VIRIDIAN

NCT #: NCT05176639

# Statistical Analysis Plan

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| SPONSOR: | Viridian Therapeutics, Inc. |
| PROTOCOL TITLE: | A [redacted] safety, tolerability and efficacy study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in normal healthy volunteers (NHVs) and subjects with thyroid eye disease (TED) |
| PROTOCOL VERSION: | Version 9.1, Amendment date: 14-AUG-2024 |
| STUDY CODE: | VRDN-001-101 (THRIVE) |
| VERSION: | V2.0 |
| DATE: | 19AUG2024 |

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# SIGNATURE PAGE

[redacted]

Viridian Therapeutics, Inc.

Signature/Date: [redacted]

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Viridian Therapeutics, Inc.

Signature/Date: _[redacted]

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Viridian Therapeutics, Inc.

Signature/Date: [redacted]

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# Table of Contents

# 1. List of Abbreviations and Definition of Terms

| Abbreviation | Term |
|---|---|
| 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 |
| 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 |
| LOCF | Last Observation Carried Forward |
| [redacted] | [redacted] |
| MAR | Missing at Random |
| MCMC | Markov Chain Monte Carlo |
| MI | Multiple Imputation |
| mITT | Modified Intent-To-Treat |
| MNAR | Missing not at Random |
| NR | Non-responder |
| 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-001-101, pivotal portion (THRIVE). The [redacted] and pivotal parts of the study will be analyzed separately, the results will not be pooled. [redacted] 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 9.1 of the protocol dated 14-AUG-2024.

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.

A brief history of protocol amendments is outlined below.

| Version | Approval Date | Salient Changes if any* |
|---|---|---|
| Amendment 4 V5.0 | 07SEP2022 | -Creation of a separate primary endpoint for Australia, EU and UK in addition to the primary endpoint for Canada and USA |
| Amendment 5 V6.0 | 29SEP2022 | -Increase in the number of secondary efficacy endpoints |
| Amendment 6 V7.0 | 12MAY2023 | -Remove endpoints, assessments and references related to facial photography |
| [redacted] | [redacted] | -Elimination of the 8 infusion arm in the pivotal portion of the study.<br>-Randomization updated to (2:1) to 5 infusions versus placebo<br>-Align the primary endpoint in terms of timepoint, sample size, and statistical assumptions with the 5-infusion treatment schedule vs placebo such that the primary endpoint will be 3 weeks after last fifth infusion (Week 15) and the sample size reduced (n ≈90 vs ≈120) to accommodate a 2 arm pivotal study design. |
| Amendment 8 V9.0 | 06SEP2023 | -Replacement of the Week 21 Visit with a Week 24 Visit.<br>-Addition of EQ-5D-5L as additional quality of life assessment. |
| Amendment 9 V9.1 | 14AUG2024 | Update secondary and exploratory endpoints for the US |

# 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, and the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of VRDN-001 in healthy volunteers (HV) and thyroid eye disease (TED) patients [redacted].

### 3.1.1 Primary Efficacy Endpoint in the Pivotal Portion of the Study

#### 3.1.1.1 USA, Canada and China

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

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

Overall Responder Rate comprises Proptosis Responder Rate in the study eye (i.e., reduction of proptosis of ≥ 2 mm from baseline in the study eye [without a corresponding increase of ≥ 2 mm in the fellow eye] as measured by exophthalmometer) at 3 weeks post the fifth infusion (i.e., Week 15) and Clinical Activity Responder Rate in the study eye (i.e., reduction in Clinical Activity Score (CAS) ≥ 2 points from baseline in the study eye [without a corresponding increase of ≥ 2 points in the fellow eye]) at 3 weeks post the fifth infusion (i.e., Week 15).

### 3.1.2 Key Secondary Endpoint in the Pivotal Portion of the Study

#### 3.1.2.1 USA

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15
- Proptosis Responder Rate in the most proptotic eye as measured by MRI/CT at Week 15
- Change from baseline in proptosis in the most proptotic eye as measured by MRI/CT at Week 15
- Change from baseline in CAS in the study eye at Week 15
- Overall Responder Rate in the study eye at Week 15
- Clinical Activity Responder Rate in the study eye at Week 15
- Diplopia Responder Rate at Week 15
- Diplopia Resolution Rate at Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

#### 3.1.2.2 Canada and China

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15
- Clinical Activity Responder Rate in the study eye at Week 15
- Change from baseline in CAS in the study eye at Week 15
- Overall Responder Rate in the study eye at Week 15
- Diplopia Resolution Rate at Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

#### 3.1.2.3 Australia, European Union, Turkey and United Kingdom

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15
- Change from baseline in CAS in the study eye at Week 15
- Diplopia Resolution Rate at Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

### 3.1.3 Key Secondary Endpoint in the Pivotal Portion of the Study

#### 3.1.3.1 USA

- Proptosis Responder Rate in the study eye as measured by exophthalmometer at Weeks 24, 36 and 52
- Proptosis Responder Rate in the fellow eye as measured by exophthalmometer at Weeks 15, 24, 36 and 52
- Change from baseline in proptosis by exophthalmometer in the study eye at Weeks 24, 36, and 52
- Change from baseline in proptosis by exophthalmometer in the fellow eye at Weeks 15, 24, 36 and 52
- Proptosis Responder Rate in the most proptotic eye as measured by MRI/CT at Weeks 24, 36 and 52
- Proptosis Responder Rate in the other eye as measured by MRI/CT at Weeks 15, 24, 36 and 52
- Change from baseline in proptosis in the most proptotic eye as measured by MRI/CT at Weeks 24, 36 and 52
- Change from baseline in proptosis in the other eye as measured by MRI/CT at Weeks 15, 24, 36 and 52
- Durability of Proptosis Response in the study eye as measured by exophthalmometer at Weeks 24, 36 and 52
- Durability of Proptosis Response in the most proptotic eye as measured by MRI/CT at Weeks 24, 36 and 52
- Time to First Proptosis Response in the study eye as measured by exophthalmometer
- Clinical Activity Responder Rate in the study eye at Weeks 24, 36 and 52
- Clinical Activity Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Change from baseline in CAS in the study eye at Weeks 24, 36 and 52
- Change from baseline in CAS in the fellow eye at Weeks 15, 24, 36 and 52
- Time to first CAS Response in the study eye
- Overall Responder Rate comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the study eye at Weeks 24, 36 and 52
- Overall Responder Rate comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Overall Responder Rate comprising Proptosis Responder Rate as measured by MRI/CT and Clinical Activity Responder Rate in the most proptotic eye at Weeks 15, 24, 36 and 52

- Overall Responder Rate comprising Proptosis Responder Rate as measured by MRI/CT and Clinical Activity Responder Rate in the other eye at Weeks 15, 24, 36 and 52
- Time to First Overall Response comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the study eye
- Diplopia Responder Rate at Weeks 24, 36 and 52
- Diplopia Resolution Rate at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the study eye at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the fellow eye at Weeks 15, 24, 36 and 52
- Change from baseline in the following parameters at Weeks 15, 24, 36 and 52:
    - Extraocular muscle volume in the most proptotic eye as determined by MRI/CT
    - Orbital fat volume in the most proptotic eye as measured by MRI/CT
    - Manual measurement of lid retraction in the study eye
    - Graves' Orbitopathy-Quality of Life (GO-QoL) combined score
    - GO-QoL activity subscale
    - GO-QoL appearance subscale
    - EQ-5D-5L QoL questionnaire
    - Visual Acuity (VA)
    - Gorman Subjective Diplopia Score
- VRDN-001, IGF-1 and anti-drug antibodies (ADA) at various time points pre- and post-infusions.

**Exploratory Endpoints in Australia, Canada, China, EU, Turkey, and UK in the Pivotal portion of the Study (THRIVE):**

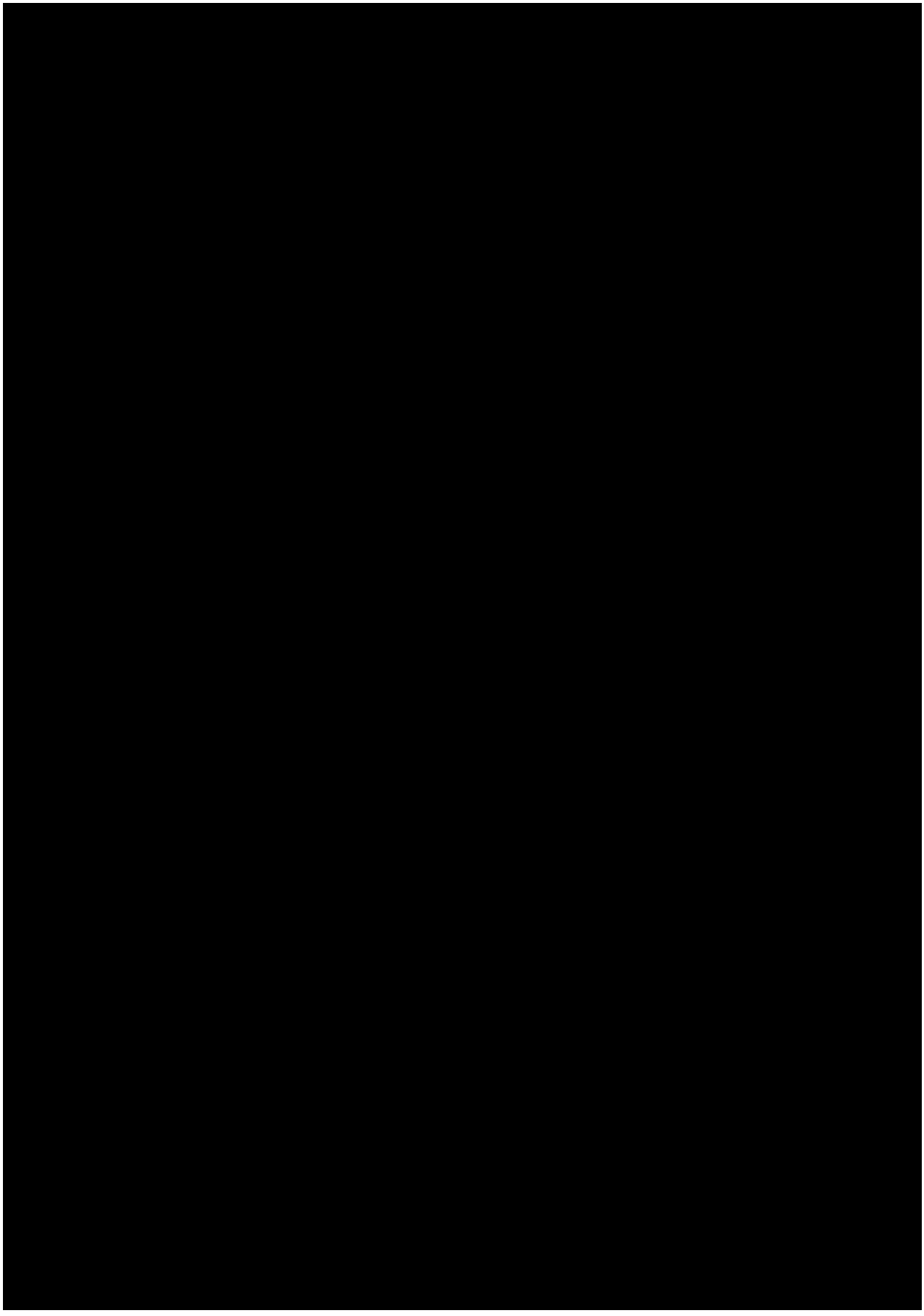
- Proptosis Responder Rate in the study eye as measured by exophthalmometer) at Week 24 (12 weeks post fifth infusion), Week 36 (24 weeks post fifth infusion) and Week 52
- Proptosis Responder Rate in the fellow eye (i.e., reduction of proptosis of ≥ 2 mm from baseline as measured by exophthalmometer) at Weeks 15, 24, 36 and 52
- Durability of Proptosis Response in the study eye at Weeks 24, 36 and 52
- Time to First Proptosis Response in the study eye
- Clinical Activity Responder Rate in the study eye at Weeks 24, 36 and 52
- Clinical Activity Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Change from baseline in CAS in the study eye at Weeks 24, 36 and 52
- Change from baseline in CAS in the fellow eye at Weeks 15, 24, 36 and 52
- Time to first CAS Response in the study eye
- Overall Responder Rate in the study eye at Weeks 24, 36 and 52
- Overall Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Time to First Overall Response in the study eye
- Diplopia Resolution Rate at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the study eye at Weeks 24, 36 and 52

- Proportion of participants with a CAS score of zero or one in the fellow eye at Weeks 15, 24, 36 and 52
- Proptosis Responder Rate in the study eye as measured by magnetic resonance imaging [MRI] or Computed Tomography [CT – where allowed by local health authorities] at Weeks 15, 24, 36 and 52
- Change from baseline in the following parameters at Weeks 15, 24, 36 and 52:
  - Proptosis in the study eye by MRI (or CT – where allowed by local health authorities)
  - Extraocular muscles in the study eye as determined by MRI (or CT – where allowed by local health authorities)
  - Orbital fat in the study eye as measured by MRI (or CT – where allowed by local health authorities)
  - Manual measurement of lid retraction in the study eye
  - Graves' Orbitopathy-Quality of Life (GO-QoL) combined score
  - GO-QoL activity subscale
  - GO-QoL appearance subscale
  - EQ-5D-5L QoL questionnaire
  - Visual Acuity (VA)
  - Gorman Subjective Diplopia Score

- VRDN-001, IGF-1 and anti-drug antibodies (ADA) at various time points pre- and post-infusions.

## 3.2 [redacted]

[redacted]



[redacted]

## 4. Overall Study Design

This study includes two portions; the [redacted] and the pivotal portion of the study (THRIVE). Details regarding the [redacted] of the study can be found in the protocol.

THRIVE will be a randomized, double masked (including the sponsor) and placebo-controlled study in active TED participants whose signs and symptoms declared themselves within 15 months of screening. The dose selected is 10 mg/kg. The study will comprise approximately 90 participants (to ensure 78 evaluable participants at the primary endpoint at 3 weeks post the fifth infusion (i.e., Week 15) randomized with an allocation ratio of 2:1 (60 participants active: 30 participants placebo), stratified at baseline by level of proptosis in the study eye (≥23 mm, Y/N) as measured by exophthalmometer, and will compare the efficacy of 5 infusions of 10 mg/kg VRDN-001 administered at 3-week intervals to placebo.

Participants in THRIVE were either randomized (1:1:1) to 5 infusions or 8 infusions versus placebo (as per all previous versions 7.0 and before of the VRND-001-101 protocol) or will be randomized (2:1) to 5 infusions versus placebo [redacted], each administered as IV infusions at 3-week intervals. All participants will receive a total of 5 to 8 infusions to maintain masking as determined by the protocol version to which the participants were randomized. For those participants previously randomized to 8 infusions and who have received greater than 5 infusions, further infusions will be discontinued if the participant signed informed consent to protocol version 8.0 or higher.

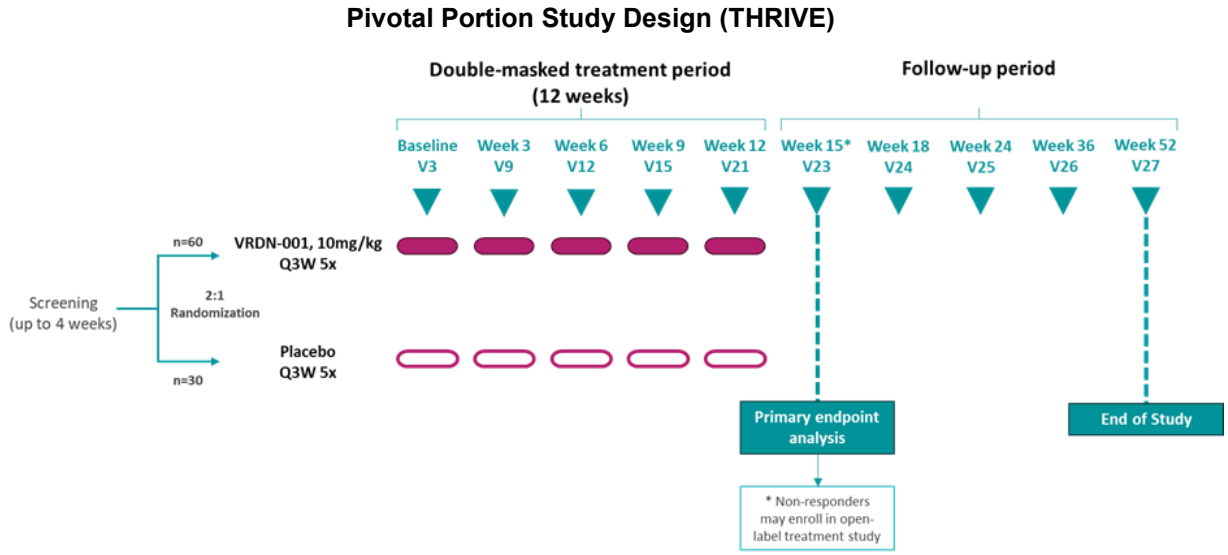
Participants who are deemed to be non-responders 3 weeks post the fifth infusion in the pivotal portion of the study may be offered the option to enroll into an open-label treatment study (separate study denoted as VRDN-001-302) where they will receive 5 further infusions of VRDN-001 at 3-week intervals 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 is defined as either:

- A participant who did not achieve a ≥ 2 mm reduction from baseline in proptosis (as measured by exophthalmometer) in the study 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 exophthalmometer) in the study eye but had a corresponding increase of ≥ 2 mm from baseline in proptosis in the fellow eye at 3 weeks post the fifth infusion (i.e., Week 15).

Measurements as described in the Schedule of Activities (SoA) in the protocol will continue to be collected through 52 weeks for those participants who are deemed to be responders (i.e., did achieve a ≥2 mm reduction in proptosis in the study eye as measured by exophthalmometer) at 3 weeks post the fifth infusion (i.e., Week 15) in the pivotal portion of the study. Participants who are non-responders at 3 weeks post the fifth infusion (i.e., Week 15) in the pivotal portion of the study and do not enroll in the open-label treatment study for a further 5 infusions will continue to have data collected through 52 weeks as described in the SoA.




## 4.1 Sample Size Justification

THRIVE has a power of greater than 90% to test the 5 infusions regimen versus placebo. The responder rate in the active arm is assumed to be 60% and 20% in the placebo arm. The assumptions for the proptosis responder rates are based on the observed outcomes in the Horizon studies, testing teprotumumab vs placebo. To this end, a multiplicity gated method will be utilized to control the Type 1 error. The testing will cover the primary and key secondary endpoints. Statistical testing will continue until a p-value crosses the threshold of 0.025. The study consists of 90 participants, randomized with allocation ratio of 2:1 over the 5 infusions dose regimen and placebo arms (approximately 60 active arm: 30 placebo arm). A comparison would reach significance if the difference in proptosis responder rate is at least 32.2%.

# 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 25$^{th}$, 50$^{th}$, 75$^{th}$ 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 combine the 5 infusion and 8 infusion treatment arms compared to placebo. The treatment groups will be displayed as follows:

- VRDN-001 (combined 5 and 8 infusions)
- Placebo

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

- VRDN-001- 5 infusions
- VRDN-001- 8 infusions
- VRDN-001 (combined 5 and 8 infusions)
- Placebo
- Overall

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

- VRDN-001 ≤5 infusions
- VRDN-001 >5 infusions
- VRDN-001 (combined ≤5 and >5 infusions)
- Placebo
- Overall

Analyses may have separate summaries by eye. The summary will be for the study eye and the fellow eye unless stated differently.

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

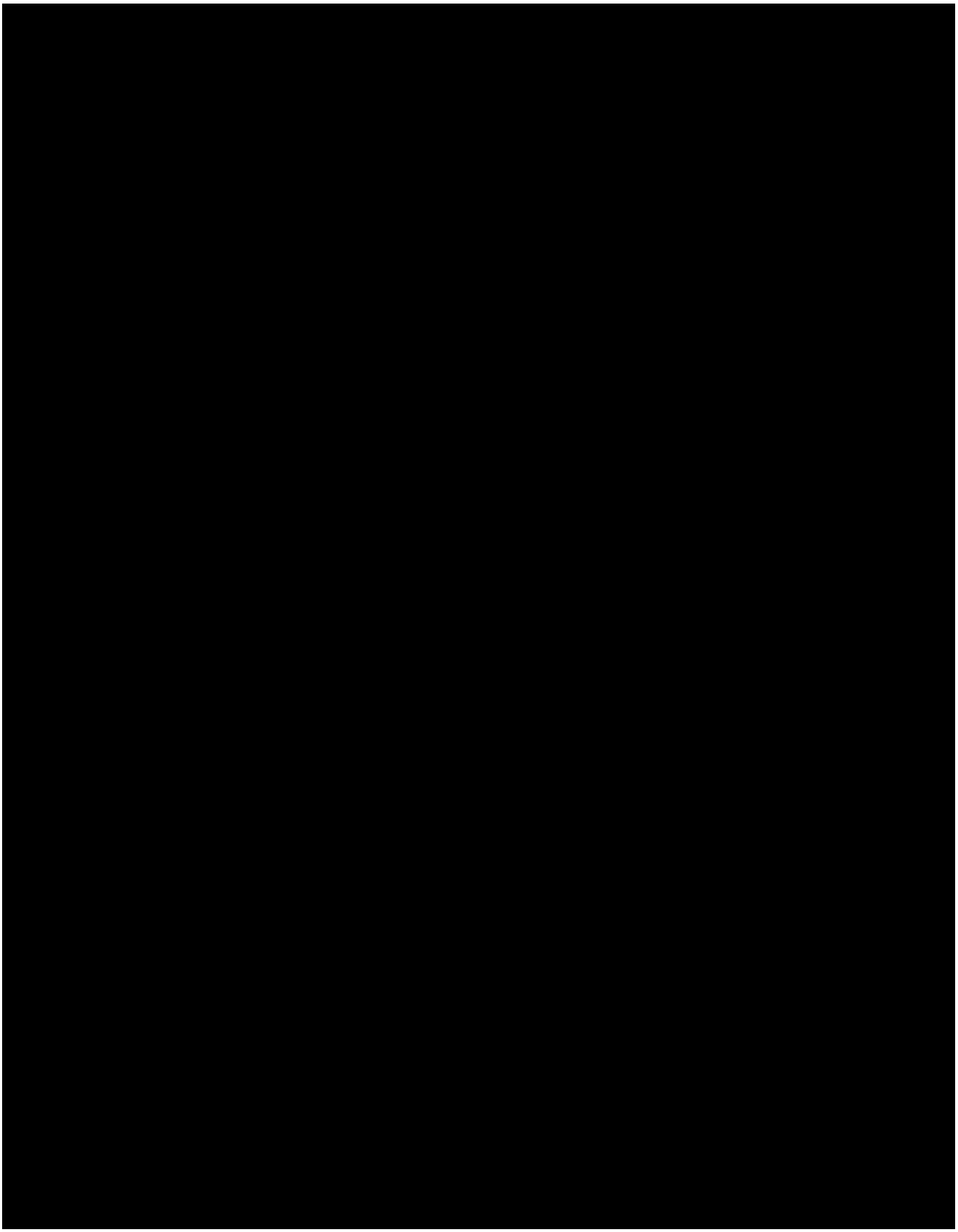
Screening period will be defined as the period before the start date of study medication.

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]



## 5.2 Planned Analyses

### 5.2.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review the safety and 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 discontinued. The following analyses include but 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 pre-specified contract research organization (CRO) personnel.

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 52 Follow-up Analysis

A second database lock will occur when the participants who were not eligible or chose not to participant in the open label extension complete the last protocol assessment or early discontinued. All 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. All analyses will be generated, even the Week 15 analysis.

## 5.3 Definition of Populations

### 5.3.1 Enrolled Population

The Enrolled population includes all subjects who signed the informed consent. This population will be utilized for disposition and patient accounting analyses.

### 5.3.2 Intention-To-Treat Population

The Intent-to-Treat (ITT) population will include all participants who were randomized into the THRIVE portion of the study, irrespective of whether study medication was administered or not. 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 THRIVE portion of the study and received at least one infusion treatments.

### 5.3.4 Safety Population

The Safety population will include all participants in the THRIVE portion of the study who 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 and number of infusions received (refer section 5).

### 5.3.5 Per-Protocol Population

The Per-Protocol (PP) population will comprise participants in the mITT population who did not have impactful major protocol violations during the double-masked treatment period. Some major protocol violations may include but not limited to:

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

The PP population will be reviewed prior to unmasking for the Week 15 analysis and the end of study analysis. This population will be analyzed according to randomized treatment assignment.

### 5.3.6 Pharmacokinetic Population

The Pharmacokinetic population will be defined in a separate analysis plan.

### 5.3.7 Pharmacodynamic Population

The Pharmacodynamic population will be defined in a separate analysis plan.

## 5.4 Subgroup Definitions

The primary and key secondary endpoints will be summarized descriptively 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
- Baseline Proptosis by the appropriate method: <23 mm and ≥23 mm
- Steroid use during the double-masked treatment period (Y/N).

Other subgroup analyses may be analyzed descriptively as appropriate.

## 5.5 Treatment Assignment and Treatment Arms

- 5 infusions of 10 mg/kg VRDN-001 administered at 3-week intervals
- 8 infusions of 10 mg/kg 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.

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:

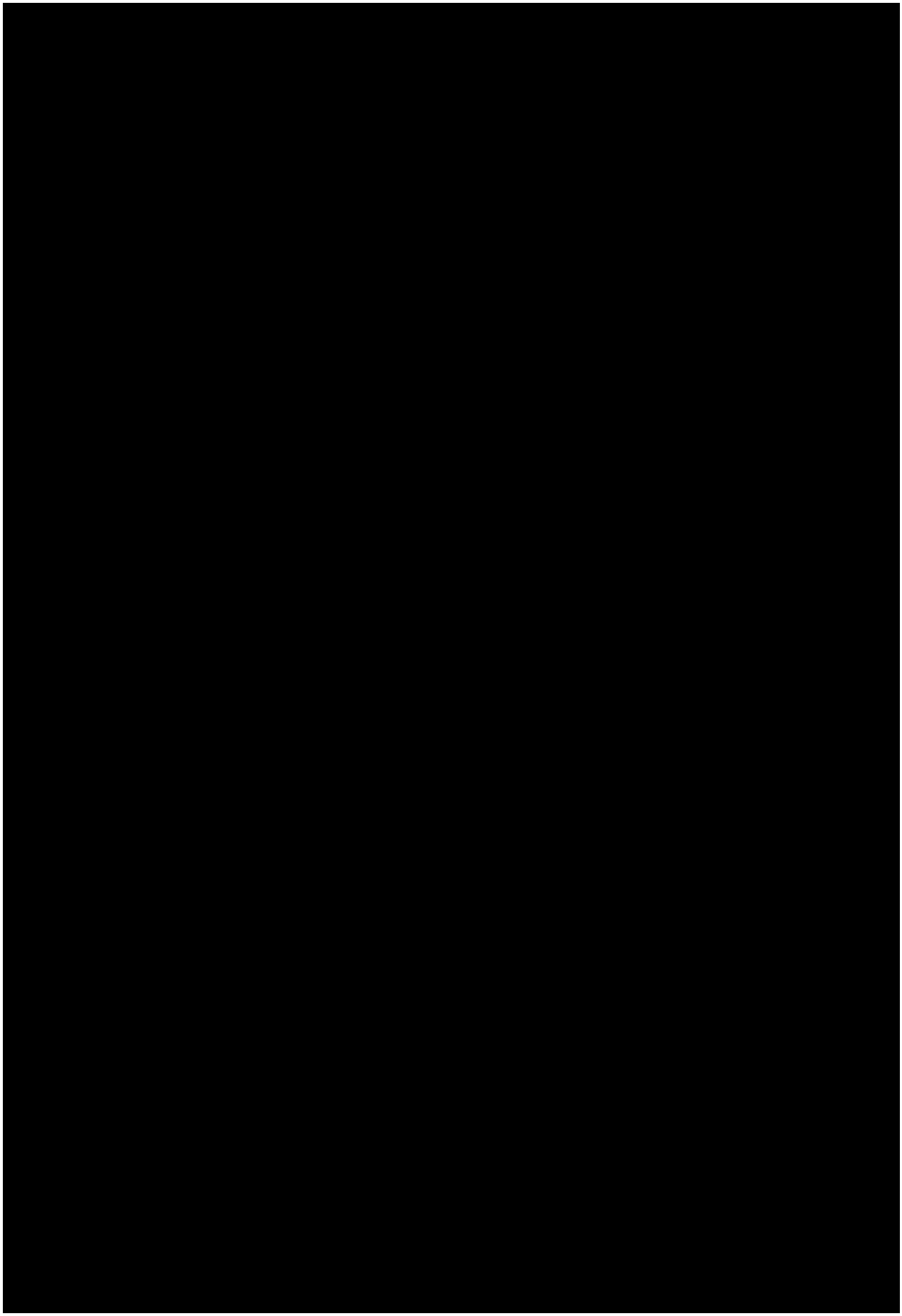
- If end date is missing, the end date will be set to the last contact date.
- If end date is incomplete:
  - if the day is missing and month/year is same as the last contact date then use last contact date, else the end date will be imputed with the last day of the month;
  - if the day and month are 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 [redacted]

[redacted]



## 5.9 Changes from the Protocol

No changes from the protocol identified.

# 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 for the ITT population.

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 deviations 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 the Week 15 and Week 52 database lock.

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.

## 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 PP populations. The variables to be summarized are as follows:

- Age (years)
- Gender at Birth (Male, Female)
- Race (Asian, Black, White, Other)
- Study Eye (OD, OS)
- Country (United States, Rest of World)
- Actual Stratification (baseline level of proptosis by exophthalmometer in the study eye (≥23 mm, Y/N))
- Initial TED onset (months) from randomization
- Audiometry: PTA (db), PTA >25 Y/N, medical history of hearing issue
- Baseline Diplopia
- Baseline CAS in the study eye
- Baseline Proptosis (by exophthalmometer 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, and ophthalmic histories, including TED 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 on the "Ophthalmic History" eCRF page.

Ophthalmic history events, excluding primary diagnosis TED 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.

A listing of ophthalmic history events and primary TED diagnosis will be provided separately.

## 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 the 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

Prior and concomitant procedures and surgeries will be collected on the "Prior and Concomitant Procedures and Surgeries" 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 where proptosis is assessed. The average of the three measurements is recorded in the database.

Proptosis responder in the study eye is defined as a reduction of proptosis of ≥ 2 mm from baseline in the study eye (without a corresponding increase of ≥ 2 mm in the fellow eye) as measured by exophthalmometer.

Durability of Proptosis Response in the study eye at Weeks 24, 36 and 52 is defined as achieving a response at Week 15, the visit of interest and any visit between these 2 visits. For example, durability of proptosis response at Week 36 is defined as having a response at Weeks 15, 24 and 36.

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

**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 scores (range, 0 to 7, with higher scores indicating greater level of inflammation).

Clinical Activity Responder in the study eye is defined as reduction in CAS ≥ 2 points from baseline in the study eye (without a corresponding increase of ≥ 2 points in the fellow eye).

Overall Responder in the study eye comprises achieving Proptosis Responder in the study eye as measured by exophthalmometer and Clinical Activity Responder in the study eye.

Time to First Clinical Activity Response in the study eye is defined as (date of first clinical activity response in the study eye - date of first administration of study medication) +1. If a participant does not achieve clinical activity response in the study eye by their Week 15 assessment, they will be censored at their last study eye CAS assessment during the double-masked treatment period, whichever is later.

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

**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 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. Details for image acquisition are outlined in the imaging user manuals provided by the central imaging reading center. 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. Images will be taken at baseline and the measurements compared at various post-treatment timepoints. Imaging will utilize T1/T2 high resolution with 1 mm slices and thickness of orbits, face and ears without contrast. Proptosis will be measured from the lateral orbital rim to the center of the cornea.

Proptosis Responder in the most proptotic eye is defined as a reduction of proptosis of ≥ 2 mm from baseline in the most proptotic eye (without a corresponding increase of ≥ 2 mm in the other eye) as measured by MRI or CT, where allowed by local health authorities.

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

Three-dimensional volumetric calculation of extraocular muscle (EOM) and orbital fat will be conducted by the central imaging reading center using MRI/CT of the orbits acquired without contrast. Details for image acquisition are outlined in the imaging user manuals provided by the central imaging reading center. Total rectus muscle volumes and orbital fat volume will be summarized descriptively for each orbit by analysis visit.

## 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 5-level 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/).

EQ-5D-5L is only collected for subjects enrolled in the study under protocol V9.0, therefore there may be limited data.

## Visual Acuity

Visual acuity (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. Where $\text{logMAR}=-1*\log_{10}$ (Snellen fraction).

The change from baseline of visual acuity will be assessed by the visual acuity line and will be defined as (Post-Baseline line - Baseline line).

**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 study eye will be the most proptotic as assessed by exophthalmometer at the last assessment performed prior to the Day 1 infusion and 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 for study eye. For statistical analysis of endpoints, which are assessed by eye, the study eye and fellow eye will be defined as noted above (i.e., as assessed by exophthalmometer). For MRI/CT based endpoints the most proptotic eye as assessed by MRI/CT is determined by the last assessment performed prior to the Day 1 IV infusion and will be used to define the most proptotic eye and the other eye. 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.

All efficacy endpoints are defined for the study eyes. Given the systemic nature of the study medication, the outcomes for the fellow eyes will also be evaluated for efficacy and safety. All analyses for primary and secondary efficacy endpoints will be repeated for the fellow eyes following similar definitions.

The study-wise one-sided type-I error level of 0.025 such that tests will be considered statistically significant if their p-value is less than 0.025 minus the statistical penalty for data reviews. The p-value for the primary analysis will be determined prior to the Week 15 database lock and will be documented in a statistical report. A gated testing methodology will be utilized to control Type 1 error. The order is as follows:

**USA**

1.) Primary Endpoint: Proptosis Responder Rate in the study eye as measured by exophthalmometer at Week 15

2.) Key Secondary Endpoint: Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15

3.) Key Secondary Endpoint: Proptosis Responder Rate in the most proptotic eye as measured by MRI/CT at Week 15

4.) Key Secondary Endpoint: Change from baseline in proptosis in the study eye as measured by MRI/CT at Week 15

5.) Key Secondary Endpoint: Change from baseline in CAS in the study eye at Week 15

6.) Key Secondary Endpoint: Overall Responder Rate in the study eye at Week 15

7.) Key Secondary Endpoint: Clinical Activity Responder Rate in the study eye at Week 15

8.) Key Secondary Endpoint: Diplopia Responder Rate at Week 15

9.) Key Secondary Endpoint: Diplopia Resolution Rate at Week 15

10.) Key Secondary Endpoint: Proportion of participants with a CAS score of zero or one in the study eye at Week 15

**Canada and China**

1.) Primary Endpoint: Proptosis Responder Rate in the study eye as measured by exophthalmometer at Week 15

2.) Key Secondary Endpoint: Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15

3.) Key Secondary Endpoint: Clinical Activity Responder Rate in the study eye at Week 15

4.) Key Secondary Endpoint: Change from baseline in CAS in the study eye at Week 15

5.) Key Secondary Endpoint: Overall Responder Rate in the study eye at Week 15

6.) Key Secondary Endpoint: Diplopia Resolution Rate at Week 15

7.) Key Secondary Endpoint: Proportion of participants with a CAS score of zero or one in the study eye at Week 15

**Australia, European Union and United Kingdom**

1.) Primary Endpoint: Overall Responder Rate in the study eye by exophthalmometer at Week 15

2.) Key Secondary Endpoint: Change from Baseline in proptosis in the study eye as measured by exophthalmometer at Week 15

3.) Key Secondary Endpoint: Change from Baseline in CAS in the study eye at Week 15

4.) Key Secondary Endpoint: Diplopia Resolution Rate Week 15

5.) Key Secondary Endpoint: Proportion of participants with a CAS score of zero or one in the study eye at Week 15

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

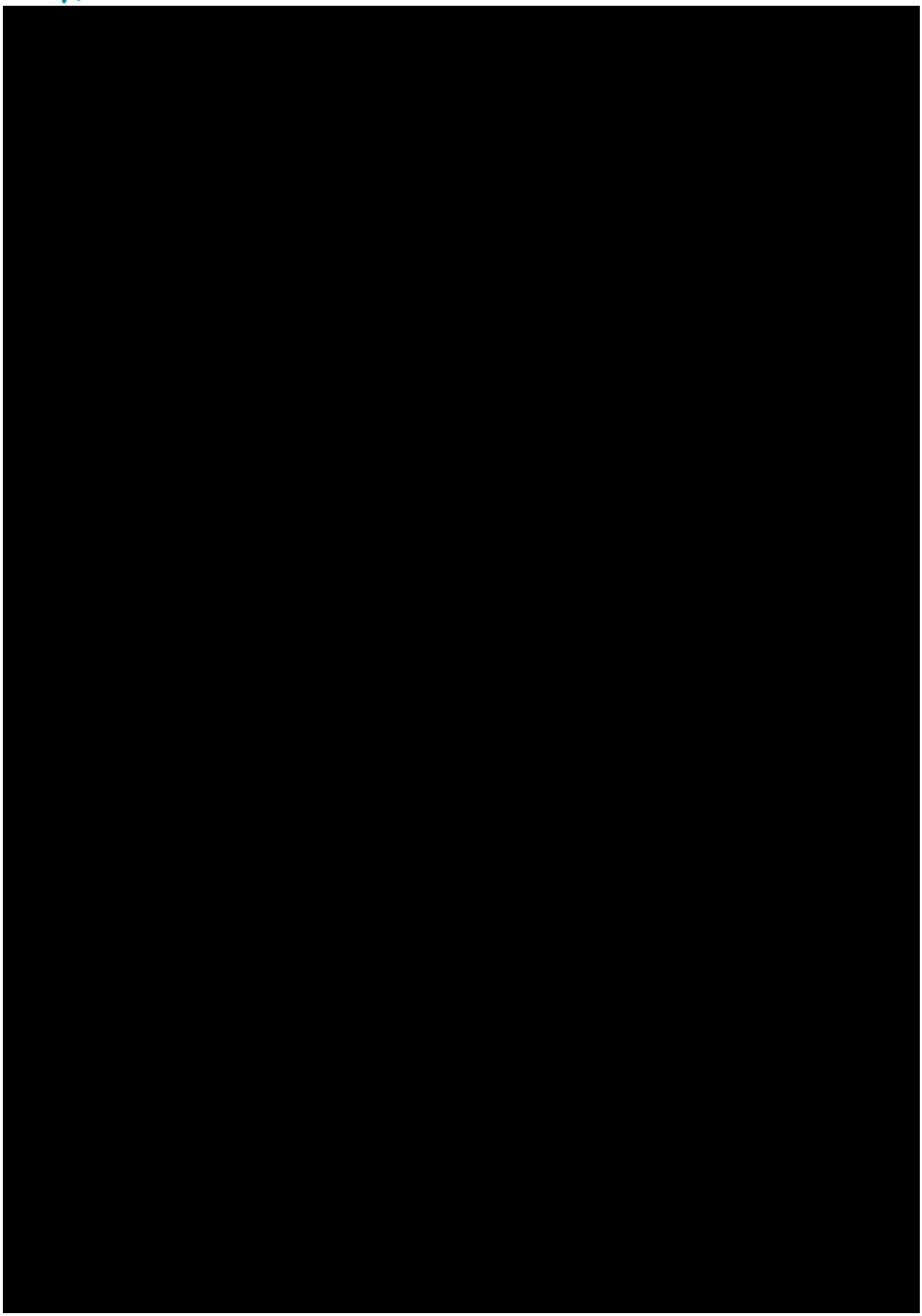
| Analysis | Endpoint | Population (Imputation, Estimand) |
|---|---|---|
| Primary Analysis of Primary Endpoint | Primary Endpoint | mITT (MI, Treatment Policy Strategy) |
| Sensitivity Analysis of the Primary Endpoint | Primary Endpoint | ITT (MI, Treatment Policy Strategy)<br>PP (MI, Treatment Policy Strategy)<br>mITT (MI, Composite Strategy)<br>ITT (MI, Composite Strategy)<br>PP (MI, Composite Strategy)<br>mITT (OC, Treatment Policy Strategy)<br>ITT (OC, Treatment Policy Strategy)<br>PP (OC, Treatment Policy Strategy)<br>mITT (NRI, Treatment Policy Strategy)<br>ITT (NRI, Treatment Policy Strategy)<br>PP (NRI, Treatment Policy Strategy) |
| Primary Analysis of Key Secondary Endpoint | Key Secondary Endpoint | [1]mITT (MI/ EXI, Treatment Policy Strategy) |
| Sensitivity Analysis Key Secondary Endpoint | Key Secondary Endpoint | [1]ITT (MI/EXI, Treatment Policy Strategy)<br>[1]PP (MI/EXI, Treatment Policy Strategy)<br>[1]mITT (MI/EXI, Composite Strategy<br>[1]ITT (MI/EXI, Composite Strategy)<br>[1]PP (MI/EXI, Composite Strategy)<br>[2]mITT (OC/ LOCF, Treatment Policy Strategy)<br>[2]ITT (OC/ LOCF, Treatment Policy Strategy)<br>[2]PP (OC/ LOCF, Treatment Policy Strategy)<br>mITT (NRI, Treatment Policy Strategy)<br>ITT (NRI, Treatment Policy Strategy)<br>PP (NRI, Treatment Policy Strategy) |

[1] The key secondary endpoint, Proptosis Responder as measured by MRI/CT at Week 15 will not be analyzed using MI but rather the EXI method for handling missing data.

[2] The key secondary endpoint, Proptosis Responder as measured by MRI/CT at Week 15 will not be analyzed using observed-cases but rather the LOCF imputation.

## 8.2 [redacted]

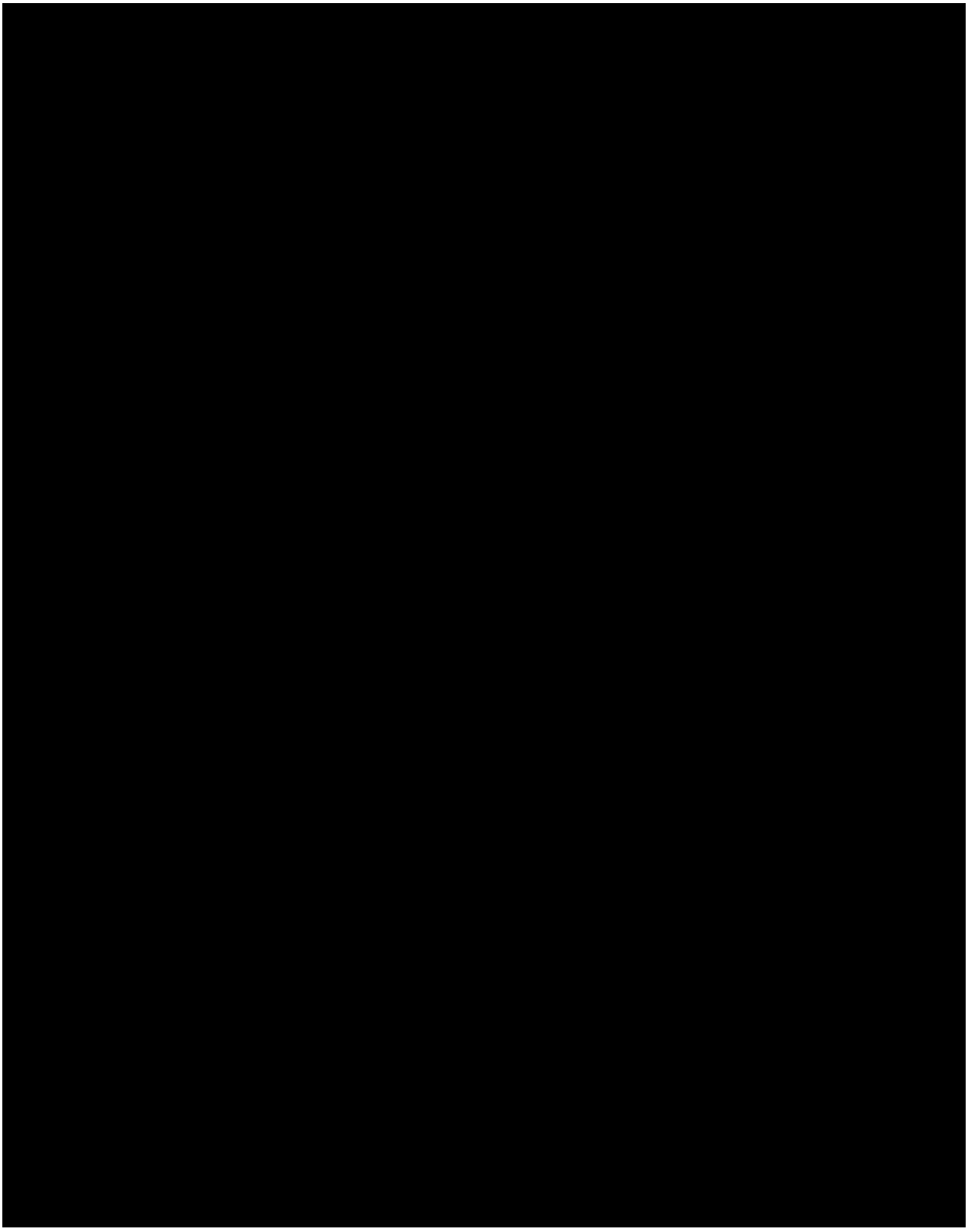
[redacted]



[redacted]

## 8.3 [redacted]

[redacted]



## 8.4 Exploratory Endpoints

### 8.4.1 Exploratory Endpoints in USA

The exploratory endpoints listed below will be analyzed using the same method described in sections 8.2 and 8.3, except all data throughout the study will be included in the statistical

models for endpoints beyond Week 15. Endpoints at Week 15 or earlier will only include data through Week 15. The exploratory endpoint will be based on the observed-cases or LOCF for MRI/CT endpoints based on the mITT population, unless noted elsewhere.

- Proptosis Responder Rate in the study eye as measured by exophthalmometer at Weeks 24, 36 and 52
- Proptosis Responder Rate in the fellow eye as measured by exophthalmometer at Weeks 15, 24, 36 and 52
- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Weeks 24, 36 and 52
- Change from baseline in proptosis in the fellow eye as measured by exophthalmometer at Weeks 15, 24, 36 and 52
- Change from baseline in proptosis as measured by MRI/CT in the most proptotic eye at Weeks 24, 36, and 52
- Change from baseline in proptosis as measured by MRI/CT in the other eye at Weeks 15, 24, 36 and 52
- Durability of Proptosis Response in the study eye as measured by exophthalmometer at Weeks 24, 36 and 52
- Durability of Proptosis Response in the most proptotic eye as measured by MRI/CT at Weeks 24, 36 and 52
- Clinical Activity Responder Rate in the study eye at Weeks 24, 36 and 52
- Clinical Activity Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Change from baseline in CAS in the study eye at Weeks 24, 36 and 52
- Change from baseline in CAS in the fellow eye at Weeks 15, 24, 36 and 52
- Overall Responder Rate comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the study eye at Weeks 24, 36 and 52
- Overall Responder Rate comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Overall Responder Rate comprising Proptosis Responder Rate as measured by MRI/CT and Clinical Activity Responder Rate in the most proptotic eye at Weeks 15, 24, 36 and 52
- Overall Responder Rate comprises Proptosis Responder Rate as measured by MRI/CT and Clinical Activity Responder Rate in the other eye at Weeks 15, 24, 36 and 52
- Diplopia Responder Rate at Weeks 24, 36 and 52
- Diplopia Resolution Rate at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the study eye at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the fellow eye at Weeks 15, 24, 36 and 52

The following endpoints will be summarized using the Kaplan-Meier method.

- Time to First Proptosis Response in the study eye as measured by exophthalmometer.
- Time to first CAS Response in the study eye
- Time to First Overall Response in the study eye as measured by exophthalmometer.

The following change from baseline endpoints will be described using summary statistics.

- Extraocular muscle volume in the most proptotic eye as determined by MRI/CT
- Orbital fat volume in the most proptotic eye as measured by MRI/CT
- Manual measurement of lid retraction in the study eye
- GO-QoL combined score
- GO-QoL activity subscale
- GO-QoL appearance subscale
- EQ-5D-5L QoL questionnaire
- Visual Acuity (VA)
- Gorman Subjective Diplopia Score

### 8.4.2 Exploratory Endpoints in Australia, Canada, China, Turkey, EU and UK

The exploratory endpoints listed below will be analyzed using the same method described in sections 8.2 and 8.3, except all data throughout the study will be included in the statistical models for endpoints beyond Week 15. Endpoints at Week 15 or earlier will only include data through Week 15. The exploratory endpoints will be based on the observed-cases or LOCF for MRI/CT endpoints based on the mITT population, unless noted elsewhere.

- Proptosis Responder Rate in the study eye as measured by exophthalmometer at Weeks 24, 36, and 52
- Proptosis Responder Rate in the fellow eye as measured by exophthalmometer at Weeks 15, 24, 36 and 52
- Durability of Proptosis Response in the study eye at Weeks 24, 36 and 52
- Clinical Activity Responder Rate in the study eye at Weeks 24, 36 and 52
- Clinical Activity Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Change from baseline in CAS in the study eye at Weeks 24, 36 and 52
- Change from baseline in CAS in the fellow eye at Weeks 15, 24, 36 and 52
- Overall Responder Rate in the study eye at Weeks 24, 36 and 52
- Overall Responder Rate in the fellow eye at Weeks 15, 24, 36 and 52
- Diplopia Resolution Rate at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the study eye at Weeks 24, 36 and 52
- Proportion of participants with a CAS score of zero or one in the fellow eye at Weeks 15, 24, 36 and 52
- Proptosis Responder Rate in the most proptotic eye as measured by magnetic resonance imaging MRI/CT at Weeks 15, 24, 36 and 52
- Change from baseline Proptosis in the most proptotic eye by MRI/CT at Weeks 15, 24, 36 and 52

The following endpoints will be summarized using the Kaplan-Meier method.

- Time to First Proptosis Response in the study eye
- Time to First CAS Response in the study eye
- Time to First Overall Response in the study eye

The following change from baseline endpoints will be described using summary statistics.

- Extraocular muscles volume in the proptotic eye as determined by MRI (or CT – where allowed by local health authorities)

- Orbital fat volume in the most proptotic eye as measured by MRI (or CT – where allowed by local health authorities)
- Manual measurement of lid retraction in the study eye
- Graves' Orbitopathy-Quality of Life (GO-QoL) combined score
- GO-QoL activity subscale
- GO-QoL appearance subscale
- EQ-5D-5L QoL questionnaire
- Visual Acuity (VA)
- Gorman Subjective Diplopia Score

## 8.5 Additional Analyses

The following analyses may be performed:

- The key secondary endpoint of proptosis responder as measured by MRI/CT with all proptosis assessments measured by CT removed and consequently imputed using the EXI imputation method.
- Proptosis Responder Rate by MRI/CT stratified by type of MRI sequence (T1, T2).
- An inter- and intra-reader variability analysis will be conducted to assess the correlation between multiple readers for the MRI/CT. The correlation coefficient and graphically displays may be provided.
- The association between the proptosis responder rate based on each of the measuring tools will be determined.

# 9. Safety Evaluation

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

Safety assessments will be made at all analysis visits and 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 and NCI-CTCAE 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
- Treatment-related TEAEs leading to discontinuation of study medication
- TEAEs leading to death
- Treatment-related TEAEs leading to death
- Serious TEAEs
- Serious TEAE related to study medication
- TEAEs of interest
- TEAEs by the maximum severity grade
- Treatment-related TEAEs by the maximum severity grade

An additional summary describing the onset of TEAE of interest (TEAEI) will be provided. The TEAEI are defined as below.

The summary of the number of infusions prior to the onset of a TEAEI will be provided. If the TEAEIs 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 AEs and SAEs will be presented in a listing.

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).

## 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<br>• ≤90 mmHg and decrease from baseline of ≥20 mmHg<br>• Decrease from baseline ≥20 mmHg |
| Diastolic blood pressure | • ≥105 mmHg and increase from baseline of ≥15 mmHg<br>• ≤50 mmHg and decrease from baseline of ≥15 mmHg<br>• Decrease from baseline ≥10 mmHg |
| Heart rate | • ≥150 beats/min and increase from baseline ≥15 beats/min<br>• ≤50 beats/min and decrease from baseline ≥15 beats/min |
| Weight | • Increase from baseline ≥7%<br>• 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.

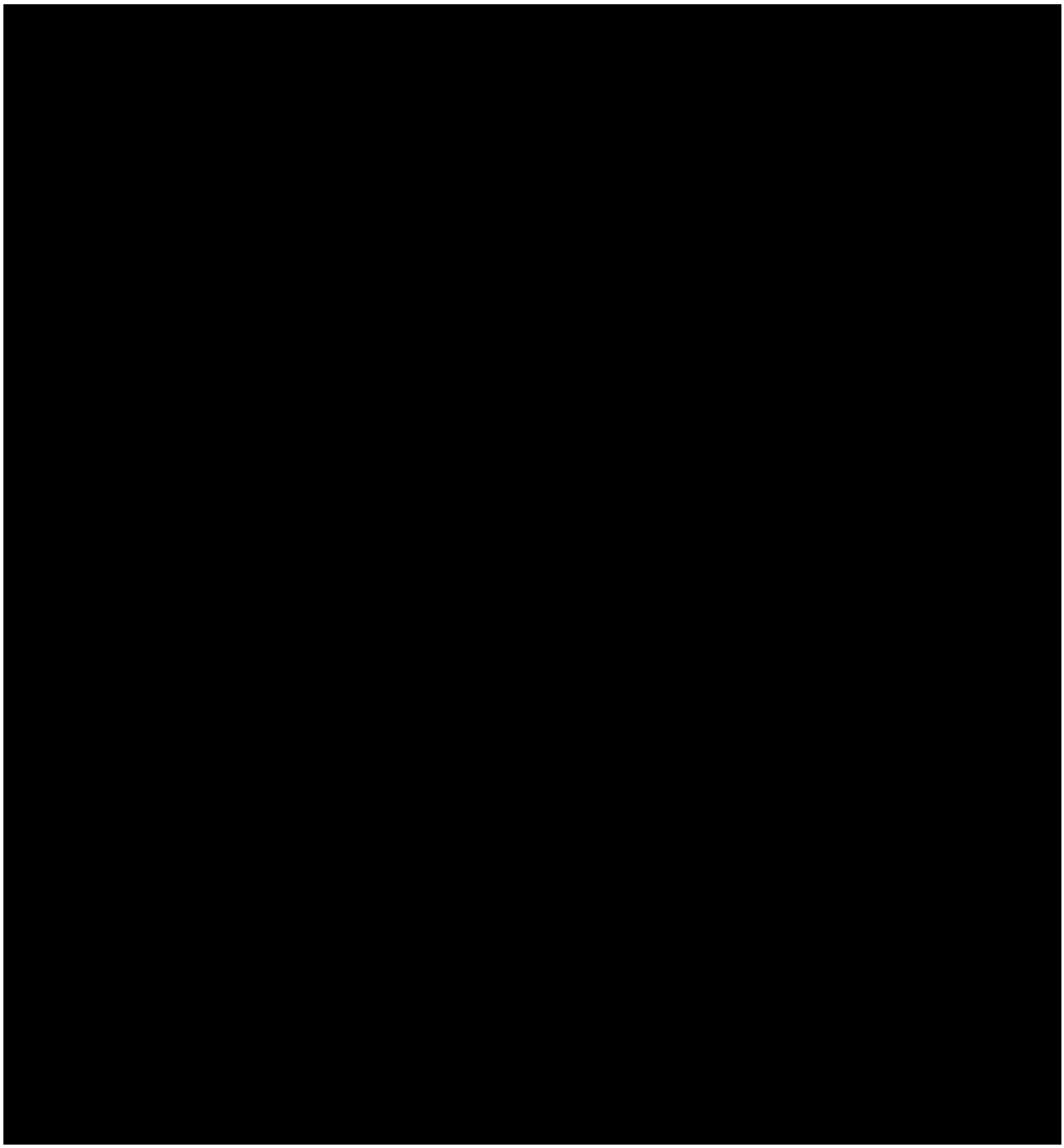
A listing of ECG test results will be provided.

## 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
- Lids / Lacrimal / Lashes
- Conjunctiva / Sclera,
- Cornea

- Corneal Staining (0, 1+, 2+, 3+, 4+),
- Anterior Chamber
- Anterior Vitreous
- AC Cells (0, 0.5/Trace, 1+, 2+, 3+, 4+)
- AC Flare (0, 0.5/Trace, 1+, 2+, 3+, 4+)
- Iris
- Pupils
- Lens Status (Aphakic, Pseudo-phakic, Phakic)
- Lens Cataract 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.

- Optic Nerve
- Macula
- Peripheral Retina and Choroid
- Vessels
- Vitreous
- Vitreous Haze (0, 0.5/Trace, 1+, 2+, 3+, 4+)
- Vitreous Cells (0, 0.5/Trace, 1+, 2+, 3+, 4+)
- Inflammatory activity (Active, Inactive)

### 9.8.3 Intraocular Pressure

IOP will be summarized by visit. An additional tabular summary of the percentage of subjects in categories of IOP (<15, 15 to <20, 20 to <25, 25 to <30, ≥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, ≥2 mm) will be presented by treatment group and analysis visit.

## 10. Pharmacokinetic Analyses

The details of the PK analysis will be provided in a separate analysis plan.

## 11. Other Endpoints

### 11.1 Pharmacodynamic Analyses

The details of the PD analysis will be provided in a separate analysis plan.

## 12. Reference

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

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