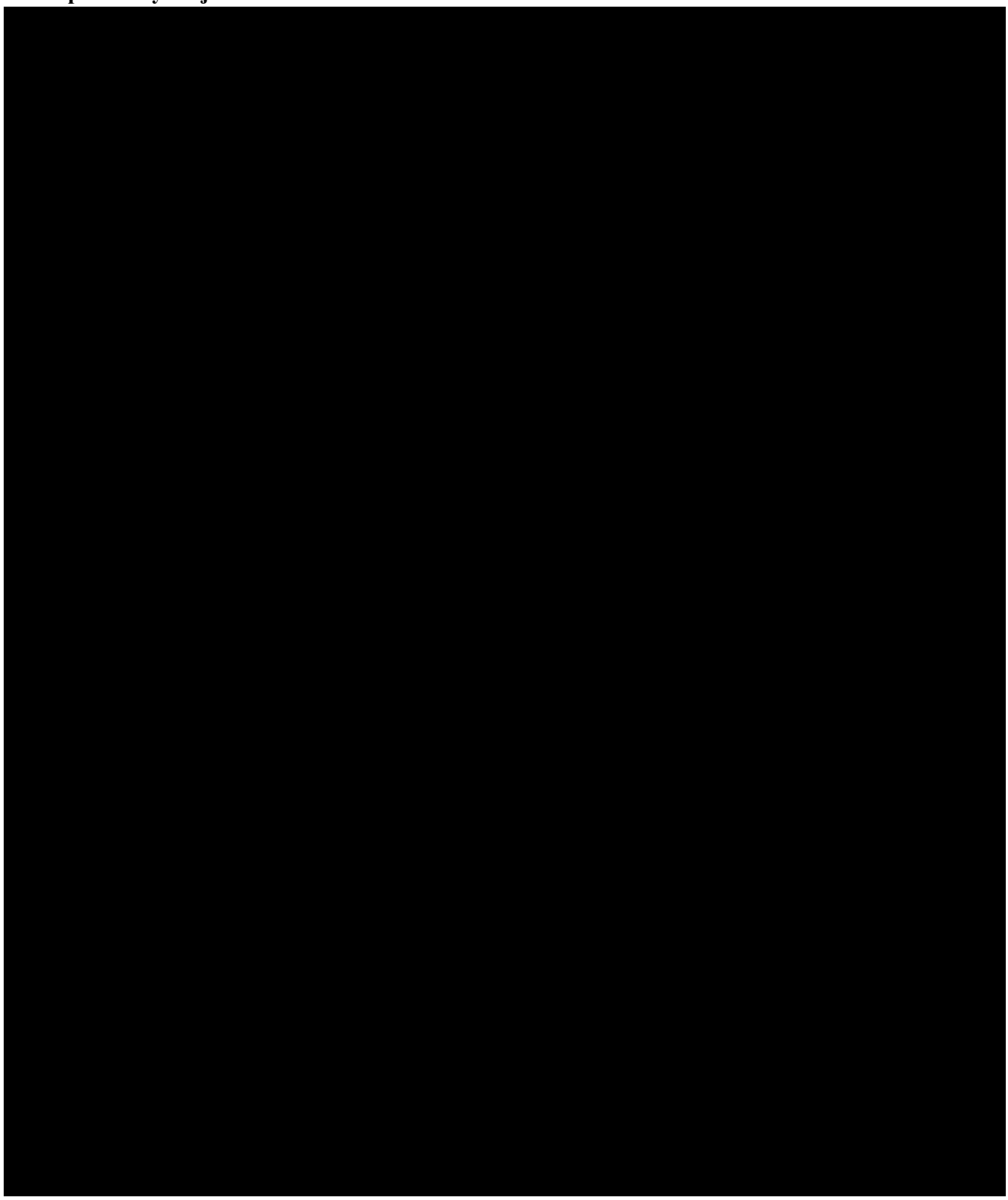
1.1.1. Primary Objective

- To examine the effects of RVT-1401 versus placebo on proptosis responder rate at Week 13
- To assess the safety and tolerability of RVT-1401 in subjects with active, moderate to severe Graves' ophthalmopathy (GO)

1.1.2. Secondary Objectives

- To assess the change in serum levels of anti-thyroid-stimulating hormone receptors (TSHR) antibodies and total immunoglobulin G (IgG) and IgG subclasses (1-4)

1.1.3. Exploratory Objectives



2. STUDY DESIGN AND CONDUCT

This trial is a Phase 2b, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, and tolerability of RVT-1401 in GO subjects.

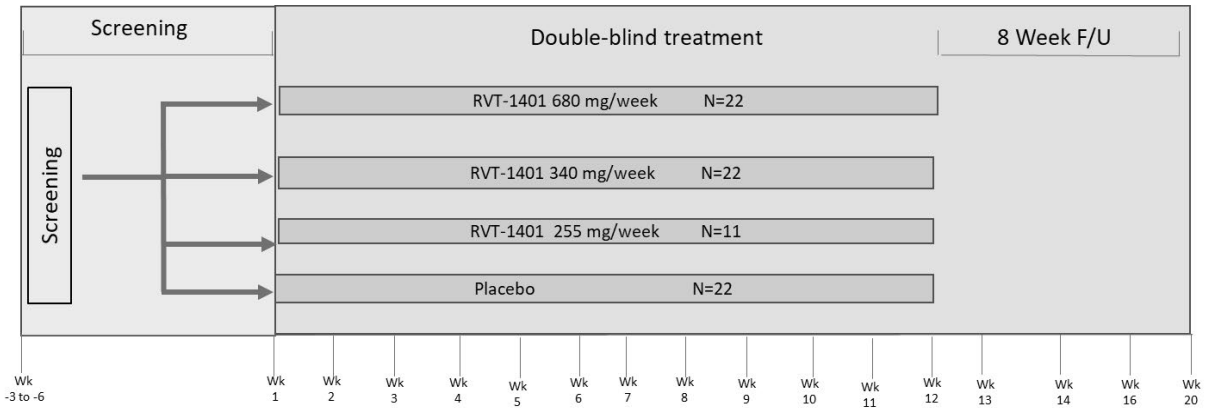
2.1. Treatment groups and duration

Patients were randomized 2:2:1:2 to RVT-1401 (680 mg/week, 340 mg/week, and 255 mg/week) or placebo. Randomization was stratified based on smoking status at the screening visit. Refer to Figure 1 for dosing regimen details. Patients were screened to determine eligibility 3 to 6 weeks prior to first dose/baseline visit.

Once eligibility was confirmed, on Day 1 subjects received RVT-1401 or placebo as weekly subcutaneous injections for 12 weeks. No dose adjustments of RVT-1401 were allowed during the study. See protocol Section 6.8 for additional information on stopping criteria. Each subject was to participate in the study for up to approximately 23 to 26 weeks (i.e., 3–6-week screening period prior to baseline, a 12-week treatment period, and an 8-week follow up period). (See Figure 1.)

To maintain the study blind, all patients received 2 injections by an unblinded designee; subjects receiving the 680 mg dose were to receive 2 injections of RVT-1401, while subjects receiving the 340 mg or the 255 mg dose were to receive 1 injection with RVT-1401 and 1 placebo injection. Patients receiving placebo were to receive 2 injections of placebo.

Figure 1. Study Design



2.2. Schedule of assessments

Following the initial dose at the Baseline Visit (Day 1), study visits occurred weekly throughout the treatment period. Following the final dose at Week 12, visits occurred weekly through Week 14 and then at Week 16 and Week 20. Refer to Table 1 for time and events.

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

Table 1. Schedule of Time and Events

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

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

	Screening[1]	Treatment Period Weekly Visit												Follow-up Period Weekly Visit (Weeks)				Early Withdrawa
Study Timepoint W=Weeks D=Day	**Within 3-6 weeks**	**W1 D1 BL**	**W2 D8**	**W3 D15**	**W4 D22**	**W5 D29**	**W6 D36**	**W7 D43**	**W8 D50**	**W9 D57**	**W10 D64**	**W11 D71**	**W12 D78**	**W13**	**W14**	**W16**	**W20**	
Time Window (days)			**+/-1 day**	**+/-1 day**	**+/-1 day**	**+/-1 day**	**+/-1 day**	**+/-1 day**	**+/-1 day**	**+/-1 da**	**+/-1 day**	**+/-1 day**	**+/-1 day**	**+/-3 days**	**+/-3 days**	**+/-3 days**	**+/-3 days**	
Anti-TSHR (Cell based)[2]		X												X		X	X	X
Anti-IGF-1R[2]		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Anti-IGF-1R (Cell based)[2]		X												X		X	X	X
RVT-1401 PK sampling[2]		X	X	X	X	X	X		X		X		X	X				X
Total IgG[2]	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Immunoglobins (IgG subclasses)[2]		X	X	X	X		X		X		X			X	X	X	X	X
Gene Expression Analysis[2]		X		X			X							X		X	X	X
Pro-Inflammatory Biomarker Multiplex[2]		X		X			X							X		X	X	X
Anti- RVT-1401 antibody[2,4]		X		X		X			X					X			X	X
Nab Assessment[2,4]		X		X		X			X					X			X	X
Drug administration		X	X	X	X	X	X	X	X	X	X	X	X					

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

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

1. Screening can take place over multiple days.
2. Vitals, ECG, safety labs, PK, and PD assessments will be collected pre-dose on dosing days where specified. Microalbumin/creatinine ratio at baseline, Week 12, and Week 20 only (if urine protein abnormal).
3. Pregnancy tests will be collected pre-dose (via urine dipstick) on dosing days where specified. Serum pregnancy tests should be collected at screening, Week 20, and early withdrawal.
4. Subjects with treatment emergent positive results (change from baseline) for anti- RVT-1401 antibody at Week 20 will be requested to return at approximately 6, 9, and 12 months 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 20 visit.
5. Local injection site reactions will be assessed at approximately 10 minutes postdose and subjects will be monitored for 30 minutes postdose.
6. GO assessments will be assessed pre-dose when collected on dosing days.
7. Photographs can be assessed pre or after each dose when performed (for participating sites).
8. The baseline orbital scan should be scheduled once all entry criteria have been met. Scans can be performed within +/- 7 days of the scheduled visit (for participating sites). Note: Week 13 and Week 20 visit scans should only be completed for subjects who are considered proptosis responders at Week 13.
9. See protocol Section 8.3.2 for details of Ophthalmic Examination.

3. ANALYSIS POPULATIONS

3.1. Intention to Treat (ITT)

This population includes all randomized subjects who receive at least one dose of RVT-1401 or placebo and had 1 post-baseline visit.

3.2. Modified Intention to Treat (mITT)

This population includes all randomized subjects who had the opportunity to complete Week 13 (not impacted by the pause before Week 13) and / or early terminated prior to the pause date and received at least 1 dose of RVT-1401 or placebo and had 1 post-baseline visit.

3.3. Safety Population

The safety population includes all randomized subjects who have received at least one dose of either RVT-1401 or placebo. Subjects will be summarized by actual treatment group.

3.4. Modified Safety Population

The modified safety population includes all randomized subjects who had the opportunity to complete the Week 13 visit (not impacted by the pause before Week 13) and/or early terminated prior to the pause date and received at least 1 dose of either RVT-1401 or placebo. This population does not include any participant that was impacted by the pause prior to Week 13.

3.5. Curtailed Safety Population

This population includes all randomized and curtailed (paused) subjects who received at least 1 dose or RVT-1401 or placebo.

4. SAMPLE SIZE AND POWER CALCULATION

The sample size determination as outlined in the protocol is as follows: “For the primary endpoint, proptosis responder rate is defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye. It will be assumed that the placebo arm will have a 5% response rate and the highest dosing arm (680 mg) will have a 50% response rate. Assuming a dropout rate of 15%, approximately 22 subjects are to be randomized to the 680 mg, 340 mg, and placebo groups. Eleven subjects are to be randomized to the 255 mg dose group. Using these assumptions, 19 subjects per arm will be sufficient to detect this treatment group difference with at least approximately 85% power using a 2-sided Fisher’s exact test assuming an alpha of 0.05.”

5. OUTCOME VARIABLE DEFINITIONS

For all efficacy assessments, the study eye is defined as the most severely affected eye in terms of proptosis at the baseline visit. In the event of both eyes being affected to the same extent, then the right eye will be used as the study eye.

5.1. Efficacy Assessments

5.1.1. Clinical Activity Score (CAS)

The CAS measures the classical signs of acute inflammation (pain, redness, swelling, and impaired function) in GO. One point is given for the presence of each of the parameters assessed. At visits where CAS is reported, the 7-item scale will be utilized, and the total score will be collected in the eCRF. The sum of all points defines clinical activity: active GO if the score is ≥ 4.

5.1.2. Gorman Score for Diplopia

Diplopia will be assessed based on 3 grades:

- Grade I - Intermittent diplopia: This is present only when the subject is fatigued,
- Grade II – Inconstant diplopia: This is present only on lateral or upward gaze,
- Grade III – Constant diplopia: This is present on straight and level gaze and is correctable.

5.1.3. Graves' Ophthalmopathy Quality of Life

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:

- Score = $100 \times$ (raw score – 8)/16, if no missing responses
- Score = $100 \times$ (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.

5.2. Efficacy Endpoints

This section presents efficacy and safety endpoints separately.

5.2.1. Primary Efficacy Endpoint

The primary efficacy variable is proptosis responder rate defined as percentage of subjects with at least 2 mm reduction in study eye without deterioration (at least 2 mm increase) in fellow eye at the end of treatment (Week 13).

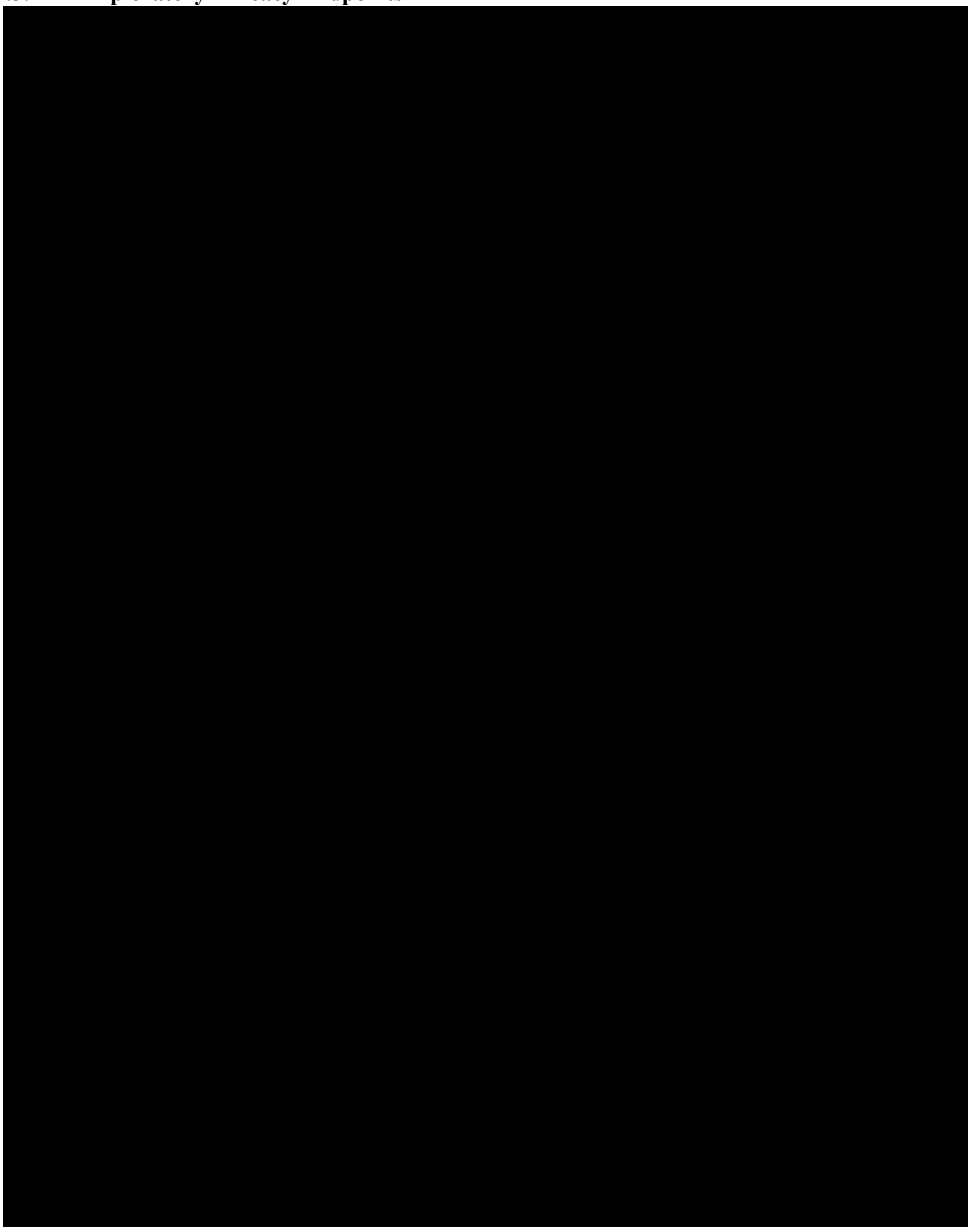
5.2.2. Secondary Efficacy Endpoints (Included in Safety Analysis)

The secondary efficacy endpoints to be included in safety analysis are as follows:

- Percent change from baseline in levels of TSHR antibodies at Week 13
- Percent change from baseline in total immunoglobulin G (IgG) at Week 13

- Percent change from baseline in IgG subclass (1 -4) at Week 13

5.2.3. Exploratory Efficacy Endpoints



5.2.4. Exploratory Efficacy Endpoints (Included in Safety Analysis)

[redacted]

6. VIOLATIONS AND DEVIATIONS

Important protocol deviations will be summarized by randomized treatment group. Sensitivity analyses for the primary and secondary efficacy outcomes will be performed if the deviations have the potential to have a non-trivial impact on the analysis.

7. STATISTICAL ANALYSIS: GENERAL CONVENTIONS

Descriptive statistics will be used to summarize results of protocol RVT-1401-2001. Standard descriptive statistics, such as mean, SD, quartiles, and other relevant percentiles, minimum, and maximum, will be calculated for continuous variables. For discrete variables, descriptive analyses will be based on numbers of participants and related percentages.

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9.4 or higher or other validated software.

The following sections describe the conventions and analyses to be used for the study.

7.1. Baseline

Baseline is the last available assessment prior to time of the first dose unless it is specified otherwise and is identified as Day 1.

7.2. Baseline Age

Subject's age in years is defined as the age at the date of consent.

- Age (year) = Floor ([date of consent – date of birth]/365.25).

7.3. Study Day

Study day is the day relative to the date of randomization. Day 1 is defined as the date of randomization, unless otherwise specified for the calculation of baseline. Assessments that occur after randomization but before the first dose of study drug are considered to occur on study Day 1.

For visits (or events) after randomization, day is calculated as:

Study day = visit (or event) date - date of randomization + 1

For visits (or events) before randomization, day is calculated as:

Study day = visit (or event) date - date of randomization

For listings (such as for adverse events) the quantity days since first (or last dose) is defined as:

days since first (or last dose) = event date – date of first (or last dose) + 1

7.4. Change From Baseline

Change from baseline is calculated using the baseline value (Section 7.1) and the value closest to the target study day, using the rules defined in Section 7.5.

7.5. Visit Windows

Because clinical visits may occur outside protocol-specified windows, instead of relying solely on visit labels in the clinical database, analysis visits and their windows are defined using derived study day. Study day is calculated for each scheduled and unscheduled assessment and compared to the target study day for each analysis visit. Data analysis and summaries are based on the collection date that is closest to the protocol scheduled target study day. Visit windows will be applied for any early withdrawal visit and for any unscheduled visits. All unscheduled and early withdrawal data will be presented in data listings. If two visits are equidistant from the target day, the earlier visit will be used. The early withdrawal and all other visits will be assigned according to Table 2. All presentations will use the analysis visits as defined in Table 2.

Table 2. Classification of Visits

Analysis Visit	Study Day Analysis Window
Week 1 Day 1	Day 1 (Randomization)
Week 2 Day 8 (+/- 1 day)	Day 5 to 11
Week 3 Day 15 (+/- 1 day)	Day 12 to 18
Week 4 Day 22 (+/- 1 day)	Day 19 to Day 25
Week 5 Day 29 (+/- 1 day)	Day 26 to Day 32
Week 6 Day 36 (+/- 1 day)	Day 33 to Day 39
Week 7 Day 43 (+/- 1 day)	Day 40 to Day 46

Analysis Visit	Study Day Analysis Window
Week 8 Day 50 (+/- 1 day)	Day 47 to Day 53
Week 9 Day 57 (+/- 1 day)	Day 54 to Day 60
Week 10 Day 64 (+/- 1 day)	Day 61 to Day 67
Week 11 Day 71 (+/- 1 day)	Day 68 to Day 74
Week 12 Day 78 (+/- 1 day)	Day 75 to Day 81
Week 13 Day 85 (+/- 3 days)	Day 82 to Day 88
Week 14 Day 92 (+/- 3 days)	Day 89 to Day 98
Week 16 Day 106 (+/- 3 days)	Day 99 to Day 119
Week 20 Day 134 (+/- 3 days)	Day 120 to Day 148
2 Weeks Post-Dose (Curtailed)	Post-Dose Day 11-20
4 Weeks Post-Dose (Curtailed)	Post-Dose Day 21-41
8 Weeks Post-Dose (Curtailed)	Post-Dose Day 42-70

7.6. Definition of Time

For visits (or events) that occur on or after randomization, time is calculated in days as:

time = visit (or event) date – date of randomization + 1

For visits (or events) that occur prior to randomization, time is calculated in days as:

time = visit (or event) date – date of randomization

For listings (e.g., for adverse events), the number of days since first (or last) dose is defined as:

days since first (or last) dose = event date – date of first (or last) dose + 1

For summaries that present distribution of time expressed in weeks and months, weeks will be defined as days divided by seven and months as days divided by 30.4.

7.7. Missing and Partial Data

For the analysis of safety variables, only partial dates may be imputed; otherwise, missing data will be treated simply as missing. The algorithms for imputation of partial dates depend upon the parameter.

Adverse event onset

- If onset date is completely missing, date is set to date of first dose.
- If year is present and month and day are missing or year and day are present and month is missing:
    - If year = year of first dose, then set month and day to month and day of first dose.
    - If year < year of first dose, then set month and day to 31 December.
    - If year > year of first dose, then set month and day to 01 January.
- If month and year are present and day is missing:

- If year = year of first dose and
- month = month of first dose, then set day to day of first dose date.
- month < month of first dose, then set day to last day of month.

- For all other cases, set date to date of first dose. Adverse event end date
  - If year is present and month and day are missing or year and day are present and month is missing, set end month and day to 31 December.
  - If month and year are present and day is missing, set the day to last day of the month.
  - If fatal event, date is set to minimum of imputed end date and death date.
  - For all other cases, set date to missing.

Concomitant medication

- If start date is completely missing, start date will not be imputed.
- If start year is present and month and day are missing or year and day are present and month is missing, set start month and day to 01 January.
- If start year and month are present and day is missing, set start day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If end year is present and month and day are missing or year and day are present and month is missing, set end month and day to 31 December.
- If end year and month are present and day is missing, set end day to last day of the month.
- The imputed dates must be logical, ensuring that no end date is after database lock or death or before the start date.

If site queries fail to resolve partial dates for laboratory values and vital signs, including for efficacy, the date is missing and will not be imputed.

Further details regarding the handling of missing values are provided in the sections describing the primary and secondary analyses which will be provided in the final SAP.

8. PARTICIPANT CHARACTERISTICS, DISPOSITION, AND EXPOSURE TO STUDY DRUG

8.1. Demographic and Baseline Characteristics (Itt, Mitt, Safety, and Modified Safety Populations)

Descriptive statistics will be used to describe demographic and baseline characteristics of the participants. Sample size, mean, SD, quartiles, minimum, and maximum will be used to summarize continuous variables, while number and percentages of participants will be used for categorical variables. The following demographic and baseline characteristics, as available, will be summarized: age, gender, ethnicity, race, smoking status, medical/thyroid history, height, body weight, physical examination, ophthalmic examination, dilated indirect ophthalmoscopy, color vision, vital signs, 12-lead electrocardiogram, pregnancy test, viral serology, QuantiFERON® – TB GOLD test result, vaccine titers, urinalysis, blood chemistry and hematology, TSH, Free T3, Free T4, Anti-TSHR, Anti-TSHR (Cell based), Anti-IGF-1R,

Anti-IGF-1R (Cell based), RVT-1401 PK sampling, Total IgG, Immunoglobins (IgG subclasses), gene expression analysis, pro-inflammatory biomarker multiplex, Anti-RVT-1401 antibody, Nab assessment, clinical activity score (CAS), proptosis, motility, lid retraction, Gorman Score for Diplopia, GO-QOL, external photographs, orbital CT scan, Methimazole (or other anti- thyroid medication) dose, adverse events, injection site reactions, and concomitant medication.

Age in years will be calculated as the integer portion of the following: ([date of randomization - date of birth] + 1) / 365.25.

Unless otherwise stated, percentages will be calculated relative to the number of participants in the safety population. All demographic data will be listed.

Summary tables will describe baseline ocular characteristics for each treatment group.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized, for each treatment group, by system organ class (SOC) and preferred term (PT). Medical history may also be listed for all participants in the safety and modified safety populations. Medical history may be sorted by treatment group and descending overall frequency, by SOC and PT, in the summary tables. Medical history data may be sorted by treatment group, participant number, start date, SOC, and PT.

8.2. Participant Disposition (Itt, Mitt, Safety, Modified Safety, and Curtailed Safety Populations)

The study has a single timepoint of evaluation for the primary outcome: Week 13. The disposition of all participants will be listed and summarized by treatment group. Tables will present the number and percentage of participants who were screened, randomized, received treatment, or withdrew from the study early by treatment group and overall. For participants who were randomized but withdrew from the study early, the number and percentage withdrawing by reason will be presented by treatment group and overall.

Participants may discontinue treatment before completion of the study for any number of reasons. Discontinuation will be summarized based on the reasons listed in the CRF. In addition, any participant may be discontinued for any sound medical reason at the discretion of the Investigator.

8.3. Treatment Exposure (Safety and Modified Safety Populations)

Administration of RVT-1401 will be summarized descriptively by randomized treatment group for each protocol-specified injection.

The presentations will also show how many participants have discontinued study treatment and the reason based on the following stopping criteria outlined in the protocol: liver chemistry, liver test abnormalities, QTc criteria, albumin monitoring criteria, and other individual stopping criteria.

For each week during the treatment period (Week 1 through Week 12), the distribution of number of injections will be summarized by treatment group.

8.4. Concomitant Medications and Therapies (Safety and Modified Safety Populations)

Information on concomitant medication may be summarized by generic name as reported on the concomitant medication CRF. Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD).

The number and percentage of participants who took at least one drug within each generic type will be presented. Participants will only be counted once if they are taking the same generic medication more than once.

9. EFFICACY ANALYSES

All significance levels will be reported as nominal. For all efficacy analyses, the stratification factor of smoking status is incorporated into the analysis. This approach differs from that outlined in the protocol which did not include smoking status in the models described for efficacy analyses.

9.1. Handling of Missing Data in Efficacy Analyses

For sensitivity analyses of the primary efficacy endpoint of proptosis responder rate, the following approaches for missing data will be used:

- Last observation carried forward (LOCF), the most recent measure of proptosis will be used to determine if the subject is a responder.
- Any missing outcome value will be assumed to be a non-responder.

All other analyses will use the observed data and missing values will not be imputed.

9.2. Primary Efficacy Analysis

For the primary analysis each of the three dose groups will be compared to placebo with the hypotheses stated as described below.

680 mg dose group

The null and alternative hypotheses for this group are as follows:

- H_{01}: the proportion of proptosis responders in the 680 mg group is equal to that of the placebo group
- H_{a1}: The proportion of proptosis responders in the 680 mg group is not equal to that of the placebo group

340 mg dose group

The null and alternative hypotheses for this group are as follows:

- H_{02}: the proportion of proptosis responders in the 340 mg group is equal to that of the placebo group
- H_{a2}: The proportion of proptosis responders in the 340 mg group is not equal to that of the placebo group

255 mg dose group

The null and alternative hypotheses for this group are as follows:

- H_{03}: the proportion of proptosis responders in the 255 mg group is equal to that of the placebo group
- H_{a3}: The proportion of proptosis responders in the 255 mg group is not equal to that of the placebo group

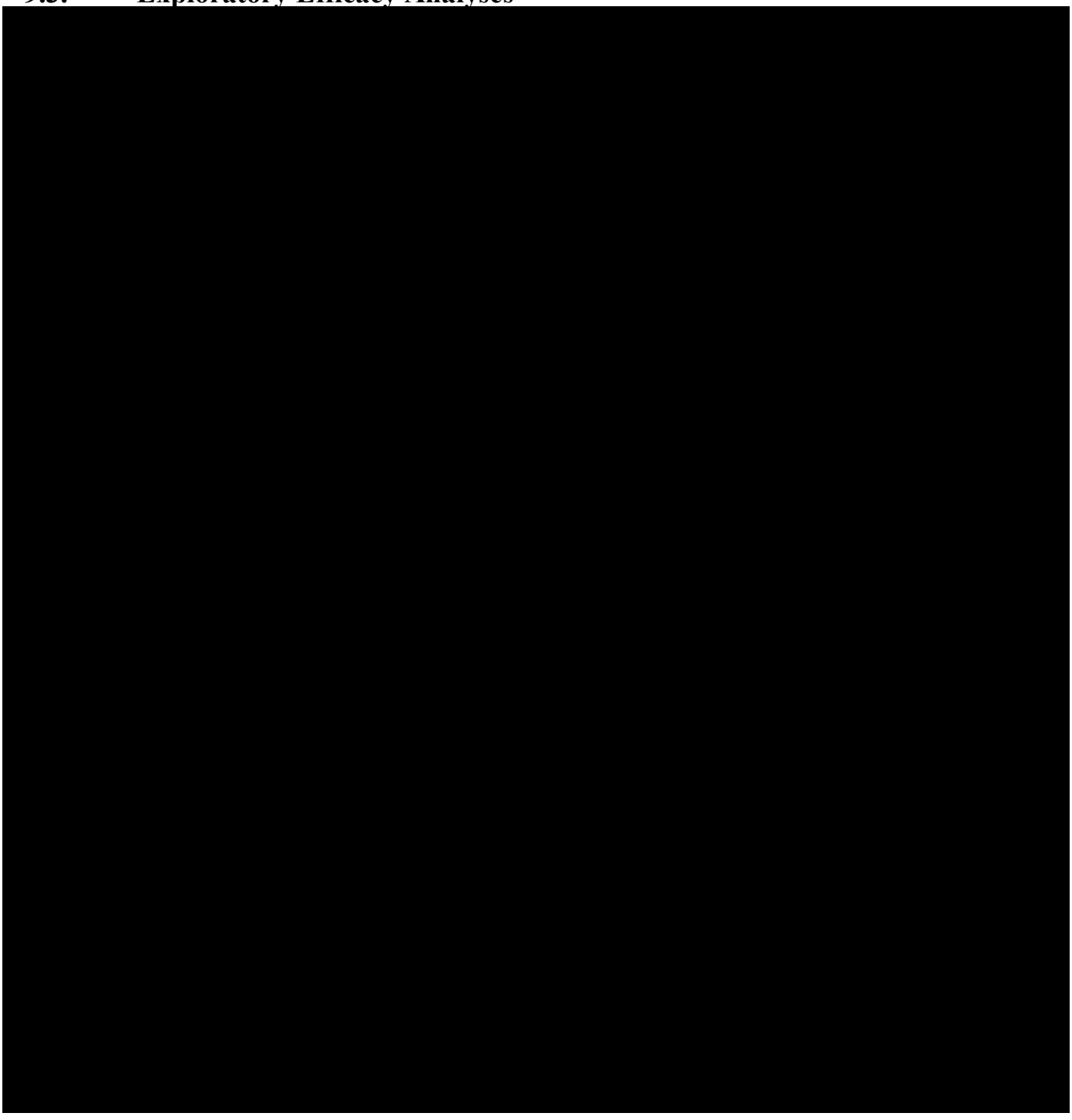
Each dose group will be compared to placebo using a stratified Mantel-Haenszel test with smoking status as the stratification factor. The details of this analysis and pseudo SAS code are provided in Section 12.1. For the primary analysis, the data will be analyzed as observed and missing values will not be imputed.

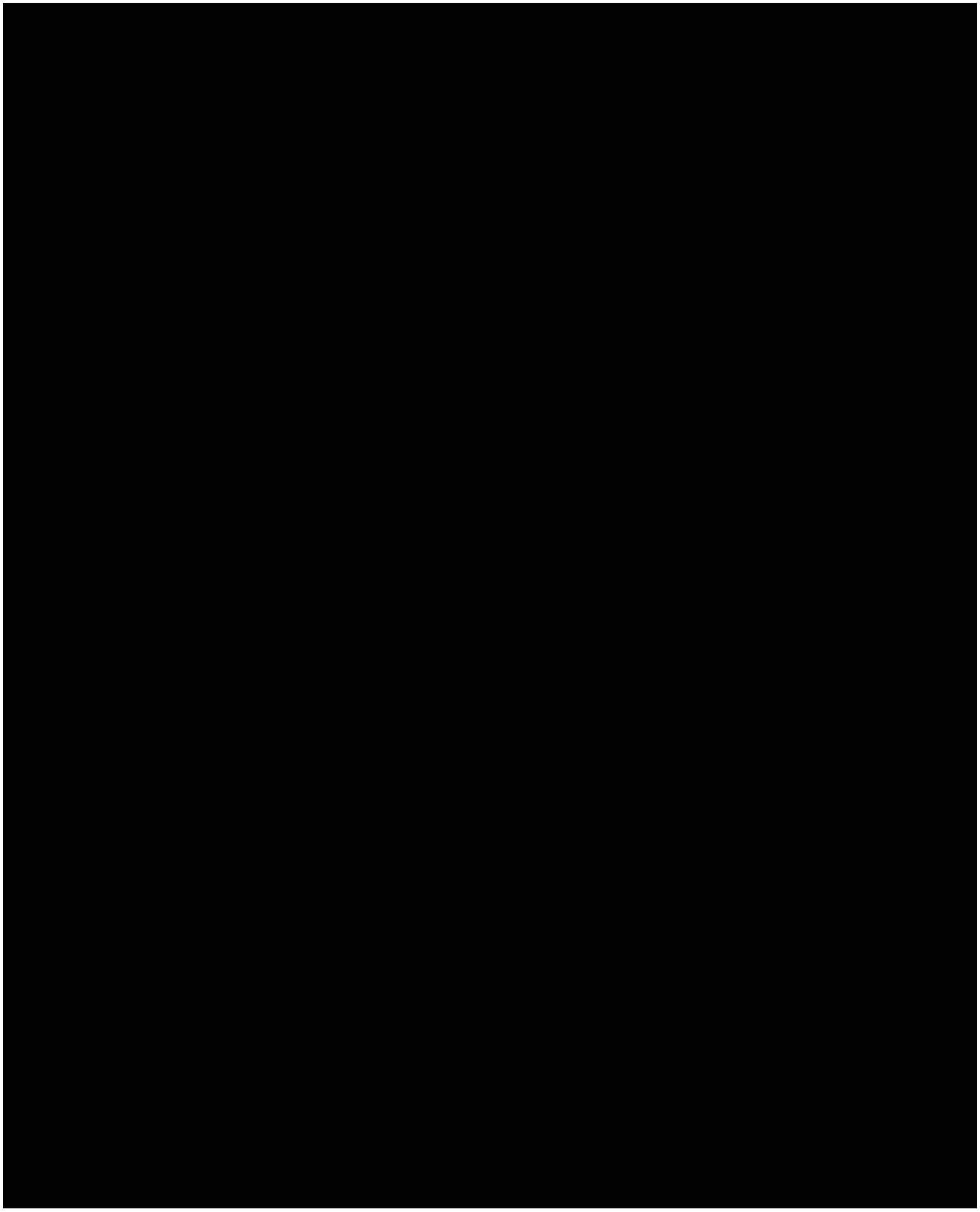
9.2.1. Sensitivity Analyses of the Primary Efficacy Analysis

The following analyses will be conducted as sensitivity analyses supporting the primary analysis:

- The primary analysis will be repeated using LOCF to replace missing values.
- The primary analysis will be repeated treating all missing values as nonresponders. All primary analyses will be presented using a forest plot.

9.3. Exploratory Efficacy Analyses





10. SAFETY ANALYSES

Listings will be provided for all subjects in the curtailed safety population.

10.1. Adverse Events (Safety and Modified Safety Populations)

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are defined as those AEs satisfying the following:

- the AE started on or after the date and time of the first dose of study drug or
- the AE started on or before 30 days after the last dose of study drug or
- the AE had no recorded start date and the stop date is not before the first dose of study drug.
- If it cannot be determined whether the AE is treatment-emergent due to a partial onset date, the date will be imputed following the rules described in Section 7.7. Verbatim terms in the eCRFs will be coded to the lowest level term; reporting will include the preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

A treatment-emergent adverse event (TEAE) is one that was not present at or before the first dose of study medication in each period or represents the exacerbation of a pre-existing condition.

The safety outputs will include descriptions of the following:

- Patients with TEAEs by Preferred Term (PT)
- Patients with TEAEs by system organ class (SOC) and PT within SOC
- Patients with any severe TEAE
- Patients with any serious TEAE
- Patients with any related TEAE
- Patients with TEAEs that result in termination from the study

Adverse events will be summarized by treatment group. When summarizing TEAEs, each subject will be counted only once within a system organ class or preferred term. Summaries that are displayed by system organ class and preferred terms will include all treatment arms and be ordered by descending order of incidence of system organ class and preferred term within each system organ class under treatment group RVT-1401 680 mg/week.

The following summaries will be presented for both the safety and modified safety populations:

- Overall summary of TEAEs that contain an overview of each item below.
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. Adverse events with missing severity will be categorized as “missing” for tabular summaries.

- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). Related AEs are those reported as "Probably Related" or "Possibly Related" and unrelated AEs are those reported as "Not Related." At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of severity Grade 3 or higher, treatment-related TEAEs by MedDRA system organ class, preferred term.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to study discontinuation.

All summarized AEs and serious AEs will be listed by subject for the safety population with a column indicating membership in the modified safety population. TEAEs considered an injection site reaction or a liver event will be identified in the AE and serious AE data listings.A listing of subjects who died will be presented for the safety population. Subject deaths will be determined from end of study data (where reason for discontinuation is death) and AE data (where Severity is "Grade 5 / Death" and outcome is "Fatal").

An AE leading to discontinuation is defined as any AE with an action code of "Drug Withdrawn" or collected as a primary reason for study completion discontinuation. A by-subject listing of AEs leading to discontinuation will be provided.

A listing of all TEAEs and AEs in the curtailed safety population will also be presented.

10.2. Clinical Laboratory Evaluations (Safety and Modified Safety Population)

For each of the evaluations described below descriptive statistics will be provided. The descriptive analyses will include a summary of the raw values and the change from baseline (mean, median, standard deviation, min, max, IQ range). Boxplots of the raw values and the change from baseline over time will also be presented.

A set of laboratory listings will be created for the safety population with a column indicating the subjects that also belong to the curtailed safety population.

Only central laboratory values will be used for these analyses.

10.2.1. Hematology

The hematology parameters, measured at baseline, Week 2, Week 3, Week 4, Week 5, Week 6, Week 8, Week 10, Week 12, Week 14, and Week 20. The parameters that will be included are as follows:

- Platelet count
- Red blood cell indices: red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, hemoglobin, hematocrit

- Automated white blood cell differential: white blood cell count (absolute), neutrophils, lymphocytes, monocytes, eosinophils, basophils, Hemoglobin A1c (only on Day 1, Week 12 and Week 20)

10.2.2. Clinical Chemistry

The clinical chemistry parameters, measured at baseline, Week 2, Week 3, Week 4, Week 5, Week 6, Week 8, Week 10, Week 12, Week 14, and Week 20. The parameters that will be included are as follows:

- Liver function: aspartate aminotransferase, total and direct bilirubin, Alanine aminotransferase, γ-Glutamyltransferase, alkaline phosphatase
- Kidney function: creatinine, blood urea nitrogen, uric acid, total protein, total carbon dioxide
- Other: Serum complement (CH50, C3), total IgG, Immunoglobulin M, Immunoglobulin A, fasting glucose at baseline and Week 12, albumin, albumin grade
- Electrolytes: potassium, chloride, sodium, calcium (total and corrected)

10.2.3. Lipid Panel

The lipid panel is measured at baseline, Week 12, and Week 20. The values to be presented include the following:

- Total cholesterol, HDL cholesterol, LDL cholesterol (calculated using Martin- Hopkins equation), non-HDL cholesterol (calculated)
- Triglycerides
- Total cholesterol/HDL cholesterol ratio
- LDL / HDL cholesterol ratio

10.2.4. Additional Analyses of Laboratory Parameters

Additional analyses in the modified safety population will include the following:

Lipid Parameters

- Tables of percentage increases in all lipid values by treatment group. For each of the lipid measures tables will be constructed presenting the number and percentage of subjects with increases ≥ 10%, ≥ 20%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 80%, ≥100%.
- Lipid parameters will be classified based on the Adult Treatment Panel Guidelines (ATP) as provided in Table 3. Frequency distributions and shift tables of these classifications will be presented by treatment group.
- Total cholesterol and triglycerides will be classified based on the CTCAE Version 5 as outlined in Table 4. Frequency distributions and shift tables of these classifications will be presented by treatment group.
- Boxplots and tables of the percent change from baseline in lipid parameters will be presented by treatment group over time.
- Spaghetti plots of all lipid values will be presented by treatment group.

Albumin

- Boxplots and tables of the percent change from baseline in albumin will be presented by treatment group over time.
- Plots of mean values and standard deviation of albumin over time will be presented by treatment group.
- Frequency distributions of values meeting the following thresholds will be presented by time and treatment group: ≤ 2.5, ≤ 2.7, ≤3.0, ≤ 3.2, and ≤ 3.5.
- Spaghetti plots of albumin will be presented by treatment group.
- Scatter plots of albumin versus LDL and total cholesterol will be presented by treatment group.

IgG

- Boxplots and tables of the percent change from baseline in total IgG will be presented by treatment group over time.
- Plots of mean values and standard deviation of total IgG over time will be presented by treatment group.
- Scatter plots of total IgG versus LDL cholesterol and total IgG versus albumin will be presented by treatment group.
- Evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be presented by treatment group.

Anti-TSHR antibodies

- Plots of mean values and standard deviation of anti-TSHR antibodies over time will be presented by treatment group.
- Plots of change from baseline values and standard deviation of anti-TSHR antibodies over time will be presented by treatment group.

- Plots of percent change from baseline and standard deviation of anti-TSHR antibodies over time will be presented by treatment group.

Additional analyses

Additional analyses in the curtailed safety population will include the following:

- Spaghetti plots of all lipid values will be presented by treatment group.
- Spaghetti plots of albumin values will be presented by treatment group.

IgG and anti-TSHR antibodies will also be analyzed using an ANCOVA model with the percent change from baseline as the outcome and treatment group and smoking stratum as covariates in ITT population. The details of this analysis are presented in Section 12.3.

Table 3. ATP Classification of Lipid Parameters

Lipid parameter	Value	Classification
Total	< 200 200 – 239 ≥ 240	Desirable Borderline high High
LDL cholesterol	< 100 100-129 130-159 160-189 ≥ 190	Optimal Near optimal/above optimal Borderline high High Very high
HDL	< 40 ≥ 60	Low High
Triglycerides	< 150 150 – 199 200 – 499 ≥ 500	Normal Borderline high High Very high

Table 4. CTCAE Classification of Total Cholesterol and Triglyceride

Parameter	Value	Grade
Cholesterol high	>300 mg/dL	1
	>300 - 400 mg/dL	2
	>400 - 500 mg/dL	3
	> 500 mg/dL	4
Hypertriglyceridemia	150 mg/dL – 300 mg/dL	1
	>300 mg/dL - 500 mg/dL	2
	>500 mg/dL - 1000 mg/dL	3
	>1000 mg/dL	4

10.2.5. Thyroid Function Tests

The following thyroid function tests, measured at baseline, Week 2, Week 3, Week 4, Week 5, Week 6, Week 8, Week 10, Week 13, Week 16, and Week 20 will be presented descriptively:

- TSH, Free T3, Free T4.

10.2.6. Additional Analyses of Thyroid Function Tests

Additional analyses of thyroid function in the modified safety population include the following:

- Plots of mean values of TSH, Free T3, and Free T4 over time by treatment group.
- Scatter plots of the Week 10 values of thyroid function (TSH, Free T3, Free T4) versus the Week 12 values of LDL cholesterol by treatment group.

10.2.7. Urinalysis

The following urinalysis measures collected at baseline, Week 2, Week 3, Week 4, Week 5, Week 6, Week 8, Week 10, Week 12, Week 14, and Week 20 will be presented descriptively:

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

10.3. Physical Examination (Safety Population)

Abnormalities identified on the physical examination will be presented as listings for the safety population.

10.4. 12-Lead Electrocardiogram (Safety Population)

Electrocardiogram (ECG) results (heart rate, PR, QRS, QT, and corrected QT interval by Fridericia (QTcF) will be summarized descriptively. 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 postbaseline (normal, abnormal and clinically significant, or abnormal but not clinically significant) at each scheduled postbaseline visit will be provided by treatment group.

Summaries of ECG data will be provided for the safety population. ECG data will also be listed.

10.5. Ophthalmic Examination (Safety Population)

The ophthalmic exams, occurring at baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, and Week 20 consisted of the following assessments:

- Best corrected visual acuity (Snellen chart)
- Automated perimetry to include a minimum of 24 degrees of visual field
- Pupil assessment to include swinging flashlight test for afferent pupillary defect
- Anterior segment slit lamp exam

- Intraocular pressure
- Posterior exam including dilated indirect ophthalmoscopy with optic disc and retinal/choroid assessment of posterior pole as well as periphery
- Color vision (Ishihara plates or equivalent)

Descriptive statistics of baseline, post-baseline, and change from baseline values, as available, for intraocular pressure will be provided by eye and treatment group for all scheduled time points. An additional summary of the results by eye and treatment group for the cornea (No Abnormalities, Keratopathy, Ulcer, Other), lens (Clear, Cataract), disc (Normal, Atrophic, Swollen), choroidal folds (Yes, No), and evidence of optic neuropathy assessments (Yes, No, Equivocal) will be presented.

10.6. Vital Signs (Safety Population)

Vital signs (temperature [°C], systolic blood pressure [mmHg], diastolic blood pressure [mm Hg], pulse rate [bpm]) will be summarized descriptively. Descriptive statistics of baseline, postbaseline, and change from baseline values for each parameter will be presented by treatment group for all scheduled time points. Vital sign values will also be listed.

10.7. Injection Site Reactions (Safety and Modified Safety Population)

The injection sites were monitored for pain, tenderness, erythema and swelling. Each injection site reaction was categorized as mild, moderate, or severe or medically significant using the grading scheme provided in the protocol.

11. CHANGE FROM PROTOCOL

Due to the early termination of this study, efficacy information obtained from this study was limited, thus the SAP has been updated, keeping the primary outcomes related to efficacy and safety, and secondary outcomes related to safety, but analyzing other secondary endpoints as exploratory.

12. APPENDIX

This appendix contains details for programming the stratified Mantel-Haenszel test and the MMRM. This code is pseudo code and may be modified at the time of analysis.

12.1. Stratified Mantel-Haenszel test

The stratified Mantel-Haenszel test will be applied to obtain a 95% confidence interval and an estimate of the risk difference between each of the dose groups and placebo.

Table 5 contains pseudo SAS code with the variables defined as follows:

- DOSE – treatment group assignment with dose of 680 mg, 340 mg, 255 mg, or placebo
- VISITNUM – denotes time of measurement (Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 13)
- SMOKE_STRAT – smoking stratum

[redacted]

[redacted]

12.2. MMRM Analysis

The MMRM models that are described for each of the efficacy endpoints will be very similar and differ only with respect to the number of timepoints included in an analysis. The within-participant correlations in the outcome over time will be modeled using an unstructured covariance structure applying the Kenward-Roger approximation for computing the denominator degrees of freedom for the tests of fixed effects. Because an unstructured covariance structure will be used with a REPEATED statement, all effects will be assigned the between-participant degrees of freedom to provide better approximations to the relevant sampling distributions.

In the unlikely situation that this model does not converge, the following strategy will be adopted:

1. First, a Toeplitz structure will be used. This method assumes that measurements from observations taken closer together in time are more highly correlated than measurements taken farther apart in time.
2. If the model using a Toeplitz structure does not converge, the model will use an autoregressive model of order 1 (AR[1]) structure, which makes the same assumption as the Toeplitz structure but is mathematically more restrictive.
3. Finally, if the model using the AR(1) structure does not converge, the model will use a compound symmetry structure, which assumes equal correlation for a participant's measurements regardless of how far apart in time they were taken.

The difference in the change from baseline is computed for each of the models through the use of an estimate or lsmeans statement.

12.2.1. MMRM code for proptosis and CAS

Table 6 contains pseudo SAS code with the variables defined as follows:

- DOSE – treatment group assignment with dose of 680 mg, 340 mg, 255 mg, and placebo with dose being equal to 1 for 680 mg, 2 for 340 mg, 3 for 255 mg, and 4 for placebo
- VISITNUM – denotes time of measurement (Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 13, Week 14, Week 16, Week 20)
- SMOKE_STRAT – smoking stratum• BASE_VAR – denotes the baseline value of the variable that is being modeled
- CHG – change from baseline in variable being modeled
- VISITNUM*DOSE – interaction of visit and dose group

The LSMEANS statement will be provide information on all possible differences for DOSE*VISITNUM. The ESTIMATE statements provide information for the specific comparison and should be checked against the LSMEANS output to ensure that the correct values were extracted.

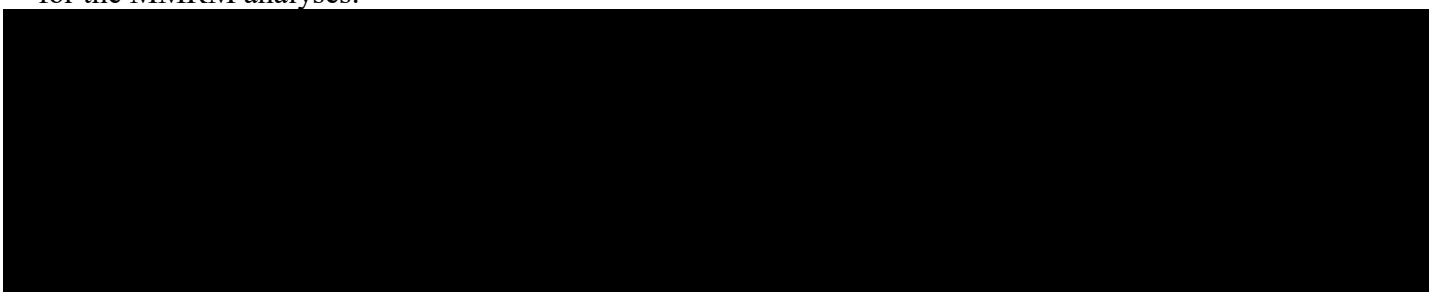
The code in Table 6 will be used for the MMRM analyses proposed in this SAP for proptosis and CAS with appropriate modifications made for the variable names and number of repeated measures. Additional example code will be provided for other endpoints. Note that the estimate statements provide the mean differences and associated significance levels for Week 13. All values can be found in the lsmeans output. The Week 13 values should be checked against those in the lsmeans output as well.

12.2.2. MMRM Code for Other Endpoints

The remaining endpoints have differing numbers of repeated measures. To obtain the mean values and associated test statistics at the timepoints of interest, the following code can be used. Note that all values can be obtained from the output of the lsmeans statement. Table 7 contains the generic code for a MMRM model with CHG denoting the change from baseline in the outcome of interest. All other variables are described in Section 12.2.1.

12.3. ANCOVA Analysis

For endpoints using ANCOVA the model will include the change from baseline as the outcome, the baseline value of the outcome, smoking stratum, and dose group as covariates. All variables are defined as for the MMRM analyses.



DocuSign

Certificate Of Completion

Envelope Id: DD023ACF33D04C479686745E6F0F7472
Status: Completed
Subject: Please DocuSign: IMV-2001_Full_Statistical_Analysis_Plan draft_v1.2_final_MMS_20May2022.docx
Source Envelope:
Document Pages: 41
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)
IP Address: [redacted]

Record Tracking

Status: Original
5/20/2022 7:37:11 AM
Holder [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signed by link sent to [redacted] Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/20/2022 7:48:05 AM Viewed: 5/20/2022 9:03:07 AM Signed: 5/20/2022 9:03:24 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Immunovant Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signed by link sent to [redacted] Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 5/20/2022 9:03:33 AM Viewed: 5/20/2022 9:35:51 AM Signed: 5/20/2022 9:36:40 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 5/20/2022 9:36:53 AM Viewed: 5/20/2022 11:54:16 AM Signed: 5/20/2022 11:54:36 AM
Immunovant Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signed by link sent to [redacted] Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	
Electronic Record and Signature Disclosure: Accepted: 8/12/2021 6:15:18 AM ID: 1ff0aca2-79b9-439e-b7fd-c714265caa3d		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/20/2022 7:48:05 AM
Certified Delivered	Security Checked	5/20/2022 11:54:16 AM
Signing Complete	Security Checked	5/20/2022 11:54:36 AM
Completed	Security Checked	5/20/2022 11:54:36 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, SHI OBO Immunovant, Inc. - GxP Compliant Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact SHI OBO Immunovant, Inc. - GxP Compliant Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

To advise SHI OBO Immunovant, Inc. - GxP Compliant Part 11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from SHI OBO Immunovant, Inc. - GxP Compliant Part 11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to [redacted] and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with SHI OBO Immunovant, Inc. - GxP Compliant Part 11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. Reason for withdrawing consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify SHI OBO Immunovant, Inc. - GxP Compliant Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by SHI OBO Immunovant, Inc. - GxP Compliant Part 11 during the course of your relationship with SHI OBO Immunovant, Inc. - GxP Compliant Part 11.