Statistical Analysis Plan

SPONSOR:	Viridian Therapeutics, Inc.
PROTOCOL TITLE:	A randomized, double-masked, placebo-controlled safety, tolerability, and efficacy study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants with chronic thyroid eye disease (TED)
PROTOCOL VERSION:	Version 5.1, Amendment date: 27NOV2024
STUDY CODE:	VRDN-001-301 (THRIVE-2)
VERSION:	V1.0
DATE:	03DEC2024

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SIGNATURE PAGE

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Viridian Therapeutics, Inc.

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
ADA	Anti-drug antibodies
AE	Adverse Events
ATC	Anatomical Therapeutical Chemical
CAS	Clinical Activity Score
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOM	Extraocular Muscle
EXI	Exophthalmometer Imputation
GEE	Generalized Estimating Equation
GLM	General Linear Model
GO-QoL	Graves' Orbitopathy-Quality of Life
HV	Healthy Volunteer
IOP	Intraocular Pressure
ITT	Intent-To-Treat
[redacted]	[redacted]
MCMC	Markov Chain Monte Carlo
MI	Multiple Imputation
mITT	Modified Intent-To-Treat
MNAR	Missing Not at Random
OC	Observed cases
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TEAESI	TEAE Of Special Interest
TED	Thyroid Eye Disease
VA	Visual Acuity
VAS	Visual Analogue Scale

2. Introduction

This Statistical Analysis Plan (SAP) was written for the clinical trial VRDN-001-301, pivotal portion (THRIVE-2). The ICH guideline E3 "Structure and Content of Clinical Study Reports", E9 "Statistical principles in clinical trials" and E9 (R1) "Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles in clinical trials" was used as a guide to the writing of the plan. The SAP was based on version 5.1 of the protocol dated 27NOV2024.

This plan may be modified until time of Week 15 database lock and unmasking of the biostatistics team. Any deviations from the analysis plan will be documented as such in the study report.

Separate plans are in place for pharmacokinetic and pharmacodynamic analyses that may occur.

3. Study Objectives, Endpoints and Estimands

3.1 Study Objectives and Endpoints

The objectives of the study are to establish the safety, tolerability and efficacy of VRDN-001 when given as 5 intravenous infusions of 10 mg/kg compared to placebo in participants with chronic TED. For statistical analysis, the most proptotic eye at the last assessment performed prior to the Day 1 IV infusion will be as determined by the given assessment modality (endpoints assessed by MRI/CT will determine most proptotic eye by MRI/CT and endpoints assessed by exophthalmometer will determine most proptotic eye by exophthalmometer measurement).

If a measurement modality is not specified for a proptosis endpoint, then it is understood that the measurement tool is MRI/CT.

3.1.1 Primary Efficacy Endpoint

3.1.1.1 USA, Canada, and China

Proptosis Responder Rate in the most proptotic eye (i.e., reduction of proptosis of ≥ 2 mm from baseline [without a corresponding increase of ≥ 2 mm in the other eye]) as measured by exophthalmometer at 3 weeks post the fifth infusion (i.e., Week 15).

3.1.1.2 Australia, Israel, European Union, Turkey and United Kingdom

Overall Responder Rate comprising Proptosis Responder Rate in the most proptotic eye (i.e., reduction of proptosis of ≥ 2 mm from baseline [without a corresponding increase of ≥ 2 mm in the other eye]) at 3 weeks post the fifth infusion (i.e., Week 15) and Clinical Activity Responder Rate in the most proptotic eye (i.e., no worsening in CAS from baseline [without a corresponding increase of ≥ 2 points in the other eye]) at 3 weeks post the fifth infusion (i.e., Week 15).

3.1.2 Key Secondary Endpoints

3.1.2.1 USA, Canada, and China

- Change from baseline in proptosis in the most proptotic eye as measured by exophthalmometer at Week 15
- Proptosis Responder Rate in the most proptotic eye at Week 15
- Change from baseline in proptosis in the most proptotic eye at Week 15
- Clinical Activity Responder Rate in the most proptotic eye as measured by exophthalmometer at Week 15
- Overall Responder Rate comprised of proptosis responder rate in the most proptotic eye as measured by exophthalmometer at Week 15 and Clinical Activity Responder rate in the most proptotic eye as measured by exophthalmometer at Week 15
- Diplopia Responder Rate at Week 15
- Diplopia Resolution Rate at Week 15

3.1.2.2 Australia, Israel, European Union, Turkey and United Kingdom

- Change from baseline in proptosis for the most proptotic eye at Week 15
- Proptosis Responder Rate in the most proptotic eye as measured by exophthalmometer at Week 15
- Change from baseline in proptosis in the most proptotic eye as measured by exophthalmometer at Week 15
- Diplopia Responder Rate at Week 15
- Diplopia Resolution Rate at Week 15

3.1.3 Exploratory Endpoints for all regions

Proptosis related exploratory endpoints will be assessed by both exophthalmometer and MRI/CT measurements in the most proptotic and other eye as determined by the corresponding measurement modality, except time to first proptosis response which will only be assessed by exophthalmometer.

Other exploratory endpoints involving assessments by eye will be analyzed for most proptotic eye and other eye as determined by exophthalmometer and for most proptotic eye and other eye as determined by MRI/CT.

- Proptosis Responder Rate in the most proptotic eye at by visit
- Durability of Proptosis Response in the most proptotic eye at Weeks 24, 36 and 52
- Proptosis Responder Rate in the other eye by visit
- Time to First Proptosis Response in the most proptotic eye
- Clinical Activity Responder Rate in the most proptotic eye by visit
- Clinical Activity Responder Rate in the other eye by visit
- Overall Responder Rate in the most proptotic eye by visit
- Overall Responder Rate in the other eye by visit

- Diplopia Responder Rate by visit
- Diplopia Resolution Rate by visit
- Change from baseline in CAS in the most proptotic eye at Week 15 for those with a baseline CAS >=3
- Change from baseline in CAS in the other eye at Week 15 for those with a baseline CAS >=3
- Proportion of participants with a CAS of zero or one in the most proptotic eye at Week 15 for those with a baseline CAS >=3
- Proportion of participants with a CAS of zero or one in the other eye at Week 15 for those with a baseline CAS >=3
- Proptosis responder rate in the most proptotic eye in participants with baseline CAS of 0 or 1 by visit
- Proptosis responder rate in the other eye in participants with baseline CAS of 0 or 1 by visit
- Proptosis responder rate in the most proptotic eye in participants with baseline CAS of 0, 1, or 2 by visit
- Proptosis responder rate in the other eye in participants with baseline CAS of 0, 1, or 2 by visit
- Proptosis responder rate in the most proptotic eye in participants with baseline CAS of ≥ 3 by visit
- Proptosis responder rate in the other eye in participants with baseline CAS of ≥ 3 by visit
- Change from baseline in the most proptotic eye and other eye where applicable in the following parameters by visit :
    - Proptosis
    - CAS
    - Extraocular muscle volume by MRI/CT
    - Orbital fat volume by MRI/CT
    - Manual measurement of lid retraction by exophthalmometer
    - Graves' Orbitopathy-Quality of Life (GO-QoL) combined score
    - GO-QoL activity subscale
    - GO-QoL appearance subscale
    - Visual Acuity (VA)
    - Gorman Subjective Diplopia Score
    - EQ-5D-5L QoL questionnaire
- VRDN-001, IGF-1 and anti-drug antibodies (ADA) at various time points pre- and post-infusions as described in Appendix 1 of the protocol

3.2 [redacted]

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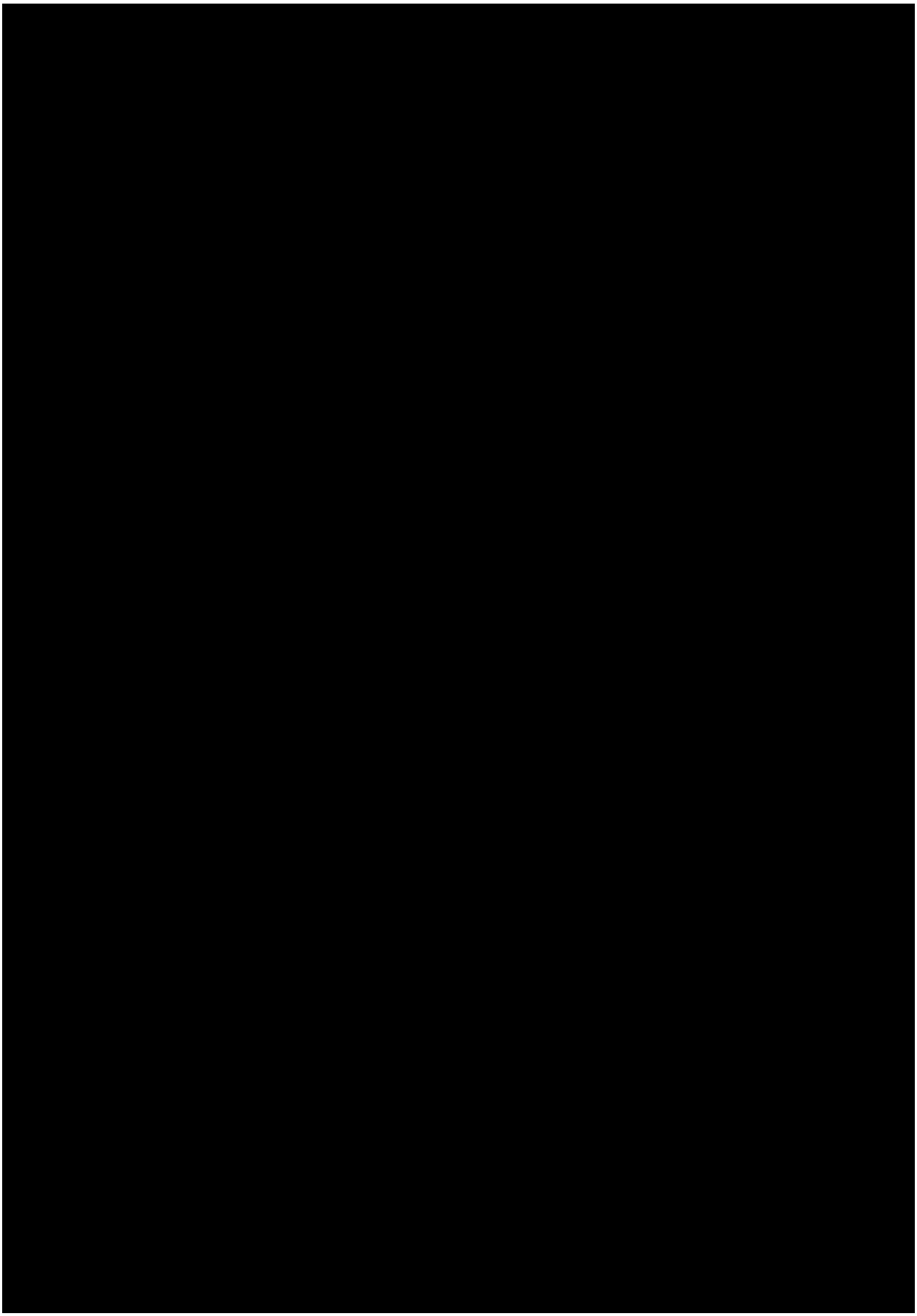

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4. Overall Study Design

The study design is a randomized, double-masked, and placebo-controlled trial, where participants, site personnel (except pharmacy personnel preparing the infusion), and sponsor will be masked to treatment. The dose selected is 10 mg/kg ([redacted] dose rationale is detailed in Section 1.8). The study will be comprised of approximately 159 participants (to ensure 137 evaluable participants at the primary endpoint at Week 15) randomized with an allocation ratio of 2:1 (approximately 106 participants active: 53 participants placebo), stratified at baseline by level of proptosis (≥23 mm, Y/N) as measured by exophthalmometer and CAS (≤1, Y/N), and will compare the efficacy of 5 IV infusions of 10 mg/kg VRDN-001 administered at 3-week intervals to placebo in chronic TED participants whose documented signs and symptoms have persisted more than 15 months before screening. At a minimum, twenty-five percent of these participants will have a baseline CAS ≤1. Approximately 20 participants with CAS ≤1 will be obtained for each of the baseline level of proptosis strata levels.

Participants who are deemed to be non-responders 3 weeks post the fifth infusion may be offered the option to enroll into an open-label treatment study where they will receive 5 further infusions of VRDN-001 at 3-week intervals for a further 12 weeks of treatment. For some countries, per local health authority requirements, participants may be unmasked prior to the decision to enroll in the open-label treatment study. A non-responder for the determination of eligibility in the VRDN-001-302 study is defined as either:

- A participant who did not achieve a ≥ 2 mm reduction from baseline in proptosis (as measured by MRI/CT) in the most proptotic eye at 3 weeks post the fifth infusion (i.e., Week 15)

OR

- A participant who achieved a ≥ 2 mm reduction from baseline in proptosis (as measured by MRI/CT) in the most proptotic eye but had a corresponding increase of ≥ 2 mm from baseline in proptosis in the other eye at 3 weeks post the fifth infusion (i.e., Week 15).

Measurements as described in the SoA will continue to be collected through 52 weeks for those participants who are deemed to be responders at 3 weeks post the fifth IV infusion (i.e., Week 15) in this study. Participants who are non-responders at 3 weeks post the fifth IV infusion (i.e., Week 15) in this study and who do not enroll into the open-label treatment study will continue to have data collected through 52 weeks as described in the SoA.

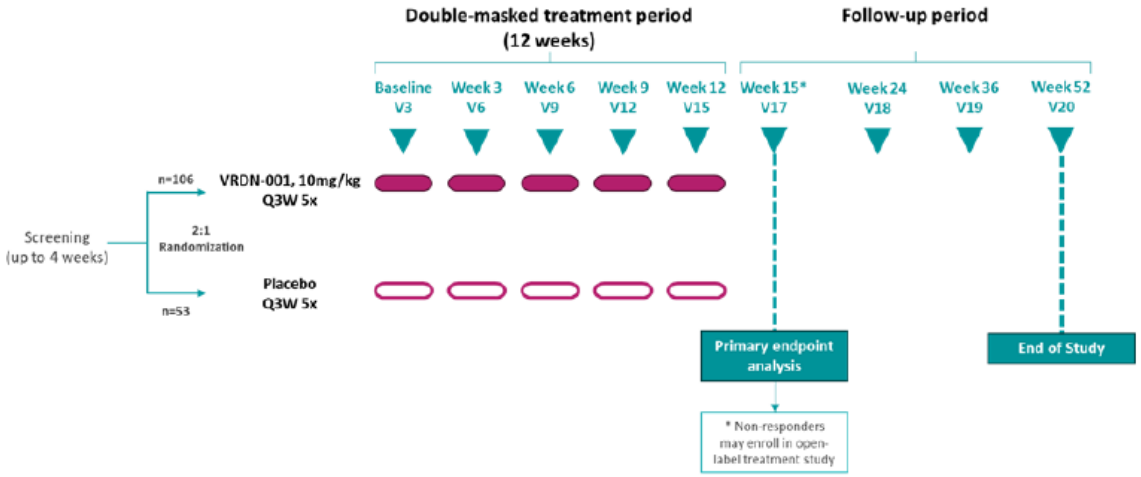


Figure X: Pivotal Portion Study Design (THRIVE)

4.1 Sample Size Justification

This study has greater than 90% power to test the active dose regimen against the placebo arm assuming a proptosis responder rate at Week 15 of 20% in the placebo arm and 50% in the active arm, using a pooled estimate for the variance. The assumptions for the proptosis responder rates are based on the observed outcomes in the VRDN-001-101 [redacted] (Investigator Brochure), teprotumumab studies, testing teprotumumab vs placebo (Smith 2017; Douglas 2020). The overall 1-sided type-I error level of 0.025 will be protected using a gated multiplicity method as will be described in a separate alpha spending report. The testing will then continue to the secondary endpoints. The study will consist of approximately 159 participants (to ensure 137 evaluable participants at the primary endpoint at Week 15), randomized with allocation ratio of 2:1 over the active dose regimen and placebo arms (approximately 106 participants in the active arm and approximately 31 participants in the placebo arm), and will be stratified at baseline by amount of proptosis (≥23 mm, Y/N) as measured by exophthalmometer and CAS (≤1, Y/N). At a minimum, twenty-five percent of these participants will have a baseline CAS ≤1. Approximately 20 participants with CAS ≤1 will be obtained for each of the baseline level of proptosis strata levels.

5. General Analysis Definitions

Data collected for this clinical trial will be analyzed with SAS (Version 9.4 or higher) for all endpoints described in this SAP.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum and maximum values. First and third quartiles may be added in case of well-known asymmetric distribution.
- Time to event data will be summarized using the Kaplan-Meier method. The 25th, 50th, 75th percentile and the corresponding 95% confidence interval will be reported as applicable.

The primary and sensitivity analyses for the primary and key secondary endpoints will display the treatment groups as following:

- VRDN-001
- Placebo

All disposition, demographic and other efficacy analyses will be presented by randomized treatment group. The treatment groups will be displayed as following:

- VRDN-001
- Placebo
- Overall

The safety analyses will be presented by the actual treatment group. The treatment groups will be displayed as follows:

- VRDN-001
- Placebo
- Overall

Listings with individual values will be provided for all data presented in the tables. These listings will be grouped by treatment arm and then sorted by participant identification number.

5.1 Study Period and Visit Window Definitions

5.1.1 Study Periods

Screening period will be defined as the period before the start date of study medication.

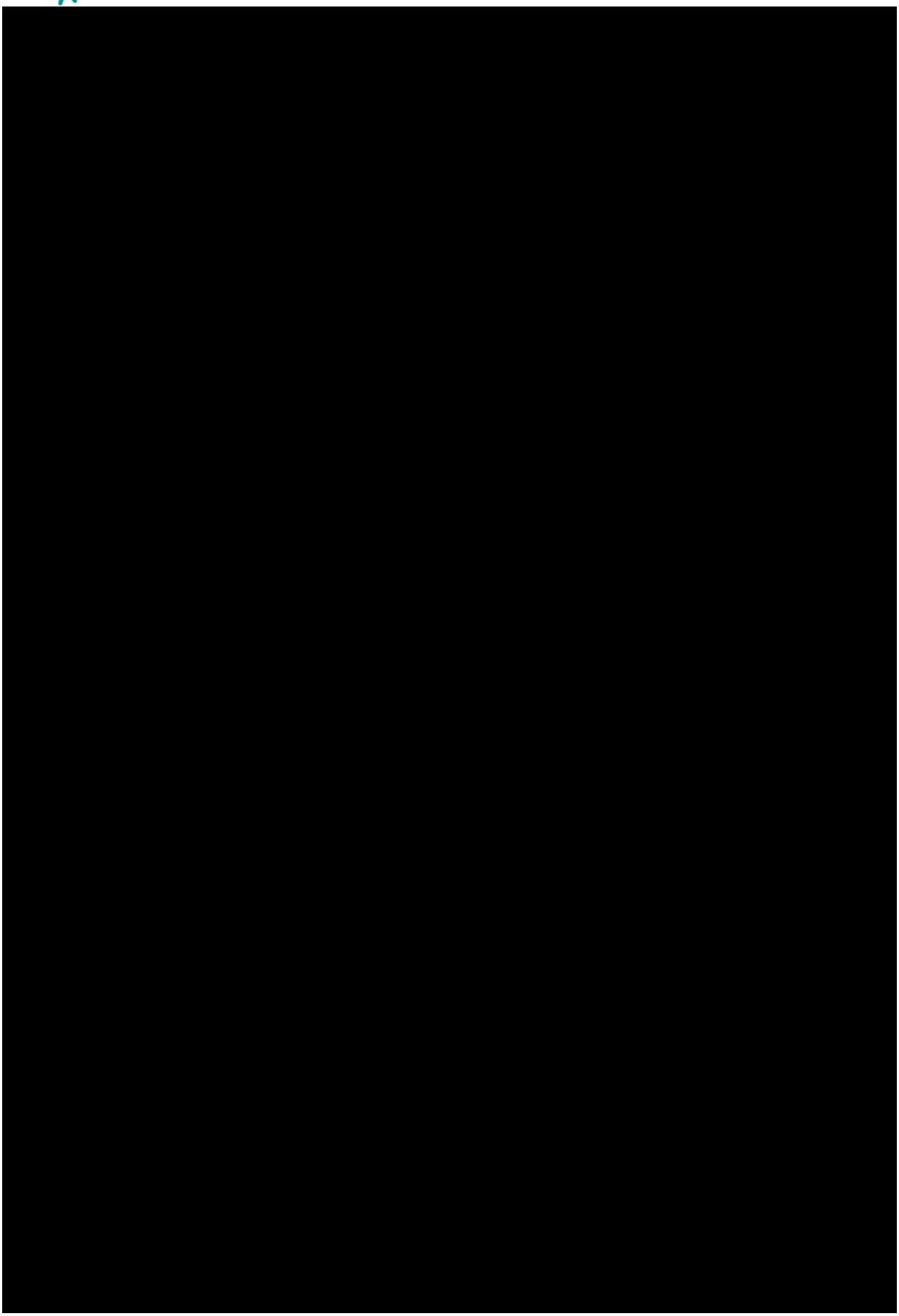
Double-masked treatment period will be defined as the period between the start date of study medication administration and the Week 15 visit (inclusive).

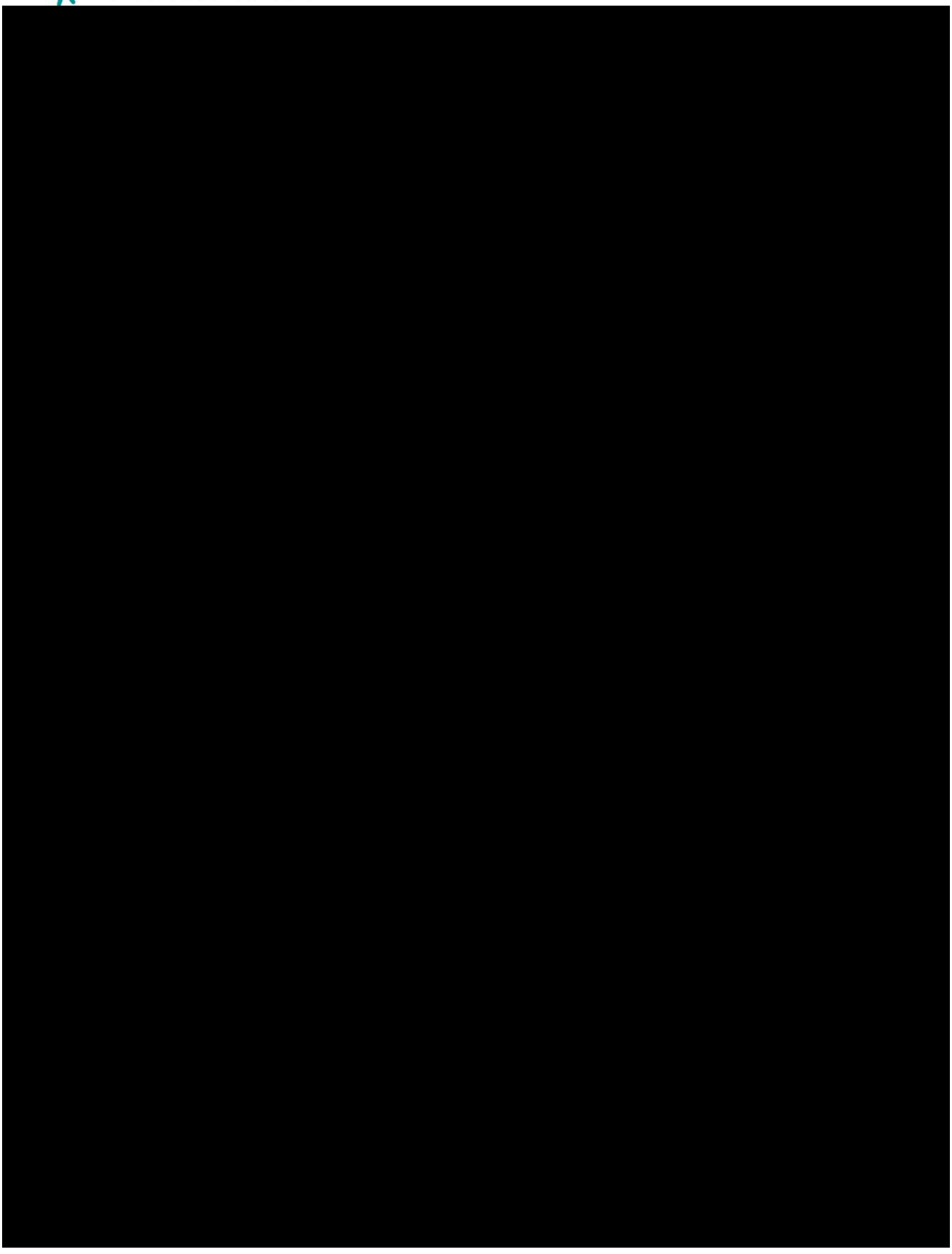
Follow-up period will be defined as the period between the day after the Week 15 visit and Week 52.

End of Treatment is approximately 3 weeks after the last infusion.

5.1.2 [redacted]

[redacted]





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5.2 Planned Analyses

5.2.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review the safety and limited efficacy data at 6-month intervals during the pivotal portion of the study. Interim ad hoc DSMB meetings may be conducted as needed to monitor clinical safety and determine if any required changes to study design should be implemented. The details of the meeting are outlined in the DSMB Charter.

5.2.2 Week 15 Primary Analysis

There will be a primary efficacy database lock and subsequent analysis when all participants complete the Week 15 assessment or have early discontinuation. The analyses will include the following but are not limited to:

- Demographic and Baseline Characteristics
- Medical History
- Ophthalmic History
- Disposition
- All primary, secondary and exploratory endpoints through Week 15
- TEAE through Week 15
- Safety data through Week 15

Due to the nature of an ongoing study at the time of the Week 15 analysis, the database and external data will contain data beyond Week 15 for some subjects at the time of the database lock for the Week 15 Analysis. Only data occurring prior or on the Week 15 visit will be included in the Week 15 Analyses.

The subject-level treatment data blind will be maintained with the exception of the Viridian and contract research organization (CRO) biostatistics team.

Additional analyses including data beyond the Week 15 visit may be produced at the time of the Week 15 Primary Analysis.

5.2.3 Week 36 and Week 52 Follow-up Analyses

An additional interim analysis will take place when all participants have completed the Week 36 visit. Additional efficacy and safety analysis after Week 15 will be examined at the Week 36 analysis. Investigators will remain masked during this analysis and until the final DBL. Selected sponsor staff will become unmasked.

The final database lock will occur when all participants who were not eligible or chose not to participate in the open label extension complete their Week 52 assessment or early discontinue.

All remaining analyses specified in this SAP will be performed. At the time of the final database lock, all Viridian team members will be unmasked to subject-level treatment data.

5.3 Definition of Populations

5.3.1 Enrolled Population

The Enrolled population includes all subjects that signed the informed consent.

5.3.2 Intent-To-Treat Population

The Intent-to-Treat (ITT) population will include all participants who were randomized into the study, irrespective of whether study medication was administered or not. This dataset will be used to report participant disposition and for the efficacy sensitivity analysis. This population will be analyzed according to randomized treatment assignment.

5.3.3 Modified Intent-To-Treat Population

The Modified Intent-to-Treat (MITT) population will include all participants who were randomized into the study and received at least one infusion treatment. This population will be used as the primary analysis population and utilized for all endpoints other than safety.

5.3.4 Safety Population

The Safety population will include all participants in the ITT population but excluding those who did not receive at least one dose of study medication. This dataset will be employed to analyze the safety endpoints. This population will be analyzed according to the actual treatment.

5.3.5 Per-Protocol Population

The Per-Protocol (PP) population will comprise of participants in the mITT population who did not have selected major protocol violations, which strongly confound the efficacy results, during the double-masked treatment period. This population will only be utilized as a sensitivity analysis for the primary and key secondary efficacy endpoints. Some major protocol violation may include but not limited to:

- Did not meet the inclusion/exclusion criteria
- Randomization error
- Received prohibited concomitant medications

The PP population will be finalized prior to unmasking for the Week 15 analysis for the analysis of the primary and secondary endpoints. This population will be analyzed according to randomized treatment assignment.

5.4 Subgroup Definitions

The primary and key secondary endpoints will be presented according to the following subgroups for the MITT population:

- Age: 18 to 34, 35 to 65, >65 years
- Sex: Male, Female
- Race: Black, Asian, White, Other
- Country: United States, Rest of World
- Randomization Stratification based on actual baseline values: < 23 mm and ≥23 mm
- Steroid use during the Treatment period (Y/N)
    a. Steroids will be identified by "ATC4CD" in ("H02AB", 'H02BX')
- CAS Score: <=1, >1

Other subgroup analyses may be analyzed descriptively as appropriate.

5.5 Treatment Assignment and Treatment Arms

- VRDN-001 administered at 3-week intervals
- Placebo

5.6 Calculated Variables

- For events that occur after the first administration of study medication, relative day will be calculated as (date of XXX -date of first administration of study medication) +1. For events that occur before the first administration of study medication, relative day will be calculated as (date of XXX -date of first administration of study medication).
- Study day 1 is defined as the day of the first administration of study medication.
- Baseline is defined as the last non-missing assessment prior to the first administration of study medication. Assessments completed on the date of study medication administration are assumed to take place before the administration, unless specified otherwise in the protocol.
- Change from baseline is defined as the post-baseline value – baseline value.
- Percent change from baseline is defined as 100*(post-baseline value – baseline value)/baseline value. If the baseline value is 0 and the post-baseline value is 0, the change from baseline and the percent change from baseline are both 0. If the baseline value is 0 and the post-baseline value is not 0, the change from baseline is the same as the post-baseline value and the percent change from baseline will be missing.
- Body Mass Index (BMI) = weight in kg / (height in m)^2.
- Age is collected in the clinical database.
- When calculating time in months utilize 30.4375 as the denominator.
- When calculating time in years utilize 365.25 as the denominator.

XXX can be any reference time point of interest (e.g. start of adverse event) in calculation of the associated duration.

5.7 Partial Dates

Partial or missing dates in general will not be imputed.

For the calculation of the time (in months) from XXX to date of IMP or randomization, the following imputation rules will be applied when the date of XXX is incomplete:

- If the day is missing: first day of the month
- If the day and month are missing: first day of January.
- If the day and month are missing and if the year is the same as the year of IMP: leave missing.

In order to evaluate if an adverse event (AE) is treatment emergent or not, and to evaluate if a medication or procedure is concomitant or not, the following rules will be applied in case of incomplete or missing dates:

- If end date is missing and the outcome is "Recovered/Resolved", the end date will be set to the last contact date.
- If end date is incomplete and the outcome of "Recovered/Resolved":
  - if the day is missing and month/year is same as the last contact date then use last contact date, else the end date will be imputed with the last day of the month;
  - if the day and month are missing: the end date will be imputed with minimum of (31 December of the year, last contact date, date of death).
- If start date is missing:
  - if end date is before the start date of IMP administration, the start date will remain missing (medical history).
  - if end date is after or on the date of IMP administration or the medication/AE is ongoing (or end date is missing), the start date will be imputed by the date of IMP administration.
- If start date is incomplete:
  - if end date is before the date of IMP administration, the start date will remain incomplete.
  - if end date is after or on the date of IMP administration or the medication/history is ongoing (or end date is missing), the start date will be imputed as follows: if the day is missing, the start date will be imputed with minimum of (the last day of the month, end date of medication/AE if available); if the day and month are missing: the start date will be imputed with minimum of (31 December of the year, end date of medication/AE if available).

However, the original date variable will not be imputed and only a temporary variable will be created in order to perform the evaluation. The temporary variable will not be used in any other calculation and will not be listed. In patient data listings, the documented date as recorded in the clinical database (i.e. without imputation), will be reported (e.g. XXMAR2014 in case of day missing, but month and year available).

5.8

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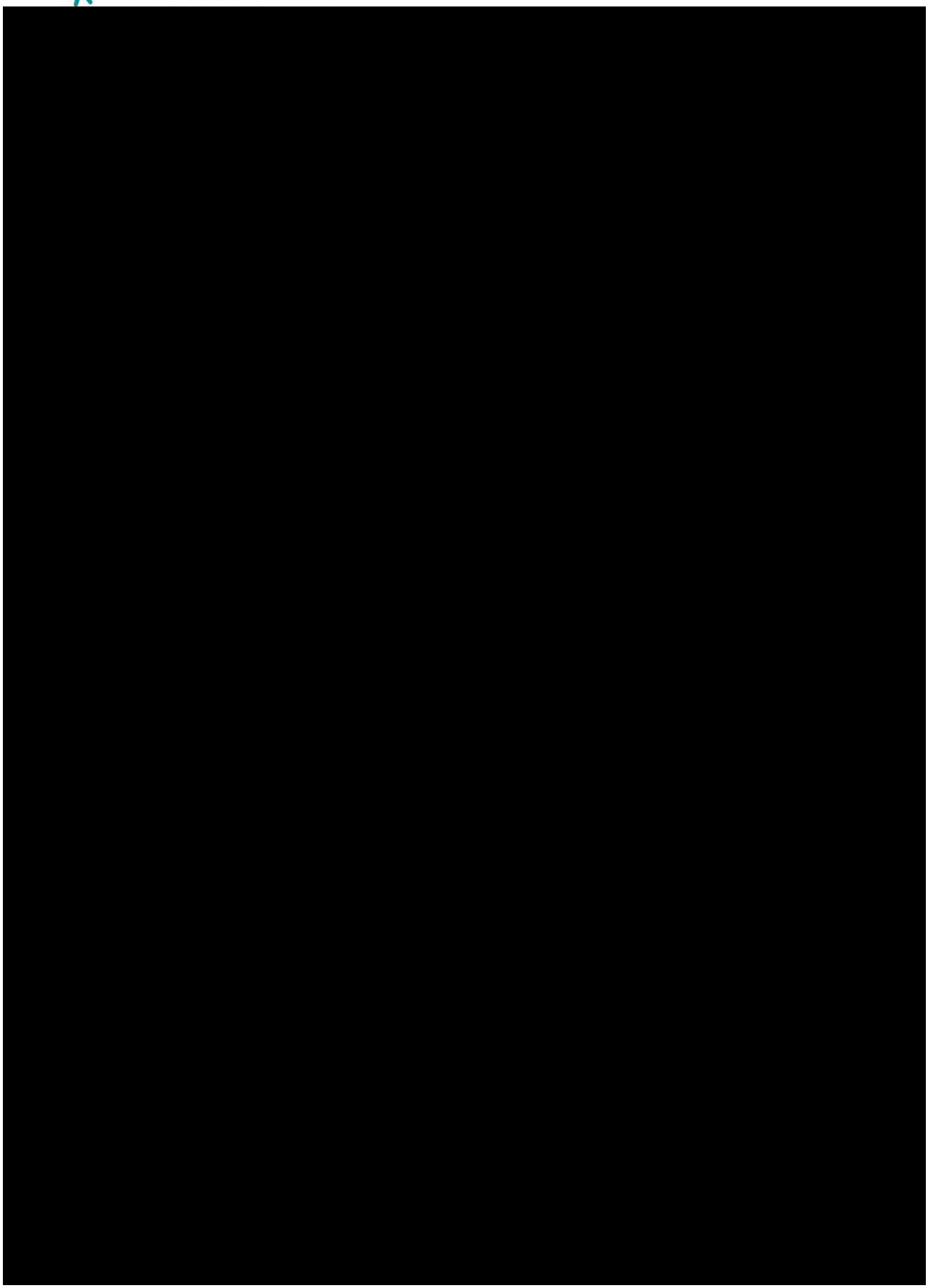


5.9 Changes from the Protocol

If there are any discrepancies between the protocol and SAP, the text in the SAP will take precedence.

6. Study Participants

6.1 Disposition of Participants

The number and percentage of participants in each population, along with number and percentage of participants who discontinue the treatment and study along with the primary reasons will be tabulated.

The number of screen failures and the reasons for screen failure will be summarized.

6.2 Protocol Deviations

The major protocol deviations will be summarized for the ITT population and MITT. The summary will include the number and percentage of subjects with at least one major protocol deviation along with the number of events. Additionally, the number, percentage, and number of events for each major deviation category will be presented. Details of all protocol deviations will be listed by participant and indicating category of protocol deviation.

Protocol deviations will be defined as major or minor by the Sponsor prior to any database locks and/or interim analyses.

It is possible that new protocol deviations will be discovered, or existing ones modified during the final Week 52 database lock. Therefore, a comparison on the protocol deviations will be reviewed and the impact to the PP population will be examined. If deemed necessary, the PP population may be regenerated with the updated population. Any updates to the PP population will be documented in the study report.

6.3 Inclusion and Exclusion Criteria

A listing of all inclusion and exclusion criteria not met will be provided for the Enrolled population.

7. Demographic and Other Baseline Characteristics

Participant demographics and baseline characteristics will be summarized for the ITT, MITT and safety populations. The variables to be summarized will include the following as well as some others as may be appropriate:

- Age (years)
- Gender at Birth (Male, Female)
- Race (Asian, Black, White, Other)
- Study Eye (OD, OS)
- Country (United States, Rest of World)
- Randomization Stratification (baseline by level of proptosis (≥23 mm, <23mm)
- Actual Stratification by Exophthalmometer (baseline by level of proptosis (≥23 mm, <23mm)
- Initial TED onset (months) from randomization
- Audiometry: PTA (db), PTA >25 Y/N
- Gorman Subjective Diplopia Grade
- Baseline CAS for both OD and OS
- Baseline Proptosis value (by Hertel and MRI/CT)

7.1 Medical History

All relevant general medical histories, including Graves' disease, will be collected on the "Medical History" eCRF page and will be used for the analysis of medical history. Procedures and surgeries are reported on a separate eCRF page and will be summarized separately.

Medical history will be summarized by system organ class (SOC) and preferred term (PT), for the ITT population. Number and percentage will be displayed for SOC and PT; including number and percentage of all participants with at least one medical history event. Participants will be counted only once at each level of reporting. The summary table will be sorted alphabetically by SOC and PT by descending overall frequency. MedDRA dictionary will be utilized for coding. The study data management plan will specify the version. The version will be included in the footnote of the appropriate output.

A listing of medical history will be provided.

7.2 Ophthalmic History

Clinically significant ophthalmic history events will be collected using box 5 on the "Medical History" eCRF page.

Ophthalmic history events will be summarized by SOC and PT for the ITT population. Number and percentage will be displayed for SOC and PT; including number and percentage of all participants with at least one ophthalmic history event. Participants will be counted only once at each level of reporting. Summary tables will be sorted alphabetically by SOC and PT by descending overall frequency. MedDRA dictionary will be utilized for coding. The study data management plan will specify the version. The version will be included in the footnote of the appropriate output and listings.

An indicator for ophthalmic history events will be included on the medical history listing.

7.3 Prior and Concomitant Medication

Prior and concomitant medications will be collected on the "Prior and Concomitant Medications" eCRF page.

Prior medications are defined as medications that start before study day 1.

Concomitant medications are defined as medications that are administered on or after the first day of study medication.

Medications that start before study day 1 and continue after will be reported as both prior and concomitant.

Prior and concomitant medications will be classified according to World Health Organization Drug Dictionary. The version of the dictionary will be specified in the data management plan and will be included in the footnote of the appropriate output.

Prior and concomitant medications will be summarized separately. The number and percentage of participants receiving a medication will be summarized by anatomical main group (1st level of the Anatomical Therapeutical Chemical (ATC) classification) and chemical subgroup (4th level of the ATC classification) for the ITT population. Participants will be counted only once at each level of reporting. Summary tables will be sorted alphabetically by ATC Level 1 and ATC level 4 by descending overall frequency.

A listing of all medications will be provided.

7.4 Prior and Concomitant Procedures and Surgeries

Concomitant procedures will be collected on the "Concomitant Procedures" eCRF page.

Prior procedures and surgeries are defined as procedures and surgeries that start before study day 1.

Concomitant procedures and surgeries are defined as procedures and surgeries that start on or after the first day of Study medication.

Procedures and surgeries that start before study day 1 and continue after will be reported as both prior and concomitant.

Prior and concomitant procedures and surgeries will be classified according to MedDRA. The version of the dictionary will be specified in the data management plan and will be included in the footnote of the appropriate output.

Prior and concomitant procedures and surgeries will be summarized separately. Prior and concomitant procedures and surgeries will be summarized SOC and PT, for the ITT population. Number and percentage will be displayed for SOC and PT; including number and percentage of all participants with at least one event. Participants will be counted only once at each level of reporting. Summary tables will be sorted alphabetically by SOC and PT by descending overall frequency.

The data will be presented in a listing.

8. Efficacy

8.1 Efficacy Assessments and Derived Endpoints

Measurement of Proptosis with Exophthalmometer

Proptosis (distance between the lateral orbital rim and the most anterior position of the cornea in millimeters (mm)) will be measured using an exophthalmometer. Three independent measurements will be performed at each visit for each eye where proptosis is assessed. The average of the three measurements is recorded in the database.

Proptosis Responder in a particular eye is defined as a reduction of proptosis of ≥ 2 mm from baseline in that same eye (without a corresponding increase of ≥ 2 mm in the other eye).

Durability of Proptosis Response in the study eye at Week 24, 36 and 52 is defined as achieving a response at Week 15, the visit of interest and any visit between. For example, durability of proptosis response at Week 36 is defined as having a response at Week 15, 24 and 36.

Time to first Proptosis Response in the study eye is defined as date of first proptosis response-date of first administration of study medication) +1. If a participant does not achieve proptosis response in the most proptotic eye by their Week 15 assessment, they will be censored at their last proptosis assessment during the double-masked treatment period.

Clinical Activity Score (CAS)

The CAS is based on seven components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica and swelling of the eyelids. Each component is scored as present or absent (scored as 1 or 0, respectively), and the CAS is given as the sum of the non-missing scores (range, 0 to 7, with higher scores indicating greater level of inflammation).

Clinical Activity Responder in a particular eye is defined as no worsening in CAS from baseline (without a corresponding increase of ≥ 2 points in the other eye).

Overall Responder in a particular eye comprises achieving Proptosis Response and Clinical Activity Response in the same eye.

Subjective Assessment of Diplopia (Gorman Subjective Diplopia Score)

Changes in diplopia grade will be assessed using the Gorman subjective diplopia score (range, 0 to 3), which includes four categories: no diplopia (absent, scored as 0), diplopia in the primary position of gaze when the patient is tired or awakening (intermittent, scored as 1), diplopia at extremes of gaze (inconstant, scored as 2), and continuous diplopia in the primary or reading position (constant, scored as 3).

Diplopia Resolution is defined as a reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia Score >0.

Diplopia Responder Rate is defined as a reduction in Gorman Subjective Diplopia Score of ≥1 from baseline for participants with baseline Gorman Subjective Diplopia Score >0.

Measurement of Proptosis by Orbital MRI/CT

Measurements of proptosis will be conducted by the central imaging reading center using MRI/CT of the orbits acquired without contrast. Measurements are conducted by two independent readers with adjudication if difference between primary readers in proptosis measurement exceeds 5% (calculated as the difference divided by the larger measurement). For analysis the average of 2 (or 3 if adjudicated) measurements will be used. Details for acquisition will be outlined in the imaging user manuals provided by the central imaging reading center. Images will be taken at baseline and the measurements compared at various post-treatment timepoints.

Measurement of Extraocular Muscle Volume and Orbital Fat Volume by MRI/CT

Three-dimensional volumetric calculation of extraocular muscle (EOM) will be conducted by the central imaging reading center using MRI/CT of the orbits acquired without contrast. Details for acquisition will be outlined in the imaging user manuals provided by the central imaging reading center. Images will be taken at baseline and the volumes compared at various post-treatment timepoints.

Three-dimensional volumetric calculation of orbital fat will be conducted by the central imaging reading center using MRI/CT of the orbits acquired without contrast. Details for acquisition will be outlined in the imaging user manuals provided by the central imaging reading center. Images will be taken at baseline and the volumes compared at various post-treatment timepoints.

Graves' Orbitopathy - Quality of Life Measurement (GO-QoL)

The questionnaire has two self-assessment subscales; one covering the impact of visual function on daily activities, and the other assessing the impact of self-perceived appearance.

Each subscale has 8 questions which are scored 1-3 and the total raw score is then mathematically transformed to a 0-100 scale, where 0 represents the most negative impact on quality of life, and 100 represents no impact. The combined score takes raw scores from both subscales and again transforms them to a single 0-100 scale. The transformed score is defined as:

Transformed score = ((sum of each score – number of completed items) /(2 × number of completed items)) X 100.

EUROQOL QUESTIONNAIRE VERSION (EQ-5D-5L)

The EQ-5D-5L is an established and validated quality of life assessment, which will be used to evaluate participants' quality of life throughout the study. The EQ-5D-5L is a standardized instrument that consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

The EQ-5D-5L index will be produced using the United States value[1] set from the EUROQOL website (https://euroqol.org/).

Visual Acuity (VA)

VA will be measured with either Snellen Eye Charts, or equivalent and using a participant's distance prescription glasses or contact lenses, as applicable. Pinhole acuity is acceptable in place of formal refraction if up to date or accurate refractions are not available. This assessment should be conducted prior to dilation of the eyes.

The change from baseline of visual acuity will be assessed by the visual acuity line and will be defined as (Post-baseline logMAR- Baseline logMAR). Where logMAR=-1*$\log_{10}$ (Snellen fraction).

Manual Measurement of Lid Retraction

Lid retraction will be recorded in mm by measuring the lid aperture along the midline of the pupil with the participant looking in the primary position while sitting relaxed and with distant fixation (midpupil to upper lid margin distance, MPLD). A change in lid retraction of 2 mm or greater is considered clinically meaningful.

8.1.1 Efficacy Analysis Procedure and Hierarchy

The most proptotic eye is determined by the last assessment performed prior to the Day 1 IV infusion by the given assessment modality (i.e., endpoints assessed by MRI/CT will determine most proptotic eye by MRI/CT and endpoints assessed by exophthalmometer will determine most proptotic eye by exophthalmometer measurement). If the baseline of MRI/CT is missing then the most proptotic eye will be determined by exophthalmometer measurement. If both eyes are equally proptotic then the eye with the worse VA will be selected. If proptosis and VA are the same for both eyes, then the right eye will be selected as the most proptotic eye. The most proptotic eye as determined by exophthalmometer is also referred to as the study eye.

All analyses for primary and secondary efficacy endpoints done by individual eye will be repeated for the other eye following similar definitions.

The study-wise one-sided type-I error level of 0.025 will be maintained as described in a separate statistical alpha spending report. The final p-value for the Week 15 analysis will be documented in the statistical report. A gated testing methodology will be utilized to control Type 1 error. The order is as following:

USA, Canada, China

1. Primary Endpoint: Proptosis Responder Rate in the most proptotic eye as measured by exophthalmometer eye at Week 15
2. Key Secondary Endpoint: Change from baseline in proptosis in the most proptotic eye as measured by exophthalmometer at Week 15
3. Key Secondary Endpoint: Proptosis Responder Rate in the most proptotic eye at Week 15
4. Key Secondary Endpoint: Change from baseline in proptosis in the most proptotic eye at Week 15

5. Key Secondary Endpoint: Overall Responder Rate comprised of proptosis responder rate in the most proptotic eye as measured by exophthalmometer at Week 15 and Clinical Activity Responder rate in the most proptotic eye as measured by exophthalmometer at Week 15
6. Key Secondary Endpoint: Clinical Activity Responder Rate in the most proptotic eye as measured by exophthalmometer at Week 15
7. Key Secondary Endpoint: Diplopia Responder Rate at Week 15
8. Key Secondary Endpoint: Diplopia Resolution Rate at Week 15

For the primary and key secondary endpoints, the method of measurement for proptosis will be MRI/CT unless stated otherwise.

Australia, Israel, Turkey, European Union and United Kingdom

1. Primary Endpoint: Overall Responder Rate in the most proptotic eye at Week 15
2. Key Secondary Endpoint: Change from baseline in proptosis in the most proptotic eye at Week 15
3. Key Secondary Endpoint: Proptosis Responder Rate in the most proptotic eye as measured by exophthalmometer at Week 15
4. Key Secondary Endpoint: Change from baseline in proptosis in the most proptotic eye as measured by exophthalmometer at Week 15
5. Key Secondary Endpoint: Diplopia Responder Rate at Week 15
6. Key Secondary Endpoint: Diplopia Resolution Rate at Week 15

For the primary and key secondary endpoints, the method of measurement for proptosis will be MRI/CT unless otherwise stated otherwise. The most proptotic eye will be defined by the corresponding measurement method.

[redacted]

The following analyses will be conducted for the primary and key secondary endpoints:

Analysis	Population (Imputation, Estimand)
USA, Canada, China Primary Analysis of Primary Endpoint	MITT (MI, Treatment Policy Strategy)
USA, Canada, China Sensitivity Analysis of the Primary Endpoint	ITT (MI, Treatment Policy Strategy) PP (MI, Treatment Policy Strategy) MITT (MI, Composite Strategy) ITT (MI, Composite Strategy) PP (MI, Composite Strategy) mITT (OC, Treatment Policy Strategy) ITT (OC, Treatment Policy Strategy) PP (OC, Treatment Policy Strategy) mITT (NRI, Treatment Policy Strategy) ITT (NRI, Treatment Policy Strategy) PP (NRI, Treatment Policy Strategy)
Australia, Israel, European Union, Turkey, United Kingdom Primary Analysis of Primary Endpoint	MITT (EXI/MI, Treatment Policy Strategy)
Australia, Israel, European Union, Turkey, United Kingdom Sensitivity Analysis of the Primary Endpoint	ITT (EXI/MI, Treatment Policy Strategy) PP (EXI/MI, Treatment Policy Strategy) MITT (EXI/MI, Composite Strategy) ITT (EXI/MI, Composite Strategy) PP (EXI/MI, Composite Strategy) MITT (OC, Treatment Policy Strategy) ITT (OC, Treatment Policy Strategy) PP (OC, Treatment Policy Strategy) mITT (NRI, Treatment Policy Strategy) ITT (NRI, Treatment Policy Strategy) PP (NRI, Treatment Policy Strategy)
USA, Canada, China Primary Analysis of Key Secondary Endpoints	MITT (MI/EXI/MI[1], Treatment Policy Strategy)
USA, Canada, China Sensitivity Analysis Key Secondary Endpoints	ITT (MI/ EXI/MI)[1], Treatment Policy Strategy) PP (MI/EXI/MI)[1], Treatment Policy Strategy) MITT (MI/EXI/MI)[1], Composite Strategy ITT (MI/EXI/MI)[1], Composite Strategy) PP (MI/EXI/MI)[1], Composite Strategy) MITT (OC/LOCF/MI)[2], Treatment Policy Strategy) ITT (OC/LOCF/MI)[2], Treatment Policy Strategy) PP (OC/LOCF/MI)[2], Treatment Policy Strategy) mITT (NRI, Treatment Policy Strategy) ITT (NRI, Treatment Policy Strategy) PP (NRI, Treatment Policy Strategy)
Australia, Israel, European Union, Turkey, United Kingdom Primary Analysis of Key Secondary Endpoints	MITT (MI, Treatment Policy Strategy)
Australia, Israel, European Union, Turkey, United Kingdom Sensitivity Analysis Key Secondary Endpoints	ITT (MI, Treatment Policy Strategy) PP (MI, Treatment Policy Strategy) MITT (MI, Composite Strategy ITT (MI, Composite Strategy) PP (MI, Composite Strategy) MITT (OC, Treatment Policy Strategy) ITT (OC, Treatment Policy Strategy) PP (OC, Treatment Policy Strategy) mITT (NRI, Treatment Policy Strategy) ITT (NRI, Treatment Policy Strategy) PP (NRI, Treatment Policy Strategy)

[1] The USA, Canada, China key secondary endpoints will have the following imputation: Change from baseline in proptosis by exophthalmometer (MI); Proptosis Responder Rate (EXI); Change from baseline in proptosis (EXI) ; Clinical Activity Responder (MI); Overall Responder Rate (MI for proptosis as measured by exophthalmometer and MI for CAS); Diplopia Resolution Rate (MI); Diplopia Responder Rate (MI); .

[2] The USA, Canada, China key secondary endpoints will have the following imputation: Change from baseline in proptosis (LOCF); Proptosis Responder Rate as measured by exophthalmometer (OC); Change from baseline in proptosis as measured by exophthalmometer

(OC); Clinical Activity Responder (OC); Overall Responder Rate (OC for proptosis by exophthalmometer and MI for CAS); Diplopia Resolution Rate (OC); Diplopia Responder Rate (OC).

8.2 [redacted]

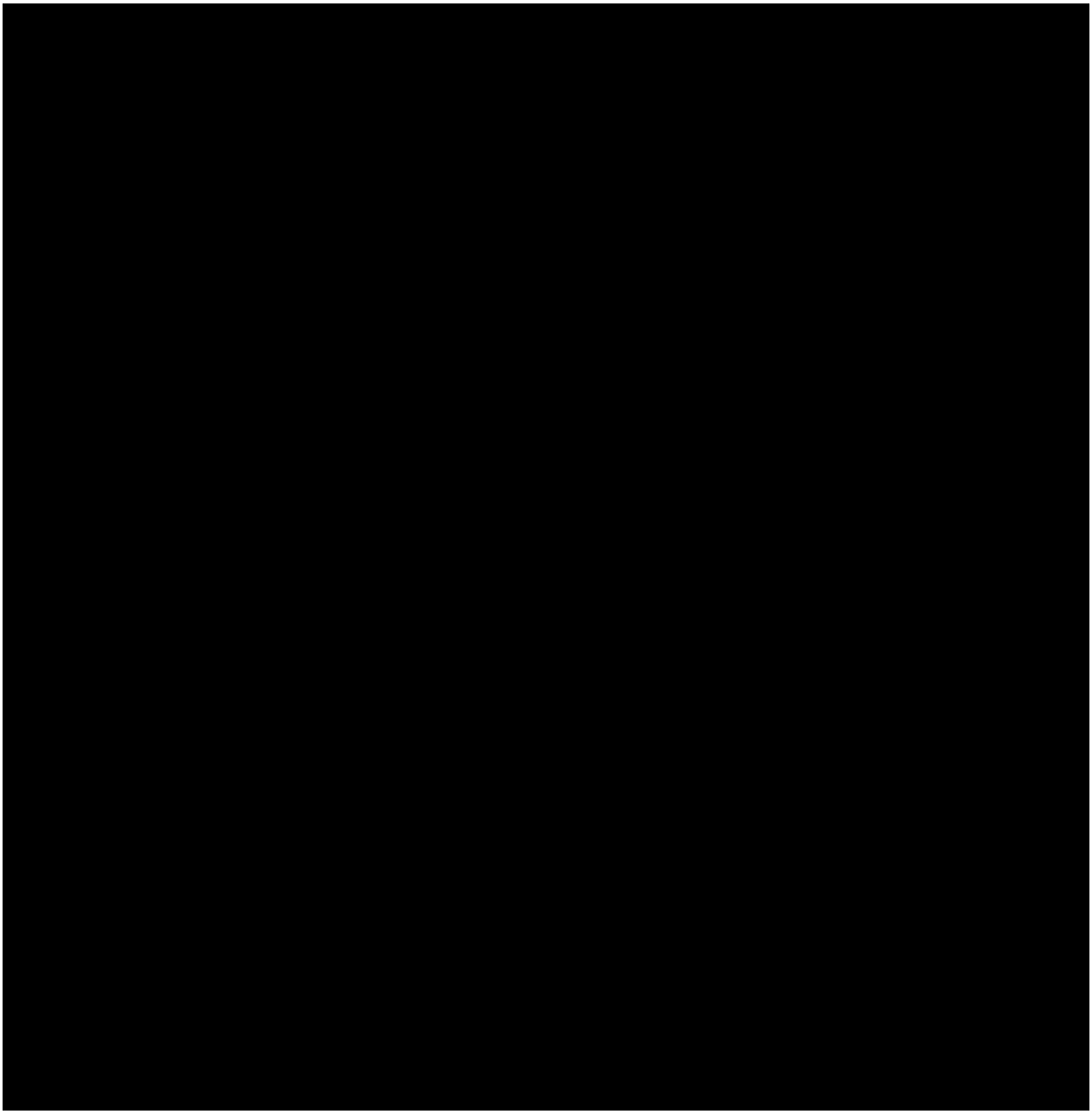
[redacted]

Only data through Week 15 will be used in the statistical models for the primary endpoints.

[redacted]

8.3 [redacted]

[redacted]



8.4 Exploratory Endpoints

The analysis for the Week 15 exploratory endpoints supported by longitudinal models will only include data up to and including Week 15. The exploratory endpoints after Week 15 supported by longitudinal models will include all available data. The Week 15 endpoints will use the same methods for handling missing data. The endpoints after Week 15 will use observed cases.

8.4.1 Exploratory Endpoints in all regions

Proptosis related exploratory endpoints will be assessed by both exophthalmometer and MRI/CT measurements in the most proptotic and other eye as determined by the corresponding measurement modality, except time to first proptosis response which will only be assessed by exophthalmometer.

Other exploratory endpoints involving assessments by eye will be analyzed for most proptotic eye and other eye as determined by exophthalmometer and for most proptotic eye and other eye as determined by MRI/CT.The exploratory endpoints listed in SAP 3.1.3 will be analyzed as below.

Risk differences and p values:

- Proptosis Responder Rate in the most proptotic eye at by visit
- Durability of Proptosis Response in the most proptotic eye at Weeks 24, 36 and 52
- Proptosis Responder Rate in the other eye by visit
- Clinical Activity Responder Rate in the most proptotic eye by visit
- Clinical Activity Responder Rate in the other eye by visit
- Overall Responder Rate in the most proptotic eye by visit
- Overall Responder Rate in the other eye by visit
- Diplopia Responder Rate by visit
- Diplopia Resolution Rate by visit

Time to Event analysis:

- Time to First Proptosis Response in the most proptotic eye

Summary statistics and p value:

- Change from baseline in CAS in the most proptotic eye at Week 15 for those with a baseline CAS >=3
- Change from baseline in CAS in the other eye at Week 15 for those with a baseline CAS >=3

Counts, percents, p values:

- Proportion of participants with a CAS of zero or one in the most proptotic eye at Week 15 for those with a baseline CAS >=3
- Proportion of participants with a CAS of zero or one in the other eye at Week 15 for those with a baseline CAS >=3
- Proptosis responder rate in the most proptotic eye in participants with baseline CAS of 0 or 1 by visit
- Proptosis responder rate in the other eye in participants with baseline CAS of 0 or 1 by visit
- Proptosis responder rate in the most proptotic eye in participants with baseline CAS of 0, 1, or 2 by visit
- Proptosis responder rate in the other eye in participants with baseline CAS of 0, 1, or 2 by visit
- Proptosis responder rate in the most proptotic eye in participants with baseline CAS of ≥ 3 by visit
- Proptosis responder rate in the other eye in participants with baseline CAS of ≥ 3 by visit

Descriptive Statistics:

- Change from baseline in the most proptotic eye and other eye where applicable in the following parameters by visit:

- Proptosis
- CAS
- Extraocular muscle volume
- Orbital fat volume
- Manual measurement of lid retraction
- Graves' Orbitopathy-Quality of Life (GO-QoL) combined score
- GO-QoL activity subscale
- GO-QoL appearance subscale
- Visual Acuity (VA)
- Gorman Subjective Diplopia Score
- EQ-5D-5L QoL questionnaire

- VRDN-001, IGF-1 and anti-drug antibodies (ADA) at various time points pre and post-infusions as described in Appendix 1 of the protocol

8.5 Additional Analyses

- The analysis of the proptosis response rate via MRI/CT with all proptosis assessments measured by CT removed and consequently imputed using the EXI imputation method.

9. Safety Evaluation

All safety analyses will be performed on the Safety population unless specified differently.

Safety assessments will be analyzed according to the analysis visits and by right or left eye if applicable. Both safety and tolerability will be evaluated by assessing the incidence of Adverse Events (AEs) and the incidence of Serious Adverse Events (SAEs).

9.1 Extent of Exposure

Exposure will be summarized for the MITT population by number of doses received as well as the average duration between doses. For the number of doses received, the highest number of doses will be determined for each participant. The table will summarize the number of participants who received that number as the highest number of doses.

The number of participants who had a dose interruption will also be summarized.

All exposure data will be presented in a listing.

9.2 Adverse Events

AEs and SAEs will be reported from the time the participant signs the informed consent to the time the participant completes the study.

AEs will be coded using the Medical Dictionary for Regulatory Activities. The dictionary versions are specified in the data management plan and will be included in the footnote for appropriate outputs. AEs will be analysed in terms of their type, incidence, severity/toxicity grade and relationship to the study treatment.

A Treatment-Emergent Adverse Event (TEAE) will be defined as an AE occurring on or after the day of the first administration of study medication. Furthermore, TEAE through Week 15

is defined as an TEAE occurring on or after the day of the first dose of study medication through the Week 15 visit (inclusive). A follow-up period TEAE is any TEAE that occurred the day after the Week 15 visit through the end of the study.

Related AEs are defined as events with a relationship to study medication equal to 'related' or with missing relationship.

The safety analysis in this section will summarize TEAEs through Week 15, Follow-up Period TEAEs and all TEAE employing discrete summaries at the participant- and event-level by SOC and PT. Participants will only be counted once at each level of summary.

An overall summary table will present the number and percentage of participants with at least one category of AE, for TEAEs through Week 15, the follow-up period TEAEs and all TEAEs.

In addition, tabulations of the number and percentage of participants who experienced TEAEs as well as severity of the events will be presented by SOC and PT. Participants will only be counted once for each preferred term. In case a participant experienced the same event more than once, the worst severity will be presented. A summary of total number of AEs will also be presented for each SOC.

The following tabulations will be presented for the Week 15 TEAEs:

- TEAEs
- Treatment-related TEAEs
- TEAEs leading to discontinuation of study medication
- Serious TEAEs

The following tabulations will be presented for the Follow-up period TEAEs:

- TEAEs
- Treatment-related TEAEs
- TEAEs leading to discontinuation of study medication
- Serious TEAEs

The following tabulations will be presented for all TEAEs:

- TEAEs
- Treatment-related TEAEs
- TEAEs leading to discontinuation of study medication
- Serious TEAEs
- Treatment-related TEAEs leading to discontinuation of study medication
- TEAEs leading to death
- Treatment-related TEAEs leading to death
- Serious TEAE related to study medication
- TEAEs of interest
- TEAEs by the maximum severity grade
- Treatment-related TEAEs by the maximum severity grade
- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- Ocular TEAE by severity/toxicity grade
- Non-ocular TEAE by severity/toxicity grade

An additional summary describing the onset of TEAE of interest (TEAEI) will be provided. The TEAEI are defined as below. They will be identified via SMQ or PT as has been prespecified.

The summary of the number of infusions prior to the onset of an adverse event of interest will be provided. If the TEAEI occurs on the day of an infusion that infusion will be considered. In other words, if a participant reported hyperglycaemia after three infusions, the onset will be considered 3 infusions. If there are multiple TEAEIs the TEAEIs with the least number of infusions prior to onset will be used for the analysis.

All deaths will be listed.

9.3 Clinical Laboratory

Parameters from the following laboratory categories will be summarised descriptively by treatment arm and analysis visit for the observed and change from baseline: serum chemistry and lipid panel, haematology (including HbA1c), coagulation and urinalysis.

Shift tables of NCI-CTCAE grade at baseline versus worst post-baseline NCI-CTCAE grade, end of treatment, end of study by CTCAE term will be produced for all gradable parameters. For the laboratory parameters that cannot be graded, shift tables will be displayed for normal, low and high.

All NCI-CTCAE grade 3/4 laboratory values will be listed by participant, parameter and date. Abnormal values will be listed for laboratory values that cannot be graded.

Other laboratory parameters will be listed, as appropriate. These will include FSH test (females only), HIV 1/2, HCV, HBV, and pregnancy test (serum and urine) results (females only).

Lab values indicated to be above or below the limit of quantitation will be imputed with the limit of quantitation. For example, if a value is recorded as >2.0 units, the numeric value will be imputed as 2.0 units. If a value is recorded as <1.5 units, the numeric value will be imputed as 1.5 units.

9.4 Vital Signs

Vital signs include body temperature (°C), respiratory rate (breaths/min), heart rate (beats/min), systolic and diastolic blood pressure (mmHg), height (cm), weight (kg) and BMI (kg/m^2). Descriptive statistics of observed values and change from baseline by analysis visit and time point will be presented.

A summary of abnormal vital signs will be presented. The criteria for identifying abnormal vital signs are presented below.

Parameter	Abnormal Criteria
Systolic blood pressure	• ≥180 mmHg and increase from baseline of ≥20 mmHg • ≤90 mmHg and decrease from baseline of ≥20 mmHg • Decrease from baseline ≥20 mmHg
Diastolic blood pressure	• ≥105 mmHg and increase from baseline of ≥15 mmHg • ≤50 mmHg and decrease from baseline of ≥15 mmHg • Decrease from baseline ≥10 mmHg
Heart rate	• ≥150 beats/min and increase from baseline ≥15 beats/min • ≤50 beats/min and decrease from baseline ≥15 beats/min
Weight	• Increase from baseline ≥7% • Decrease from baseline ≥7%

A listing of vital signs data will be provided.

9.5 ECG

ECG results will be tabulated by analysis visit and timepoint as "normal", "abnormal, not clinically significant" or "abnormal, clinically significant". A shift from baseline table will also be presented. Shift tables at baseline versus worst post-baseline assessment, end of treatment and end of study will be produced.

A listing of ECG test results will be provided.

9.6 Physical Findings

A listing of physical examination data will be provided.

9.7 [redacted]

[redacted]

9.8 Ophthalmic Variables

9.8.1 Slit Lamp Biomicroscopy

The results (normal/abnormal not clinically significant/ abnormal clinically significant, unless otherwise specified) of the following ophthalmic variables will be summarized by eye and analysis visit.

- Motility (Abnormal, Normal)
- Lids / Lacrimal / Lashes (Abnormal, Normal)
- Conjunctiva / Sclera (Abnormal, Normal)
- Cornea (Abnormal, Normal)
- Corneal Staining (0,1+,2+3+,4+),
- Anterior Chamber (Abnormal, Normal)
- Anterior Vitreous (Abnormal, Normal)
- AC Cells (0, 0.5+, 1+, 2+, 3+, 4+)
- AC Flare (0, 0.5+, 1+, 2+, 3+, 4+)
- Iris/Anterior Chamber (Abnormal, Normal)
- Pupils (Abnormal, Normal)
- Lens Status (Aphakic, Pseudo-phakic, Phakic)
- Lens Phakic Grade by type (Nuclear, Cortical, Posterior subcapsular): (0,1,2,3,4)

9.8.2 Fundoscopy

The results (normal/abnormal not clinically significant/ abnormal clinically significant, unless otherwise specified) for the following variables will be summarized by eye and analysis visit.

9.8.3 Intraocular Pressure

Intraocular Pressure (IOP) will be summarized by visit. An additional tabular summary of the percentage of subjects in categories of IOP (<15 mmHg, 15 to <20 mmHg, 20 to <25 mmHg, 25 to <30 mmHg, ≥30 mmHg) will be presented by treatment group and analysis visit.

9.8.4 Manual Measurement of Lid Retraction

Observed and change from baseline will be summarized by treatment group and analysis visit. An additional tabular summary of the percentage of subjects in categories of change from baseline (<2 mm, ≥2 mm) will be presented by treatment group and analysis visit.

Reference

Craig B, Rand K. Choice Defines QALYs. A US Valuation of the EQ-5D-5L Med Care 2018;00: 000–000

Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: Complete with Docusign: VRDN-001-301 SAP 03DEC2024 (4).docx
Source Envelope:
Document Pages: 39 Signatures: 4
Certificate Pages: 6 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
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Envelope Originator:
[redacted]
6200 Lookout Rd #100
Boulder, CO 80301
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Status: Original
12/3/2024 2:49:05 PM
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Signer Events	Signature	Timestamp
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Electronic Record and Signature Disclosure: Accepted: 4/26/2024 5:29:46 PM ID: [redacted]		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/3/2024 1:12:36 PM Viewed: 12/3/2024 2:48:07 PM Signed: 12/3/2024 2:48:58 PM
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Electronic Record and Signature Disclosure: Accepted: 12/3/2024 1:23:28 PM ID: [redacted]		

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
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Completed	Security Checked	12/3/2024 2:48:58 PM

Payment Events	Status	Timestamps

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Statistical Analysis Plan Addendum

SPONSOR:	Viridian Therapeutics, Inc.
PROTOCOL TITLE:	A randomized, double-masked, placebo-controlled safety, tolerability, and efficacy study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants with chronic thyroid eye disease (TED)
PROTOCOL VERSION:	Version 5.1, Amendment date: 27NOV2024
STUDY CODE:	VRDN-001-301 (THRIVE 2)
VERSION:	V0.1
DATE:	07AUG2025

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2. Planned Analysis Clarification

The exploratory endpoint for durability of proptosis response in the most proptotic eye as measured by exophthalmometer or MRI/CT will be based on the Treatment Policy estimand and missing data will be handled using the multiple imputation approach as described above. The durability (defined at Week XX as having the response at Week 15, Week XX, and every visit between) at each timepoint will be summarized by the total number of observations achieving durability response divided by the total number of data points (number subject achieving response at Week 15 X 50 imputation)

3 Additional Supplementary and Supportive Analyses

3.1 Supportive Durability Analysis

A supportive analysis for durability of proptosis response in the most proptotic eye as measured by exophthalmometer or MRI/CT at Weeks 24, 36, and 52 will be presented and missing data will be handled using the multiple imputation approach as described above. This supportive analysis will define durability at Week XX as achieving a response at Week 15 and Week XX. For example, durability of proptosis response at Week 52 is defined as being a responder at Week 15 and Week 52. Similar supportive analyses for durability will also be added for diplopia response, diplopia resolution, overall response in the most proptotic eye, and CAS of 0 or 1 (in participants with baseline CAS >=3) response in the study eye and CAS 0 or 1 for the most proptotic eye endpoints.

The durability at each timepoint will be summarized by the total number of observations achieving durability response divided by the total number of data points (number of subjects achieving response at Week 15 X 50 imputations.)

3.2 Proptosis Recurrence Rates

Proptosis recurrence rates at Weeks 24, 36, and 52 in the most proptotic eye as measured by exophthalmometer or MRI/CT, will be summarized. Recurrence at Week XX is defined as an increase in proptosis of ≥2 mm compared to Week 15. Furthermore, recurrence will be summarized by participants whose proptosis recurred and are still a responder, and participants whose proptosis recurred but are no longer a responder.

No worsening will also be summarized at Weeks 24, 36 and 52, which is defined as <2mm worsening (increase in proptosis) from the proptosis at Week 15.

These endpoints will be summarized by the total number of observations achieving status divided by the total number of data points (number subject achieving response at Week 15 X 50 imputation.

4. Observed Case Analysis

It is noted that observed case analysis will be conducted on the following endpoints

- Durability of proptosis response via exophthalmometer and MRI/CT in most proptotic eye at Week 24, 36, 52
- Proptosis recurrence rates at Week 24, 36, and 52 in the most proptotic eye as measured by exophthalmometer and MRI/CT
- Durability of CAS 0 or 1 (in participants with baseline CAS >=3) response in most proptotic eye at Week 24, 36, and 52
- Durability of overall response in most proptotic eye at Week 24, 36, and 52
- Durability of diplopia response at Week 24, 36, and 52
- Durability of diplopia resolution at Week 24, 36, and 52

5. Additional Subgroups

Additional subgroups based on tobacco use (current/previous/never) are defined for subgroup analyses in addition to the ones presented in Section 5.4 of the SAP.

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