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VRDN-001-101



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)

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Viridian Therapeutics, Inc.,
221 Crescent Street
Suite 103A
Waltham, MA 02453
USA

Phone – 617-272-4600
Fax – 617-272-4601
www.viridiantherapeutics.com

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INVESTIGATOR'S AGREEMENT

Study Title

A [REDACTED], 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)

My signature confirms that I have carefully read, and that I understand, this protocol. I agree to follow the study procedures as outlined in this protocol in compliance with Good Clinical Practice and all other regulatory requirements, including provision for the well-being of the study participants according to the ethical principles stated in the Declaration of Helsinki.

This protocol and the referenced Investigator's Brochure contains confidential information with respect to products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties until this information becomes a matter of public knowledge, or until a formal agreement for that purpose has been entered into by the parties.

Printed Name of Investigator

Signature of Investigator

Date

SIGNATURE PAGE

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)

Version/Date: 9.1 USA/ 14-Aug-2024

Protocol Approver: [REDACTED]
[REDACTED]
Viridian Therapeutics, Inc.

[REDACTED]
Signature/Date: _____

Protocol Author: [REDACTED]
[REDACTED]
Viridian Therapeutics, Inc.

Statistician: [REDACTED]
[REDACTED]
Viridian Therapeutics, Inc.

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SYNOPSIS

Name of Sponsor/Company: Viridian Therapeutics, Inc.
Investigational Product: VRDN-001
Protocol Number: VRDN-001-101
Version Number and Date: Version 9.1 USA, Amendment date: 14-Aug-2024
Study 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)
Phase of Study: 1/2/3
Number of Participants (planned): Up to 154 participants [REDACTED], approximately 90 additional participants with active TED in the pivotal portion of the study [THRIVE])
Number of Trial Sites: HVs in a single US site, and TED participants in approximately 80 sites in Australia, Canada, China, EU, Turkey, UK and USA.
Objectives: To establish the safety, tolerability, and efficacy of VRDN-001, and the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of VRDN-001 in HV and TED patients [REDACTED].
Safety Endpoints: Adverse Events (AEs) and Serious Adverse Events (SAEs) will be monitored and recorded throughout the duration of the study. All clinically significant changes in other safety measurements will be recorded as AEs.
Primary Efficacy Endpoint in the USA, Canada and China in the Pivotal portion of the Study (THRIVE): Proptosis Responder Rate in the study eye (i.e., reduction of proptosis of ≥ 2 mm from baseline [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)
Primary Efficacy Endpoint in Australia, EU, Turkey and UK in the Pivotal portion of the Study (THRIVE): Overall Responder Rate comprising Proptosis Responder Rate in the study eye (i.e., reduction of proptosis of ≥ 2 mm from baseline [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 CAS ≥ 2 points from baseline [without a corresponding increase of ≥ 2 points in the fellow eye]) at 3 weeks post the fifth infusion (i.e., Week 15)

Key Secondary Endpoints in the USA in the Pivotal portion of the Study (THRIVE):

- 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 3 weeks post the fifth infusion (i.e., 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 comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the study eye at Week 15
- Clinical Activity Responder Rate in the study eye at Week 15
- Diplopia Responder Rate (i.e., reduction in Gorman Subjective Diplopia Score of ≥ 1 from baseline for participants with baseline Gorman Subjective Diplopia Score >0) at Week 15
- Diplopia Resolution Rate (i.e., reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia Score >0) at Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

Note for Secondary and Exploratory endpoints for USA: The most proptotic eye or study eye at baseline for proptosis endpoints will be based on the measurement method for the corresponding endpoint (i.e., for proptosis endpoints measured by exophthalmometer, most proptotic eye or study eye will be determined by exophthalmometer and for endpoints measured by MRI/CT, it will be determined by MRI/CT). For endpoints other than proptosis, the study eye will be determined by exophthalmometer.

Key Secondary Endpoints in Canada and China in the Pivotal portion of the Study (THRIVE):

- 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 (i.e., reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Diplopia Score >0) at Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

Key Secondary Endpoints in Australia, EU, Turkey and UK in the Pivotal portion of the Study (THRIVE):

- 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 (i.e., reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia Score >0) Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

Exploratory Endpoints in the USA in the Pivotal portion of the Study (THRIVE):

- 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 as described in [Appendix 1C](#)

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 as described in Appendix 1C

Trial Rationale:

The overall safety data from this ongoing study in [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]. Thus, 10 mg/kg was chosen as the selected dose for the pivotal portion of the study. The purpose of the pivotal cohort of this study is to confirm safety and efficacy in a larger randomized and placebo-controlled study of active TED participants.

The rationale for selecting 5 infusions as the dosing regimen in the active TED pivotal portion of the study (THRIVE) is based on available interim VRDN-001 data and published information for teprotumumab ([Smith et al, 2017](#), [Douglas et al, 2020](#)) have demonstrated that more than 90% of the proptosis response is observed following the first 5 infusions with minimal further improvement thereafter. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] These results suggest that the required duration of treatment with VRDN-001 may be less than seen with teprotumumab.

Trial Design:



The pivotal portion of the study (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 10mg/kg [REDACTED]; dose rationale is detailed in [Section 1.8](#) of the full protocol). The study will comprise 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 the pivotal portion of this study (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 participants previously randomized to 8 infusions and who have received greater than 5 infusions, further infusions will be discontinued. The active TED Pivotal portion of the trial is ongoing.

Participants who are deemed to be non-responders at 3 weeks post the fifth infusion (i.e., Week 15) in the pivotal portion of the study 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 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 exophthalmometer) in the study eye at 3 weeks post the fifth infusion (i.e., Week 15)

OR

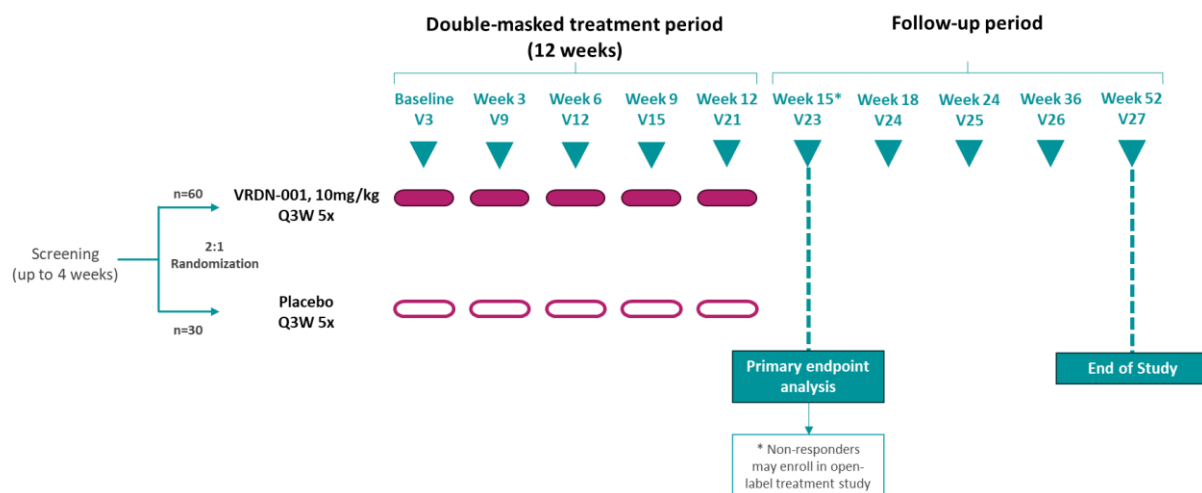
- A participant who achieved a ≥ 2 mm reduction from baseline in proptosis (as measured by exophthalmometer) in the study eye but had a corresponding increase of ≥ 2 mm from baseline in proptosis in the fellow eye at 3 weeks post the fifth infusion (i.e., Week 15).

The Day-1/Day 1 visit(s) in the open-label treatment study (separate study denoted as VRDN-001-302) are to be conducted within 4 weeks of the 3 weeks post the fifth infusion assessment (i.e., Week 15) in the VRDN-001-101 pivotal study (THRIVE). More than 4 weeks may be allowed between the completion of the 3 weeks post the fifth infusion assessment (i.e., Week 15) in the pivotal study and the Day-1/Day 1 visit of the open-label treatment study with prior written approval by the Sponsor.

Measurements as described in the SoA 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 who do not enroll into the open-label treatment study will continue to have data collected through 52 weeks as described in the SoA.

Overall Study Design Schematic

Pivotal Portion Study Design (THRIVE)



Study procedures

[REDACTED]. The active TED Pivotal portion of the trial is fully enrolled and ongoing.

The study procedures for [REDACTED] and active TED pivotal portions of the study are outlined in the SoAs found in [Appendices 1A, 1B and 1C](#), respectively.

In the pivotal portion of the study (THRIVE), participants in both treatment arms will receive the same number of infusions administered at 3-week intervals to maintain masking.

Ocular assessments will be performed on both eyes. The study eye for determination of eligibility and stratification will be the most proptotic as measured 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 Visual Acuity (VA) will be selected. If proptosis and VA are equal in both eyes, then the right eye will be selected as the study eye.

At the Investigator's discretion or at the request of the participant an unscheduled visit may be conducted at any time.

An independent DSMB will review safety and limited efficacy data at 6-month intervals during the pivotal portion of the study, with interim ad hoc DSMB meetings as required, to monitor clinical safety and determine if any required changes to study design should be implemented. Additionally, the safety data will be reviewed on an ongoing basis by the Sponsor and any concerns will be immediately addressed and escalated to the independent DSMB, as needed.

Study Duration: This study commenced at the end of 2021 and enrollment is estimated to be completed in the first quarter of 2024. Each enrolled participant will be in the study as follows: [REDACTED] and TED pivotal participants for up to 52 to 56 weeks following the first dose. The end of the study will be when the last participant's last visit has occurred.

Inclusion Criteria:

[REDACTED]
[REDACTED] are now described in [Appendices 4 and 5](#), respectively.

Active TED Pivotal (THRIVE) participants

Participants must:

1. Be able to understand the study procedures and the risks involved and be willing to provide written informed consent before the first study-related activity
2. Be an adult male or female participant, at least 18 years of age or older
3. Have had a clinical diagnosis of TED with a CAS of ≥ 3 on the 7-item scale for the study eye
4. Have moderate to severe (i.e., has an appreciable impact on daily living) active TED associated with proptosis of ≥ 3 mm above normal values for race and gender in the opinion of the investigator and at least one of the following: lid retraction of ≥ 2 mm, moderate or severe soft tissue involvement, inconstant or constant diplopia,

- spontaneous retrobulbar pain or pain on eye movement, swelling of the conjunctiva, eyelids or plica, or redness of the eyelids or plica in the study eye
5. Have documented evidence of ocular symptoms or signs associated with active TED that began within 15 months prior to study screening
 6. VRDN-001 can be started concomitantly with attempts to achieve euthyroid status. Underlying thyroid status is not an inclusion criterion.
 7. Not require expected immediate surgical ophthalmological or orbital surgery in the study eye for any reason
 8. VRDN-001 can be used with caution in patients with diabetes mellitus. Diabetic participants should be monitored by their endocrinologist or other appropriately trained personnel and have at study entry a glycated hemoglobin (HbA1c) of <8.5%
 9. If female, have a negative serum pregnancy test at screening and further negative urine tests immediately before each dose of study medication following the last dose of study medication as described in [Appendix 1C](#).
If the participant is a woman of childbearing potential (including those with <2 years since the onset of menopause, amenorrhea for <2 year, or not surgically sterile); such participants must agree to use an acceptable method of contraception such as a condom and a second highly effective method of contraception as described in [Section 4.4](#) from Screening up to and including 100 days after the last dose of study medication. If the participant is initiating hormonal contraception at time of Screening or within one cycle of Day 1, participant agrees to use a double-barrier method of contraception until completing one-full cycle of hormonal contraception. An acceptable double-barrier combination method is a condom with either diaphragm or sponge with spermicide
 10. Be surgically sterile males for at least 6 weeks, or agree to use an acceptable method of contraception such as a condom and a second highly effective method of contraception as described in [Section 4.4](#) from Screening up to and including 100 days after the last dose of study medication
 11. Be willing and able to comply with all the requirements of the protocol for the entire duration of the study

Exclusion Criteria

are now described in [Appendices 4 and 5](#), respectively.

Active TED Pivotal (THRIVE) participants

Participants must not:

1. Have received prior treatment with another anti-IGF-1R therapy or any investigational agent for TED
2. Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future.
3. Have corneal decompensation in the study eye unresponsive to medical management
4. Have a decrease in CAS of ≥ 2 points in the study eye between screening assessment and Day -1

5. Have a decrease in proptosis of ≥ 2 mm in the study eye between screening assessment and Day -1
6. Have had previous orbital irradiation or decompression surgery involving excision of fat for TED to the study eye's orbit
7. Have history of or screening audiometry assessment of significant (as determined by the Investigator) ear pathology, relevant ear surgery or hearing loss
8. Have inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease)
9. Have used systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study medication (topical steroids or multivitamins that contain selenium are permitted)
10. Have received other immunosuppressive agents, including rituximab, or tocilizumab, for any condition, including TED, within 8 weeks prior to the first dose of study medication
11. Have received any other therapy for TED within 8 weeks prior to the first dose of study medication (artificial tears are permitted)
12. Have received an investigational agent for any condition within 8 weeks prior to the first dose of study medication
13. Have a pre-existing ophthalmic condition in the study eye which in the opinion of the Investigator, would confound interpretation of the study results
14. Be a pregnant or lactating woman
15. Be an active alcoholic or illicit drug user or considered at high risk of relapse by the Investigator
16. Have a known hypersensitivity to any of the components of VRDN-001 or placebo formulations, or prior hypersensitivity to monoclonal antibodies (mAbs)
17. Have any condition, which in the opinion of the Investigator, would preclude inclusion in the study
18. Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2)
19. Have a positive test for active hepatitis B or hepatitis C infection
20. Have previously participated in this study or any study of VRDN-001
21. French participating sites only: In accordance with the provisions of articles L.1121-5 et seq. of the Public Health Code, pregnant or breast-feeding women, persons deprived of their liberty by a judicial or administrative decision, persons under psychiatric care without their consent, minors and adults under a legal protection measure must not be included

Note: Prior thyroidectomy, radioactive iodine (RAI) treatment, or orbital decompression surgery limited to bone only are NOT exclusions.

Investigational Product, Dosage and Mode of Administration:

VRDN-001 is a humanized mAb directed to IGF-1R. VRDN-001 will be provided as a solution containing ■ mg/mL or ■ mg/mL of antibody in 4.0 mL extractable volume in ■ R vials, frozen at $-20 \pm 5^{\circ}\text{C}$.

The pharmacist or other qualified, trained and delegated individual preparing the infusion bags will be unmasked to treatment and will either dispense [REDACTED] bags of saline with or without VRDN-001 added, according to the Randomization and Trial Supply Management (RTSM) System. The volume of saline removed from the bags will equal the volume of VRDN-001 added to maintain masking. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Statistical Methods:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The pivotal portion of the study (THRIVE) will be randomized, double-masked (including sponsor) and placebo controlled and will consist of approximately 90 participants randomized (to ensure 78 evaluable participants at the primary endpoint at Week 15) with an allocation ratio of 2:1 (60 participants active: 30 participants placebo) and will be stratified by amount of proptosis (≥ 23 , mm Y/N) in the study eye at baseline as measured by exophthalmometer. The study will have greater than 90% power to test the 5 infusion regimen versus placebo. The responder rate in the active arm is assumed to be 60% and 20% in the placebo arm. 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 minus a statistical penalty for data reviews. The p-value for the primary analysis will be documented prior to the Week 15 primary analysis database lock. As the efficacy analysis 3 weeks post the fifth infusion would allow the evaluation of the primary endpoint, the database will be locked and analysed at that time. Measurements as described in the SoA will continue to be collected through 52 weeks. All safety data collected after the Week 15 efficacy timepoint will be included in the safety follow-up. The investigator will remain masked to participant level treatment regimen for the remainder of the study where allowed by local health authorities. In by visit summaries, the 5 infusion arm and 8 infusion arm may be combined in comparison to placebo.

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ADA	Anti-drug antibody
ADL	Activities of daily living
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC ₀₋₇	Area under the curve from time zero to seven days
bpm	Beats per minute
CAS	Clinical Activity Score
CFR	Code of Federal Regulations
CL	Clearance
C _{max}	Maximum plasma concentration
CMP	Clinical monitoring plan
COVID-19	SARS-CoV-2 coronavirus pandemic
CRO	Contract research organization
eCRF	Electronic case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
EQ VAS	EQ visual analogue scale
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
GEE	Generalized estimated equation
GLM	General linear model
GO-QoL	Grave's Orbitopathy-Quality of Life
G protein	Guanine nucleotide-binding protein
HbA1c	Glycated hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HV	Healthy volunteer
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IGF-1R	Insulin-like growth factor-1 receptor
IND	Investigational new drug
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LM	Laboratory Manual
mAb	Monoclonal antibody
████	████████████████████
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputations
MRD	Marginal reflex distance
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCT	National clinical trial
NHV	Normal healthy volunteer
NOAEL	No observed adverse effect level

Abbreviation or Specialist Term	Explanation
PD	Pharmacodynamic
PHI	Protected health information
PK	Pharmacokinetic
PM	Pharmacy Manual
PPM	Protocol Procedures Manual
PP	Per protocol
PTA	Pure Tone Average
QTcF	Corrected QT (interval between Q and T waves on the ECG) by Fredericia
QoL	Quality of life
RTSM	Randomization and trial supply management
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SOP	Standard operating procedure
SPR	Surface plasmon resonance
$t_{1/2\lambda z}$	Terminal elimination half-life
TEAE	Treatment emergent adverse event
TED	Thyroid eye disease
TSHR	Thyroid stimulating hormone receptor
T_{max}	Time of maximum plasma concentration
UK	United Kingdom
ULN	Upper limit of normal
US, USA	United States of America
VA	Visual acuity
V_{ss}	Volume of distribution at steady state
WHO	World Health Organization

1. INTRODUCTION

1.1. BACKGROUND ON THYROID EYE DISEASE

Thyroid Eye Disease (TED) is an autoimmune condition most commonly associated with Graves' disease and hyperthyroidism but can also be found in patients who are euthyroid or hypothyroid. Pathological remodeling of the orbit and periorbital tissues results in varied presentations which include dry eyes, increased lacrimation, local irritation and eyelid retraction. As the pathophysiology progresses, signs and symptoms increase to include proptosis, diplopia, restriction of ductions and versions and optic nerve compression, with ensuing vision loss.

Graves' disease affects approximately 1% to 2% of the adult population ([Minakaran 2013](#)) with approximately 40% of patients with Graves' disease declaring signs or symptoms of TED during their lifetime ([Mohyi 2018](#)). Typically, onset of TED occurs approximately 18 months following the diagnosis of Graves' disease ([Gillespie 2012](#)). TED is more common in women than men (annual incidence of 16 per 100,000 versus 3 per 100,000, respectively), as is Graves' disease, albeit with no significant ethnic predisposition. Median age at diagnosis is 43 years. Risk factors for TED include female gender, middle age and smoking; indeed, risk of TED is increased 7 to 8 times in smokers. In addition, a positive family history of TED is observed in 61% of TED patients ([FDA Tepezza Summary Review](#)).

The disease course has historically been said to transition from an active and progressive phase (characterized by inflammation of orbital and external periorbital tissues) to a more stabilized and fibrotic, inactive phase, though this nomenclature is inexact and changing. Active TED has been characterized by local inflammation of conjunctivae, orbital fat and extraocular muscles, and is said to last between 1-3 years ([Bahn 2010](#)). Inactive, or chronic, TED occurs when the autoimmune inflammation dampens, leaving sequelae of expanded, fibrotic orbital tissues and dysfunctional, tethered extraocular muscles, though evidence exists that even chronic TED patients may exhibit an underlying inflammatory component that needs to be further understood ([Ugradar et al, 2022](#)).

The pathophysiology of TED is incompletely understood. Stimulation of inflammatory cytokines causes proliferation of the orbital fibroblasts which in turn produce collagen and glycosaminoglycans in the extracellular matrix ([Prabhakar 2003](#); [Wiersinga 2001](#)). The polyanionic charge and the high osmotic pressure of this matrix substance cause swelling of the extraocular muscles ([Wiersinga 2001](#)). In addition, a subgroup of orbital fibroblasts differentiate into new mature fat cells (adipogenesis), which adds to increased orbital tissue volume ([Sorisky 1996](#)). There is also a role for the humoral-mediated immune response ([Han 2006](#)) in which thyrotropin receptor autoantibodies and immunoglobulins targeting insulin-like growth factor-1 receptors contribute to fibroblast activation and glycosaminoglycan secretion ([Eckstein 2009](#); [Ezra 2012](#)). Levator and Muller muscle inflammation and fibrosis account for upper eyelid retraction, which is seen in up to 90% of affected patients ([Bahn 2010](#)). Proptosis is caused by the expansion of orbital fat (type 1 orbitopathy), extraocular muscles (type 2 orbitopathy), or both ([Hiromatsu 2000](#)). Blindness is caused by compression of the optic nerve, presumably within the apex of the orbit. Dramatic proptosis itself can lead to visual loss via exposure keratopathy and corneal ulceration ([Bahn 2010](#); [Barrio-Barrio 2015](#); [Kahaly 2005](#)). This constellation of signs and symptoms causes difficulty with working, driving, reading and other activities of daily living, and leads to psychosocial distress and social withdrawal ([Wickwar 2015](#)).

Ultimately, the alterations in the extracellular matrix lead to proptosis, strabismus, diplopia and disfigurement of facial and periorbital anatomy. Many patients with TED endure at least 5 to 7 years of medical and surgical therapy before reaching a point of stability, transformed physically, emotionally and visually, with overwhelming dysfunction in their quality of life ([Patel 2019](#)).

1.2. AVAILABLE THERAPIES FOR THYROID EYE DISEASE

Treatment during the active phase of the disease focuses on preserving sight and the integrity of the cornea as well as anti-inflammatory measures. There had been no direct therapy available for the diplopia and proptosis, or periorbital edema and lid retraction. Treatment of TED has historically included vitamins (selenium), corticosteroids (systemically), topical agents to dampen the inflammation, anterior segment antibiotics to address corneal ulcers, and symptomatic relief for exposure keratopathy. Such therapies are generally incomplete and unsatisfactory both for the patient and treating physicians. As symptoms and signs become more severe, the only alternatives were extraocular muscle surgery, orbital radiation and orbital decompression. Again, even these interventions were incomplete and often unrewarding. Biologic therapies such as adalimumab (Humira®), infliximab (Remicade®) and etanercept (Enbrel®) have been used to treat TED, but there are scarce data from randomized, placebo-controlled studies to support the use of these monoclonal antibodies for the TED indication, and none are licensed for this use by FDA ([Wickwar 2015](#)).

Teprotumumab, a fully human monoclonal immunoglobulin specifically binds and blocks signal transduction of the IGF-1R and IGF-1R / TSHR complex on orbital fibroblasts ([Ugradar et al. 2022](#)). Teprotumumab was recently approved by the FDA for the treatment of TED in the USA. In both Phase 2 and Phase 3 randomized, double-masked clinical trials (NCT01868997 and NCT03298867), teprotumumab was more effective than placebo in reducing proptosis, diplopia and inflammation in patients with active TED ([Smith 2017](#); [Douglas 2020](#)). In both trials, only patients with ocular symptoms that presented within 9 months of diagnosis were studied. Similarly, in a more recent randomized, double-masked, placebo-controlled Phase 4 clinical trial (NCT04583735), teprotumumab was more effective than placebo in reducing proptosis in participants with chronic TED and low CAS. This Phase 4 trial evaluated patients with an initial diagnosis of TED between 2 to 10 years (mean duration of 5.2 years) and low levels of disease activity (mean CAS of 0.4). While this therapy has been a transformational intervention for patients ([Douglas 2021](#)), it requires eight infusions over 24 weeks, administered at an infusion center, and is often accompanied by mild adverse events described in [Section 1.6.2](#) below.

1.3. RATIONALE FOR VRDN-001 AS AN ALTERNATIVE TREATMENT FOR THYROID EYE DISEASE

IGF-1R is a transmembrane protein structurally similar to the insulin receptor, and is widely expressed on the surface of many cells throughout the various tissues and organs of the human body ([Beck 2001](#)). It mediates the effects of IGF-1, a hormone important in cell division and growth. The principle underlying pathology of TED is the activation of an inflammatory cascade within the orbital cone, primarily due to autoantibodies against the thyroid stimulating hormone receptor (TSHR) which has been shown to exhibit cross talk (transactivation) with the IGF-1R, a phenomenon that is a well-established signaling mechanism between G protein-coupled receptors and receptor tyrosine kinases ([Krieger 2015](#); [Place 2017](#)). Transactivation between the TSHR and the IGF-1R forms the basis for the therapeutic use of anti-IGF-1R mAbs in TED.

Over-expression of the IGF-1R has been demonstrated within the orbital cone of TED patients, and it has been surmised that antibodies specifically formulated to block the IGF-1 receptor may disrupt the IGF-1R and TSHR transactivation, thereby attenuating the TED inflammatory cascade ([Naik 2010](#)). The anti-IGF-1R approach has proven to be clinically valuable. In January 2020, teprotumumab, an anti-IGF-1R mAb, was approved by the FDA for the treatment of TED, presenting a ground-breaking option in the management of a condition with previously few effective treatment alternatives. A 6-month course of infusion of this antibody provides reduction in proptosis and inflammatory symptoms in patients with recent onset, active TED ([Smith 2017](#), [Douglas 2020](#)). While teprotumumab represents a transformational new treatment for TED patients, it has been associated with side effects, including infusion-related reactions, inflammatory bowel disease, hyperglycemia, muscle spasms, fatigue, nausea, diarrhea, and hearing impairment ([Patel 2019](#); [Douglas 2021](#)).

Antagonism studies showed that VRDN-001 inhibited binding of IGF-1 to a greater extent than teprotumumab. Similarly, VRDN-001 antagonized IGF-1 mediated signaling more fully and may provide a comparable level of efficacy and an improved safety profile in TED patients when administered at similar or lower doses and/or using a more convenient dosing regimen.

Additional details can be found in [Section 1.7](#) of this protocol and the Investigator's Brochure (IB).

1.4. HISTORY OF VRDN-001 DEVELOPMENT

VRDN-001 is a humanized IgG1κ monoclonal antibody targeting human IGF-1R. The murine antibody, EM164, from which VRDN-001 is derived, was generated in mice immunized with cells expressing human IGF-1R. Hybridoma supernatants were screened for specific binding to IGF-1R-expressing cells and for absence of binding to cells expressing the human insulin receptor. The selected EM164 antibody was shown to bind with high affinity to isolated or cell-surface human IGF-1R and to potently inhibit IGF-1 stimulated autophosphorylation of the IGF-1R intracellular domain, while lacking inhibitory activity against insulin-stimulated autophosphorylation of the insulin receptor ([Maloney 2003](#)).

A humanized version of EM164, referred to as AVE1642, was developed by ImmunoGen, Inc. by replacing surface accessible residues in the murine variable region framework of the heavy and light chains with surface residues found in naturally occurring human antibodies, and then grafting the light and heavy chain variable domain sequences onto the human Igκ and Igγ1 constant region sequences, respectively. AVE1642 was confirmed to bind with high affinity and selectivity to human IGF-1R and to inhibit autophosphorylation of the receptor stimulated by IGF-1.

AVE1642 was the subject of a previous U.S. investigational new drug (IND) application sponsored by Sanofi-Aventis (Sanofi) to investigate the safety and potential efficacy of this antibody for the treatment of certain cancers that overexpress IGF-1R. Four early phase clinical trials were completed, in which more than 100 patients were treated with AVE1642 as monotherapy or in combination with chemotherapy. Although the antibody was generally well-tolerated in the context of these trials, the development of AVE1642 for oncology was halted due to lack of efficacy. Sanofi inactivated the U.S. IND in 2011 and the IND was subsequently withdrawn in 2016.

Viridian has licensed the rights to develop the AVE1642 antibody sequence for the treatment of thyroid eye disease and this molecule is designated as VRDN-001. The company has developed a new production cell line [REDACTED]

[REDACTED] The manufacturing process has also been updated to accord with modern standards of monoclonal antibody production, resulting in a process with higher yield and a product with equivalent or improved quality attributes compared with AVE1642.

1.5. NONCLINICAL STUDIES OF VRDN-001

1.5.1. Pharmacodynamic Studies

VRDN-001 binds IGF-1R protein with high affinity ($K_D = [REDACTED]$ nM) and exhibits slow dissociation ($k_d = [REDACTED]$ s⁻¹) in surface plasmon resonance (SPR) experiments. In both human ocular choroid fibroblasts and A549 lung cancer cells, VRDN-001 inhibited IGF-1-stimulated IGF-1R phosphorylation in a dose-dependent manner. IC₅₀ values were [REDACTED] nM in both cell types and greater than 95% inhibition of phosphorylation was observed with VRDN-001 concentrations in the [REDACTED] nM range ([REDACTED] µg/mL). Assessment of VRDN-001 binding to recombinant human insulin receptor by ELISA and antagonism of insulin-mediated signaling in the hepatocarcinoma HepG2 cell line demonstrated that VRDN-001 lacks significant affinity to the closely related insulin receptor and does not inhibit insulin signaling through its receptor.

1.5.2. Safety Pharmacology

No standalone safety pharmacology studies were conducted with VRDN-001 but safety pharmacology endpoints, including clinical observations for CNS effects, ECG, blood pressure and respiratory rates, were evaluated in the both the [REDACTED] repeat-dose toxicity study in cynomolgus monkeys (see [Section 1.5.4](#)). No compound-related effects were noted on these parameters up to the highest dose tested (50 mg/kg/administration). Additional information can be found in the IB.

1.5.3. Pharmacokinetics

The pharmacokinetics of VRDN-001 have been evaluated in non-human primates during a single dose PK study, a [REDACTED] repeat dose toxicity study, and a [REDACTED] GLP repeat-dose toxicity study. The PK profile of VRDN 001 was found to be similar to other IgG1 monoclonal antibodies, displaying low plasma clearance, [REDACTED]

[REDACTED]. For the [REDACTED] repeat-dose toxicokinetic (TK) study (refer to [Section 1.5.4](#)), parameters were evaluated following [REDACTED] intravenous infusions of [REDACTED] mg/kg of VRDN-001. VRDN-001 peak plasma concentration (C_{max}) and exposure (AUC) increased approximately in proportion with dose in the range of [REDACTED] mg/kg/administration, with greater than proportional increases from [REDACTED] mg/kg to [REDACTED] mg/kg. Female and male monkeys showed similar exposure after infusion. Exposure increased from Day 1 to Day 190, with expected accumulation due to the VRDN-001 half-life combined with the weekly dosing interval. Repeat dose TK parameters obtained from the Day 190 TK curves were comparable for the [REDACTED] mg/kg groups and were characterized by half-lives ranging from [REDACTED] days

and low serum clearance (██████████ mL/kg/hour). Half-lives were lower (██████████ days) and clearance values were higher (██████████ mL/kg/hour) in some ██████████ mg/kg animals, due to increased clearance from target mediated drug disposition and anti-drug antibody development. Mean volume of distribution was consistent across dose groups and ranged from ██████████ mL/kg.

1.5.4. ██████████

1.6. CLINICAL STUDIES OF ANTIBODIES TARGETING IGF-1R

1.6.1. Oncology Studies

Several mAbs directed against IGF-1R (R1507 [teprotumumab], cixutumumab, figitumumab, dalotuzumab, ganitumab, robatumumab and AVE1642), have been studied extensively in clinical trials in oncology, where many common tumor types, such as colon, breast, prostate, and others, aberrantly overexpress the receptor. Most of those studies utilized the mAbs in combination with various chemotherapeutic agents and are described in more detail in the Investigator's Brochure (IB) for VRDN-001.

1.6.2. TED Studies

Teprotumumab (Tepezza®), previously called R1507, RV-001 and HZN-001, is an anti-IGF-1R antibody approved by the FDA for the treatment of TED. Teprotumumab as monotherapy was evaluated in two randomized, double-masked placebo-controlled trials in TED involving a total of 171 participants, including 83 participants who were randomized to receive infusions of teprotumumab every three weeks for a total of eight doses. The current Tepezza prescribing label summarizes the following most common adverse reactions (incidence greater than 5%) in these studies: muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia, headache, weight decreased, menstrual disorders and nail disorder. Infusion reactions, exacerbation of pre-existing inflammatory bowel disease, hyperglycemia and hearing impairment including hearing loss are included as labeled warnings/precautions ([Tepezza Label 7/2023](#)).

1.7. CLINICAL EXPERIENCE WITH VRDN-001

1.8. RATIONALE FOR THE DOSE AND REGIMEN SELECTED FOR THIS STUDY

The dose level of VRDN-001 to be used in the pivotal portion of this study is 10 mg/kg. The rationale for the selection of the 10 mg/kg dose is based on the clinical safety and efficacy data in the [REDACTED] and is supported by a combination of nonclinical pharmacology and clinical pharmacokinetic data which predict that a dose of 10 mg/kg is required to achieve necessary exposure in target tissues for >95% of participants treated.

1.8.1. Rationale for Dosing Regimen Selected For This Study

The rationale for selecting 5 infusions as the dosing regimen in this study is based on available interim VRDN-001 data and published information for teprotumumab ([Smith et al, 2017](#), [Douglas et al, 2020](#)) have demonstrated that more than 90% of the proptosis response is observed following the first 5 infusions with minimal further improvement thereafter. [REDACTED]

[REDACTED] These results suggest that the required duration of treatment with VRDN-001 may be less than seen with teprotumumab.

1.8.2.**1.8.3. Clinical Safety and Efficacy**

From a clinical safety perspective, there were no differential safety signals across any of the dose levels and no toxicity concerns at the dose levels [REDACTED]

[REDACTED] Thus, 10 mg/kg was chosen as the selected dose based on the dose effect across the totality of clinical endpoints, a well-tolerated safety profile, and potential for achieving the necessary exposure in target tissues in >95% of participants treated.

1.8.4. Clinical Pharmacokinetics

Preliminary non-compartmental analysis of the data from VRDN-001-101 in HVs indicates that VRDN-001 displayed [REDACTED]

1.9. RATIONALE FOR THIS CLINICAL TRIAL

Teprotumumab, a mAb directed against the IGF-1 receptor, was shown to be effective in reducing proptosis, diplopia and inflammation in patients with active TED ([Smith 2017](#); [Douglas 2020](#)). Therefore, VRDN-001, also a mAb directed against the IGF-1 receptor, may provide therapeutic benefit in TED patients. The overall safety data from this ongoing study in

Thus, 10 mg/kg was chosen as the selected dose for the pivotal portion of the study. The purpose of the pivotal cohorts of this study is to confirm safety and efficacy in a larger randomized and placebo-controlled study of active TED participants.

1.10. POTENTIAL RISKS AND BENEFITS OF PARTICIPATION IN THIS STUDY

The potential risks of treatment with VRDN-001 are based on findings from the participants dosed to date with VRDN-001 and with teprotumumab ([Tepezza Label 7/2023](#)), an anti-IGF-1R monoclonal antibody approved in the US for treatment of TED. Specific risk details and the risk mitigation and toxicity management guidance for VRDN-001 treatment are described fully in [Section 9.7](#).

Patients in the placebo arm have no individual benefit from participating in this study whereas patients assigned to VRDN-001 have a potential individual benefit from this treatment. Participants who are deemed non-responders (did not 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 study (for some countries this will only be permitted once the study is completed and unmasked) will 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.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. OBJECTIVE

To establish the safety, tolerability, and efficacy of VRDN-001, and the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of VRDN-001 in HV and TED patients

2.2. SAFETY ENDPOINTS

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be monitored and recorded throughout the duration of the study. All clinically significant changes in other safety measurements will be recorded as AEs.

2.3. PRIMARY EFFICACY ENDPOINT IN THE PIVOTAL PORTION OF THE STUDY (THRIVE)

2.3.1. Primary Efficacy Endpoint in the USA, Canada and China in the Pivotal portion of the Study (THRIVE)

Proptosis Responder Rate in the study eye (i.e., reduction of proptosis of ≥ 2 mm from baseline [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)

2.3.2. Primary Efficacy Endpoint in Australia, EU, Turkey and UK in the Pivotal portion of the Study (THRIVE)

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

2.4. KEY SECONDARY EFFICACY ENDPOINTS

2.4.1. Key Secondary Endpoints in the USA in the Pivotal portion of the Study (THRIVE):

- 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 3 weeks post the fifth infusion (i.e., 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 comprising Proptosis Responder Rate as measured by exophthalmometer and Clinical Activity Responder Rate in the study eye at Week 15
- Clinical Activity Responder Rate in the study eye at Week 15
- Diplopia Responder Rate (i.e., reduction in Gorman Subjective Diplopia Score of ≥ 1 from baseline for participants with baseline Gorman Subjective Diplopia Score >0) at Week 15
- Diplopia Resolution Rate (i.e., reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia Score >0) at Week 15

- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

Note for Secondary and Exploratory endpoints for USA: The most proptotic eye or study eye at baseline for proptosis endpoints will be based on the measurement method for the corresponding endpoint (i.e., for proptosis endpoints measured by exophthalmometer, most proptotic eye or study eye will be determined by exophthalmometer and for endpoints measured by MRI/CT, it will be determined by MRI/CT). For endpoints other than proptosis, the study eye will be determined by exophthalmometer.

2.4.2. Key Secondary Endpoints in Canada and China in the Pivotal portion of the Study (THRIVE):

- 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 (i.e., reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Diplopia Score >0) at Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

2.4.3. Key Secondary Endpoints in Australia, EU, Turkey and UK in the Pivotal portion of the Study (THRIVE):

- 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 (i.e., reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia Score >0) Week 15
- Proportion of participants with a CAS score of zero or one in the study eye at Week 15

2.5. EXPLORATORY ENDPOINTS

2.5.1. Exploratory Endpoints in USA in the Pivotal portion of the Study (THRIVE):

- 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 as described in [Appendix 1C](#)

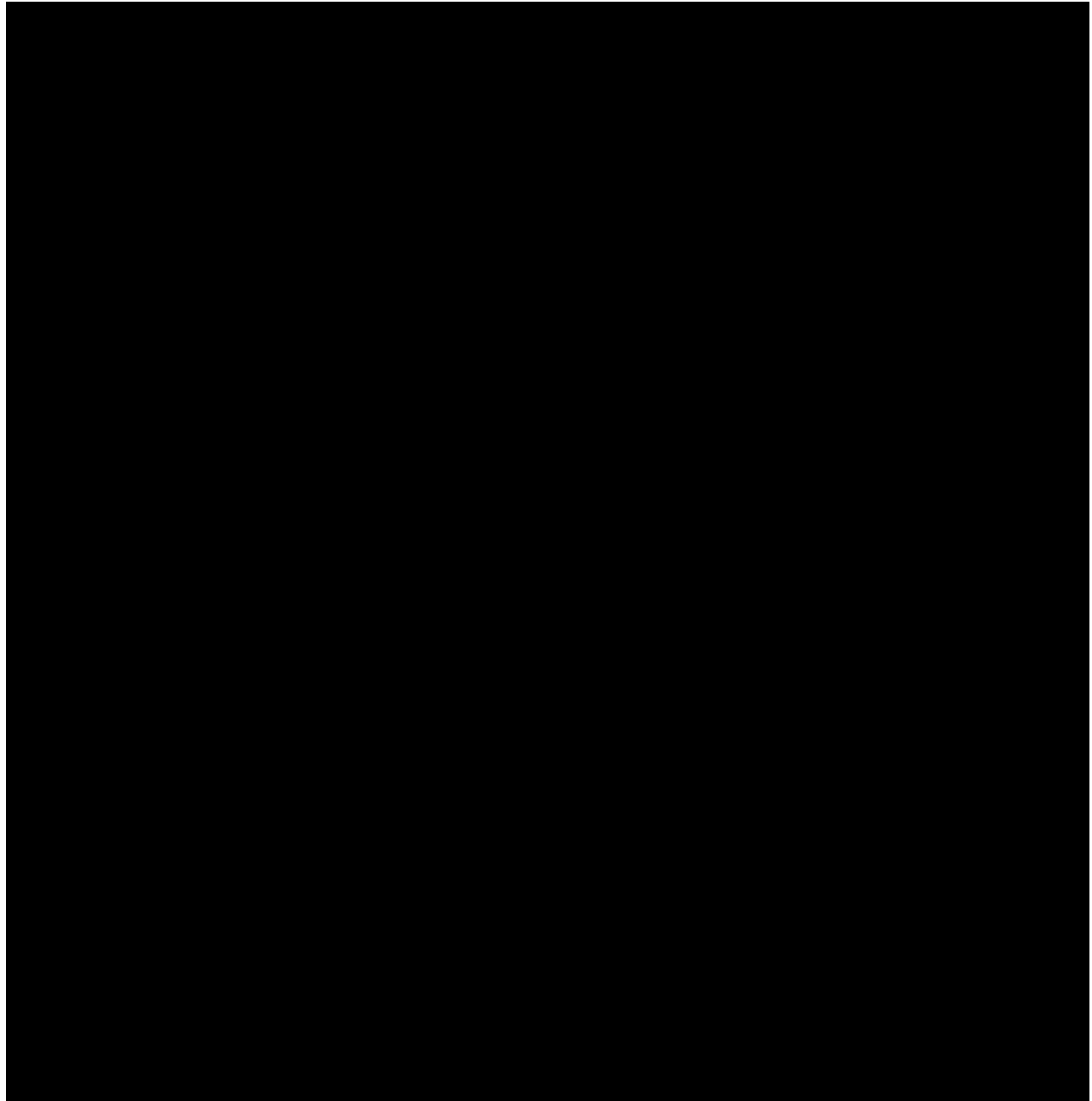
2.5.2. Exploratory Endpoints in Australia, Canada, China, EU, Turkey and UK in the Pivotal portion of the Study (THRIVE):

- 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 ADA at various time points pre- and post-infusions as described in Appendix 1C.

3. INVESTIGATIONAL PLAN

3.1. THE OVERALL STUDY DESIGN



The pivotal portion of the study (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 [REDACTED] [REDACTED] dose rationale is detailed in Section 1.8). The study will comprise 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 the pivotal portion of this study (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. The active TED Pivotal portion of the trial is ongoing.

Participants who are deemed to be non-responders 3 weeks post the fifth infusion (i.e., Week 15) in the pivotal portion of the study 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 determination of eligibility in the VRDN-001-302 study is defined as either:

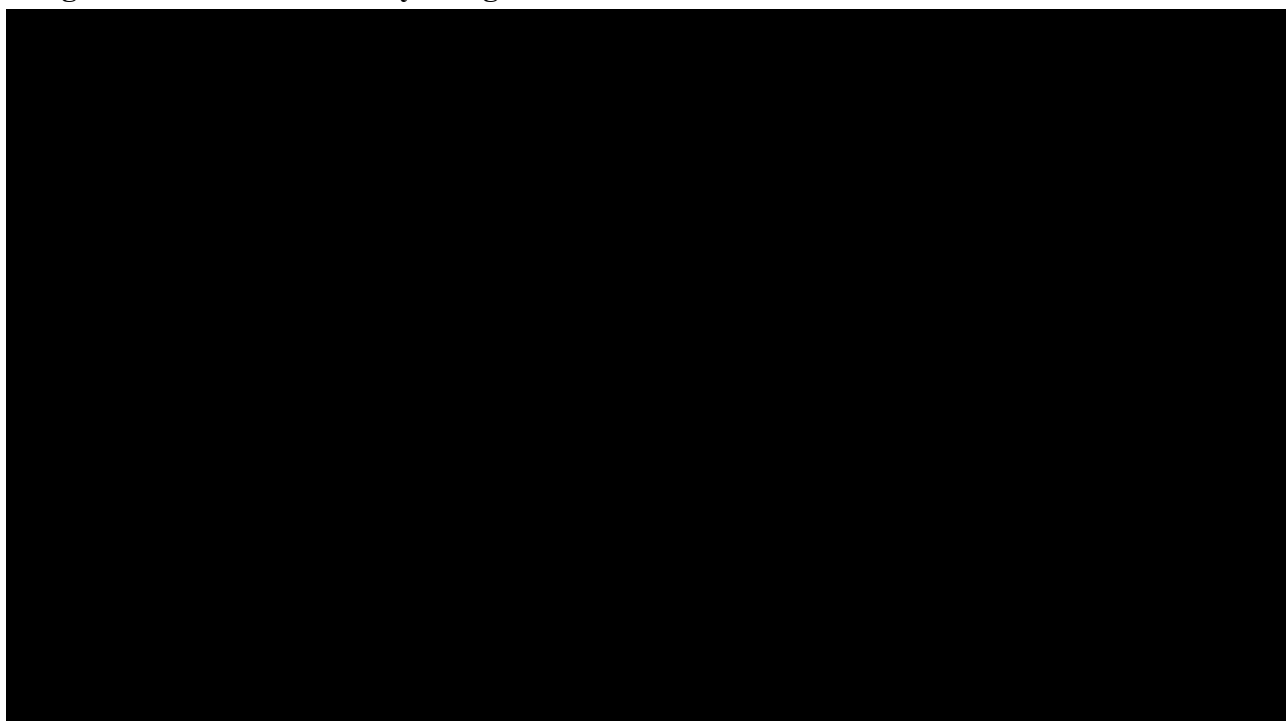
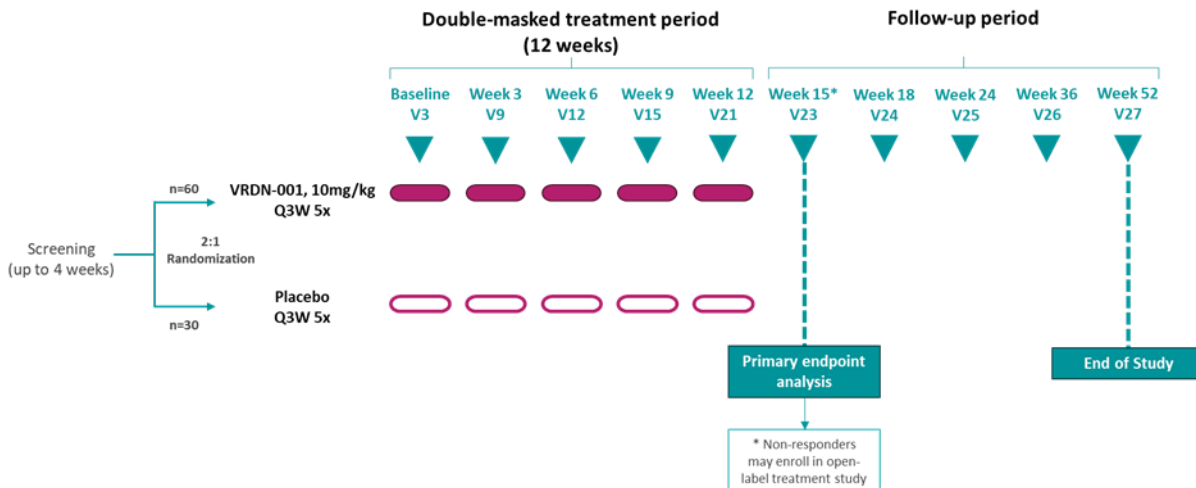
- A participant who did not achieve a ≥ 2 mm reduction from baseline in proptosis (as measured by exophthalmometer) in the study eye at 3 weeks post the fifth infusion (i.e., Week 15)

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).

The Day-1/Day 1 visit(s) in the open-label treatment study (separate study denoted as VRDN-001-302) are to be conducted within 4 weeks of the 3 weeks post the fifth infusion assessment (i.e., Week 15) in the VRDN-001-101 pivotal study (THRIVE). More than 4 weeks may be allowed between the completion of the 3 weeks post the fifth infusion assessment (i.e., Week 15) in the pivotal study and the Day-1/Day 1 visit of the open-label treatment study with prior written approval by the Sponsor.

Measurements as described in the SoA 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.

Figure 1: Overall Study Design Schematic**Figure 2: Pivotal Portion Study Design (THRIVE)**

3.2. OVERALL STUDY PROCEDURES

██████████. The active TED Pivotal portion of the trial is fully enrolled and ongoing.

The study procedures for the ██████████ and active TED pivotal portions of the study are outlined in the SoAs found in [Appendices 1A](#), [1B](#) and [1C](#), respectively.

In the pivotal portion of the study (THRIVE), participants in both treatment arms will receive the same number of infusions administered at 3-week intervals to maintain masking. Ocular

assessments will be performed on both eyes. The study eye for determination of eligibility and stratification will be the most proptotic as measured 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 Visual Acuity (VA) will be selected. If proptosis and VA are equal in both eyes, then the right eye will be selected as the study eye.

At the Investigator's discretion or at the request of the participant, an unscheduled visit may be conducted at any time.

An independent DSMB will review safety and limited efficacy data at 6-month intervals during the pivotal portion of the study, with interim ad hoc DSMB meetings as required, to monitor clinical safety and determine if any required changes to study design should be implemented. Additionally, the safety data will be reviewed on an ongoing basis by the Sponsor and any concerns will be immediately addressed and escalated to the independent DSMB, as needed.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1. NUMBER OF PARTICIPANTS

Up to 154 participants [REDACTED], and approximately 90 additional participants with active TED in the pivotal portion of the study [THRIVE]).

4.2. NUMBER AND LOCATION OF TRIAL SITES

HVs in a single US site, and TED participants in approximately 80 sites in Australia, Canada, China, EU, Turkey, UK and USA.

4.3. PARTICIPANT ELIGIBILITY CRITERIA

4.3.1. Participant Inclusion Criteria

[REDACTED] are now described in [Appendices 4](#) and [5](#), respectively.

4.3.1.1. Active TED Pivotal (THRIVE) Participants

Participants must:

1. Be able to understand the study procedures and the risks involved and be willing to provide written informed consent before the first study-related activity
2. Be an adult male or female participant, at least 18 years of age or older
3. Have had a clinical diagnosis of TED with a CAS of ≥ 3 on the 7-item scale for the study eye
4. Have moderate to severe (i.e., has an appreciable impact on daily living) active TED associated with proptosis of ≥ 3 mm above normal values for race and gender in the opinion of the investigator and at least one of the following: lid retraction of ≥ 2 mm, moderate or severe soft tissue involvement, inconstant or constant diplopia, spontaneous

- retrobulbar pain or pain on eye movement, swelling of the conjunctiva, eyelids or plica, or redness of the eyelids or plica in the study eye
5. Have documented evidence of ocular symptoms or signs associated with active TED that began within 15 months prior to study screening
6. VRDN-001 can be started concomitantly with attempts to achieve euthyroid status. Underlying thyroid status is not an inclusion criterion.
7. Not require expected immediate surgical ophthalmological or orbital surgery in the study eye for any reason
8. VRDN-001 can be used with caution in patients with diabetes mellitus. Diabetic participants should be monitored by their endocrinologist or other appropriately trained personnel and have at study entry a glycated hemoglobin (HbA1c) of <8.5%
9. If female, have a negative serum pregnancy test at screening and further negative urine tests immediately before each dose of study medication following the last dose of study medication as described in [Appendix 1C](#).
10. If the participant is a woman of childbearing potential (including those with <2 years since the onset of menopause, amenorrhea for <2 year, or not surgically sterile); such participants must agree to use an acceptable method of contraception such as a condom and a second highly effective method of contraception as described in Section 4.4 from Screening up to and including 100 days after the last dose of study medication. If the participant is initiating hormonal contraception at time of Screening or within one cycle of Day 1, participant agrees to use a double-barrier method of contraception until completing one-full cycle of hormonal contraception. An acceptable double-barrier combination method is a condom with either diaphragm or sponge with spermicide
11. Be surgically sterile males for at least 6 weeks, or agree to use an acceptable method of contraception such as a condom and a second highly effective method of contraception as described in Section 4.4 from Screening up to and including 100 days after the last dose of study medication
12. Be willing and able to comply with all the requirements of the protocol for the entire duration of the study

4.3.2. Participant Exclusion Criteria

are now described in [Appendices 4](#) and [5](#), respectively.

4.3.2.1. Active TED Pivotal (THRIVE) Participants

Participants must not:

13. Have received prior treatment with another anti-IGF-1R therapy or any investigational agent for TED
14. Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future.
15. Have corneal decompensation in the study eye unresponsive to medical management
16. Have a decrease in CAS of ≥ 2 points in the study eye between screening assessment and Day -1

17. Have a decrease in proptosis of ≥ 2 mm in the study eye between screening assessment and Day -1
18. Have had previous orbital irradiation or decompression surgery involving excision of fat for TED to the study eye's orbit
19. Have history of or screening audiometry assessment of significant (as determined by the Investigator) ear pathology, relevant ear surgery or hearing loss
20. Have inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease)
21. Have used systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study medication (topical steroids or multivitamins that contain selenium are permitted)
22. Have received other immunosuppressive agents, including rituximab, or tocilizumab, for any condition, including TED, within 8 weeks prior to the first dose of study medication
23. Have received any other therapy for TED within 8 weeks prior to the first dose of study medication (artificial tears are permitted)
24. Have received an investigational agent for any condition within 8 weeks prior to the first dose of study medication
25. Have a pre-existing ophthalmic condition in the study eye which in the opinion of the Investigator, would confound interpretation of the study results
26. Be a pregnant or lactating woman
27. Be an active alcoholic or illicit drug user or considered at high risk of relapse by the Investigator
28. Have a known hypersensitivity to any of the components of VRDN-001 or placebo formulations, or prior hypersensitivity to monoclonal antibodies (mAbs)
29. Have any condition, which in the opinion of the Investigator, would preclude inclusion in the study
30. Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2)
31. Have a positive test for active hepatitis B or hepatitis C infection
32. Have previously participated in this study or any study of VRDN-001
33. French participating sites only: In accordance with the provisions of articles L.1121-5 et seq. of the Public Health Code, pregnant or breast-feeding women, persons deprived of their liberty by a judicial or administrative decision, persons under psychiatric care without their consent, minors and adults under a legal protection measure must not be included

Note: Prior thyroidectomy, radioactive iodine (RAI) treatment, or orbital decompression surgery limited to bone only are NOT exclusions.

4.4. CONTRACEPTION GUIDELINES

Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy by using highly effective contraception from Screening up to and including 100 days after the last dose of study medication.

Males must agree to take appropriate precautions to avoid fathering a child from Screening up to and including 100 days after the last dose of study treatment and must consent to using an acceptable method of contraception such as a condom and a highly effective second method

(examples provided below), surgical sterilization (by one of the partners), postmenopausal partner (meeting the definition above), or abstinence.

The following methods have been determined to be highly effective (< 1% failure rate per year when used consistently and correctly) ([Trussell 2011](#); [Clinical Trials Facilitation and Coordination Group 2020](#)) and are permitted under this protocol for use by the participant and their partners as well as female participants of childbearing potential:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments, when this is in line with the preferred and usual lifestyle of the participant;
- Oral, intravaginal, or transdermal combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation;
- Oral, injectable, or implanted progestogen-only hormonal contraception associated with inhibition of ovulation;
 - Note: Progestogen-only “mini-pills” are not considered highly effective methods of contraception for this protocol because inhibition of ovulation is not their primary mechanism of action.
- Intrauterine device (IUD);
- Intrauterine hormone-releasing system (IUS)
- Vasectomy or vasectomized partner, provided that the partner is the sole sexual partner of the female trial participant and that the vasectomized partner has received medical assessment of the surgical success;
- Bilateral oophorectomy/bilateral salpingectomy with or without hysterectomy or bilateral tubal ligation at least 6 weeks prior to taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up levels of luteinizing hormone, FSH, and/or estradiol.
 - Female participants who have undergone surgical sterilization by oophorectomy alone will have FSH levels assessed at Screening.

4.5. WITHDRAWAL OF PARTICIPANTS

Every effort will be made to have all participants attend all study visits and receive all doses of study drug. Participants can voluntarily withdraw from study treatment and from the study completely at any time during the study. Every effort will be made to complete study follow-up procedures as defined in [Appendices 1A](#), [1B](#) and [1C](#), where permitted by local health authorities and Ethics Committees (EC)/Institutional Review Boards (IRB), if participants terminate the study treatment early.

Participants may receive rescue therapy at any time during the trial at the discretion of the Investigator. Participants must be discontinued from study treatment prior to initiation of rescue therapy, which could include systemic steroid treatment or surgical intervention (or teprotumumab in the US). Participants who receive rescue therapy will continue to be followed for safety until trial completion. Furthermore, participants will not be deprived of care if alternative treatment options become available during the course of the study and may withdraw consent at any time during their study participation to receive alternative therapy.

If a participant discontinues study treatment (including rescue therapy with steroids, which would require discontinuation of study treatment) or is withdrawn from the study for any reason, the study site must immediately notify the medical monitor (contact information can be found in the PPM). The date and the reason for discontinuation must be recorded on the electronic case report form (eCRF).

In the event a participant revokes consent to participate during the study, whenever possible the participant should return for the final scheduled end of study visit. The specific study assessments performed at the final scheduled end of study visit will be dependent on those assessments permitted by local health authorities and ECs/IRBs. End of Study visit assessments are indicated in the [Appendices 1A](#), [1B](#) and [1C](#).

Study participants will be monitored continuously during the study for an exacerbation or new diagnosis of, inflammatory bowel disease, glucose intolerance which cannot be managed, any hearing impairment that the participant feels outweigh any benefit of therapy on their TED, and as a result the participant is removed from the study if the investigator believes it is in the participant's best interest. In addition, participants will also be removed from the study if the treating physician sees any signs of acute sight-threatening compressive optic neuropathy that requires surgical decompression.

In the event that a participant discontinues prematurely from the study because of a treatment emergent adverse event (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or study baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

A participant may withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Progressive disease (worsening of the disease)
- Unacceptable toxicity
- Participant's withdrawal of consent: at any time, a participant's participation in the study may be terminated at his/her request
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the participant's termination from the study
- General or specific changes in the participant's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- Failure of the participant to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits)
- Lost to follow-up: the participant stopped coming for visits, and study personnel were unable to contact the participant
- Pregnancy

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at their study site for any reason, including safety or low enrollment.

Note that the term “withdrawal of consent” is used only when the participant no longer wishes to participate in the trial and no longer authorizes the Investigators to make efforts to continue to obtain their outcome data.

4.6. FOLLOW-UP OF PARTICIPANTS WITH ADVERSE EVENTS

Any AE that is not resolved by the end of the study or upon discontinuation of the participant's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if available), or is shown to not be attributable to the study drug or procedures.

4.7. FOLLOW-UP OF PARTICIPANTS AFTER DISCONTINUATION OF STUDY TREATMENT

The CRF will clearly distinguish between reasons for non-adherence (that is, for not receiving randomized therapy and hence for being “off study treatment”) versus non-retention (that is, for not obtaining outcome information and hence for being “off study”). All participants will be followed until death or trial completion, where possible, even if they discontinue study treatment or initiate other treatment.

5. TREATMENT OF PARTICIPANTS

5.1. DESCRIPTION OF VRDN-001

VRDN-001 is a humanized mAb directed against IGF-1R and will be provided as a solution containing [REDACTED] mg/mL or [REDACTED] mg/mL of antibody in 4.0 mL extractable volume in [REDACTED] R vials, frozen at $-20 \pm 5^{\circ}\text{C}$.

5.1.1. Administration of VRDN-001

The pharmacist or other qualified, trained and delegated individual preparing the infusion bags will be unmasked to treatment and will either dispense [REDACTED] [REDACTED] bags of saline with or without VRDN-001 added, according to the RTSM system assignment. The volume of saline removed from the bags will equal the volume of VRDN-001 added to maintain masking. [REDACTED]

Further details on dose and volumes of infusate per body weight calculations are provided in the Pharmacy Manual (PM). The study drug will be administered by medical professionals trained in emergency procedures and with immediate access to resuscitation equipment.

5.1.2. Storage, Accountability and Compliance

VRDN-001 will be stored frozen in a secure area at $-20 \pm 5^{\circ}\text{C}$ (see PM). Access to the study treatment will be limited to authorized site staff only. Temperature of the storage location of VRDN-001 at the site must be monitored using a calibrated monitoring device and documented.

If a discrepancy is noted, the appropriate individual at the Sponsor or designee must be notified immediately, in accordance with the PM.

The pharmacist or other designated individual will maintain records of the amount of VRDN-001 delivered to the infusion clinic, the inventory at the clinic, the distribution to and amount infused to each participant, and the return of materials to the Sponsor or disposal at the infusion clinic if approved by the Sponsor and per institution policy and verified by the Clinical Research Associate. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log and unique code numbers assigned to the product and study participants.

5.2. PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary and tabulated and recorded in the eCRF, as applicable.

Prior to the first infusion visit, any medication including systemic corticosteroids, immunosuppressive agents or any other therapy for the treatment of TED that is administered to the participants prior to enrollment into the study as allowed per protocol must be recorded in the eCRF as prior medication. The entry must include the dose, regimen, route, indication and dates of use.

After the first infusion visit, any medication that is administered to the participants during the course of the study must be recorded in the eCRF as concomitant medication. The entry must include the dose, regimen, route, indication and dates of use.

5.2.1. Prohibited Concomitant Medications

The following therapies are expressly prohibited throughout the study: Systemic steroids, any other anti-IGF-1R therapy, insulin receptor inhibitors, anti-TSHR monoclonal antibodies, any immunomodulating therapies and selenium (multivitamins containing selenium to meet daily dietary requirements are allowed). Additionally, treatment with radioactive iodine (RAI) for any condition is prohibited throughout the study.

6. CONDUCT OF STUDY AND STUDY VISITS

The Sponsor will implement proactive approaches to minimize the number of participants who have missed assessments, especially of the primary endpoint of the trial. The targeted level of data capture for the primary endpoint is set to 95% in order to achieve a high quality of trial conduct. Effective procedures will be implemented during enrollment and follow-up to enhance achieving this target level of retention. During the trial conduct, the Sponsor will monitor the masked data to ensure the achievement of the target level of data capture.

6.1. CONDUCT OF STUDY FOR ALL PARTICIPANTS

6.1.1. Screening and Informed Consent

All participants will receive a written informed consent form (ICF) describing this study and providing sufficient information to make an informed decision about participating in this study.

Written informed consent must be obtained before any protocol specific procedures are performed. All participants will receive a signed copy of their ICF and the original ICF must be maintained within the participant's study records.

The Investigator is responsible for ensuring that a careful and thorough informed consent procedure is implemented before a participant enters the study and at any time during the study should ICF changes be introduced. This includes, but is not limited to: (1) providing a quiet place for the participant to read the ICF and allowing ample time for this review; (2) ensuring that qualified medical personnel are available to directly answer questions that a participant may have; (3) ensuring that each potential study participant understands that their medical treatment will not be otherwise affected based on the decision whether or not to participate in the study, that their participation is completely voluntary, and that they can opt to stop participation in the study at any time for any reason; and (4) ensuring that a full copy of the signed ICF is given to the participant to take home for their medical records. The process for obtaining informed consent should also be documented in the participant's source documentation.

Participants are educated during the informed consent process about the continued scientific relevance of their data even if they discontinue treatment, as well as the deleterious effect that missing data has on trial integrity and credibility.

The study procedures are outlined in the SoA in [Appendices 1A, 1B and 1C](#).

7. OPTHALMIC ASSESSMENTS FOR TED PARTICIPANTS

All ophthalmological assessments will be performed on both eyes at the visits specified in [Appendices 1A, 1B and 1C](#). Detailed descriptions of the assessments outlined in this section are described in the accompanying PPM. **The GO-QoL and EQ-5D-5L must be performed before any other assessments on the visit days when it is required.**

7.1. GRAVES' ORBITOPATHY - QUALITY OF LIFE MEASUREMENT (GO-QoL)

The Graves' ophthalmopathy quality of life questionnaire will be completed by TED participants. 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. A change of 8 points or greater on an individual subscale or the combined score on the 0-100 scale has been shown to be clinically meaningful ([Terwee 1998](#)).

7.2. 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 version which is made up of a 2 page questionnaire 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 participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. 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 VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement ([EuroQol Research Foundation online](#)).

7.3. 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 and the three measurements recorded. A change in proptosis of 2 mm or greater is considered clinically meaningful. This must be performed by a physician and the same physician must perform the measurement and the same exophthalmometer should be used for an individual participant throughout the course of the study. Additionally, the base setting for the exophthalmometer should be recorded at the Screening visit and available to the physician at each clinical encounter, and the same base setting used for each subsequent measurement.

7.4. MANUAL MEASUREMENT OF LID RETRACTION

Lid retraction will be recorded in millimeters (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). This must be performed by a physician and the same physician must perform the measurement for an individual participant throughout the course of the study. A change in lid retraction of 2 mm or greater is considered clinically meaningful.

7.5. 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 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.

7.6. MEASUREMENT OF ORBITAL FAT VOLUME BY MRI/CT

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.

7.7. MEASUREMENT OF EXTRAOCULAR MUSCLE 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.

7.8. CLINICAL ACTIVITY SCORE

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). This must be performed by a physician and the same physician must perform the assessment for an individual participant throughout the course of the study. For those who start the study with a non-zero value, a change of at least 2 points is considered clinically meaningful ([Mourits 2003](#)).

7.9. 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). The same assessor must perform the assessment for an individual participant throughout the course of the study. For those who at baseline have a non-zero value, a reduction of at least one grade is considered clinically meaningful. Diplopia resolution defined as a Gorman subjective diplopia score of zero will be assessed for all those who at baseline had a non-zero score.

7.10. INTRAOCULAR PRESSURE

IOP measurements will be performed using the site's standard tonometry assessment method (e.g., Goldmann® or Tonopen®). For any given participant, the same IOP assessment method will be used for the duration of the study.

7.11. BIOMICROSCOPY

Biomicroscopy will be performed with a slit lamp to examine the anterior and posterior chambers of the eye. The examinations will include an assessment of the lids/lashes, conjunctiva, cornea, iris/anterior chamber, lens and anterior vitreous.

7.12. FUNDOSCOPY

The dilated fundus exam will include assessment of vitreous, retina/macula/choroid and optic nerve.

7.13. VISUAL ACUITY

Visual Acuity 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.

8. SAFETY ASSESSMENTS FOR ALL PARTICIPANTS

All safety assessments will be performed at the visits specified in [Appendices 1A, 1B and 1C](#).

8.1. MEDICAL HISTORY

Medical history will be recorded at Screening. Investigators should document the occurrence, signs and symptoms of the participant's preexisting conditions, including all prior significant illnesses. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption, illicit drug use and smoking history, if applicable.

Illnesses first occurring or detected during the study (from time of consent), and/or worsening of a concomitant illness during the study, are to be documented as AEs on the eCRF. All changes not present at time of consent or described in the past medical history and identified as clinically relevant must be recorded as AEs.

8.2. VITAL SIGNS

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements), height and weight will be evaluated at visits specified in [Appendices 1A, 1B and 1C](#). Vital signs will be measured after the participant has been resting in a sitting position for at least 5 minutes. Whenever possible, blood pressure measurements should be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the Investigator's discretion. Any clinically significant vital sign measurement abnormalities must be recorded as AEs.

8.3. PHYSICAL EXAMINATION

A complete physical examination (head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; neurological and musculoskeletal systems) will be performed by a physician or other appropriately trained, delegated and licensed personnel at visits specified in the SoA. A symptoms-directed physical examination will be performed at every study infusion visit and may be performed at any other time throughout the trial as determined by any new signs or symptoms.

8.4. ELECTROCARDIOGRAM

A 12-lead, resting ECG will be obtained at Screening and the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the participant from the study. An

assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, and assessed as clinically significant by the Investigator, then the abnormality will be documented as an AE on the eCRF. ECGs will also be performed at visits specified in [Appendices 1A, 1B and 1C](#).

8.5.

8.6. LABORATORY ASSESSMENTS

Clinical laboratory tests will include 12-hour fasting serum chemistry and lipid panel,   hematology, HbA1c, coagulation panel and urinalysis. Serum and urine pregnancy tests in all females will be performed as described in [Appendices 1A, 1B and 1C](#).

The analytes and blood collection, sample processing and shipment to the central laboratory facility are detailed in the accompanying PPM for this study and described in more detail in the Laboratory Manual (LM). Blood and urine samples will be collected at Screening, immediately before the first infusion and then as described in [Appendices 1A, 1B and 1C](#). Additional tests may be performed at any time during the study as considered necessary by the Investigator.

In addition, blood samples for PK analyses, IGF-1 levels and ADA will be shipped via the central laboratory facility but analyzed by different vendors. The timing of sample collection is described in [Appendices 1A, 1B and 1C](#). On the days of the first and fourth infusions, blood samples for PK will be taken by an indwelling venous cannula (inserted in the opposite forearm to the infusion arm) before starting the infusion, at 5 to 10 minutes before the end of the infusion and at 2 hours (± 15 minutes) and 4 hours (± 15 minutes) after completion of the infusions.

TED participants will be offered home/office-based blood draws at certain visits, which will be performed by visiting nurses at a third-party vendor, if they prefer not to return to the doctors' office.

Urinalysis by routine urine dipstick analyses will be performed at the site, and a microscopic analysis will be performed and analyzed by the central laboratory if any abnormalities are found during the dipstick analyses. All laboratory reports must be reviewed, signed and dated by the Investigator. A legible copy of all reports must be filed with the participant's medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE. Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

Table 1: List of Safety Laboratory Analytes

Hematology	Serum Chemistry	Urine Analysis (Dipstick)
Basophil (Absolute/Percent)	Albumin	Appearance
Eosinophil (Absolute/Percent)	ALT	Bilirubin
Monocyte (absolute/Percent)	ALP	Blood
Hb	AST	Color
HbA1c	Amylase	Glucose
Hct	Bilirubin, Direct and Total	Ketones
Lymphocyte (Absolute/Percent)	BUN	Leucocyte Esterase
Red Cell Distribution Width	Calcium	Nitrite
MCV	Carbon dioxide (Bicarbonate)	pH
Neutrophil (Absolute/Percent)	Chloride	Protein
Platelets	Cholesterol	Specific gravity
RBC	CK Total (or CPK)	Urobilinogen
WBC	Creatinine serum	
MCH	GGT	Microscopic (if dipstick abnormal):
MCHC	Glucose (Fasting)	Bacteria
	HDL	Crystals (Calcium Oxalate, Triphosphate & Uric Acid)
	LDH	Epithelial Cells (Renal Tubular, Squamous & Transitional)
	LDL	Casts (Granular, Hyaline, Waxy, RBC & WBC)
	Lipase	
	Magnesium	
	Phosphorus	RBC
	Potassium	WBC
	Sodium	Yeast
	Total Protein	
	Triglycerides	
	Uric Acid	
Coagulation: PT/INR & aPTT		
Infectious diseases: HIV 1/2, Hepatitis B and Hepatitis C		
Other: FSH at screening for all females		
Pregnancy test: A serum pregnancy test will be performed at screening and urine test prior to each infusion and at designated timepoints in the protocol for all females		

9. SAFETY MONITORING

The safety and tolerability of drug treatment will be assessed through the collection and analysis of AEs, vital signs, ECGs, physical exams, audiometry, ocular examinations (for TED participants), and laboratory tests. All safety assessments and protocol specified tests, including occurrence of AEs, intensity/severity, relationship to study drug, and treatment or action taken to resolve the event, will be performed by qualified study personnel and/or the evaluating physicians who are listed on the Delegation of Responsibilities Log.

For the purposes of safety monitoring, baseline is defined as the value from the last assessment or blood sample taken before the first infusion.

The study medical monitor will review SAEs and AEs on an ongoing basis [REDACTED]

9.1. DATA SAFETY AND MONITORING BOARD

An independent DSMB will oversee the safety of the study and make all decisions related to dose escalation, DLTs and MTD in [REDACTED] of the study. Thereafter, the independent DSMB will review safety and limited efficacy data from the active TED Pivotal portion of the study at 6-month intervals, with interim ad hoc DSMB meetings as required, to monitor clinical safety and determine if any required changes to study design should be implemented.

Additionally, the safety data will be reviewed on an ongoing basis by the Sponsor and any concerns will be immediately addressed and escalated to the independent DSMB, as needed. The DSMB Charter for this study describes its roles and responsibilities and identifies its members. The charter also outlines a plan for disseminating study data and can be made available on request.

9.2. DEFINITIONS OF ADVERSE EVENTS

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to, the following:

Any clinically significant worsening of a pre-existing condition other than TED is considered to be an AE. However, worsening of TED is considered to be “disease progression” or “lack of efficacy” and need not be reported as an AE unless it or the signs and symptoms associated with TED are more severe than expected for the participant’s condition.

An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing

- Test result requires significant additional concomitant drug treatment, or other therapy or intervention
- Test result leads to a change in trial dosing or discontinuation of study drug
- Test result is considered to be an AE by the Investigator or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

A clinical diagnosis, rather than the changes in laboratory or other assessment should be recorded on the eCRF as appropriate (e.g., anemia versus low hemoglobin value, bundle branch block rather than abnormal ECG).

9.3. SERIOUS ADVERSE EVENTS

Any adverse experience occurring at any dose that results in any of the following outcomes is classified as a serious adverse event (SAE).

- Results in death
- Life threatening or life-threatening suspected adverse reaction (SAR) (see below for definition)
- Results in persistent or significant disability/incapacity (see below for definition)
- Requires participant hospitalization or prolongs participant hospitalization (see below for definition)
- Results in a congenital anomaly/birth defect in a neonate/infant

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include dysthyroid optic neuropathy, retinal detachment, retinal tear requiring an intervention, or other ocular AEs that may cause permanent visual loss initially without symptoms, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The sponsor or the DSMB may also request to upgrade an adverse event to serious criteria based on their assessment as an important medical event.

Life-threatening AE or life-threatening suspected adverse reaction (SAR) refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported by the PI. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery, or other elective procedures). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls in the same category.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

9.4. ADVERSE EVENT RECORDING AND REPORTING

AEs and SAEs should be reported from the time the participant signs the informed consent to the time the participant completes the study. Relatedness to VRDN-001/Placebo infusion and/or study procedures is determined by the Investigator. All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents. All AEs and SAEs for screened participants will be recorded on the eCRF.

Study Investigators must follow-up on all AEs, SAEs, and other reportable events until the events have resolved, returned to baseline, or in case of permanent impairment, until the condition stabilizes. If, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease, the Investigator must record their reasoning for this decision in the participant's source documentation and on the eCRF. Any medication or other intervention necessary for the treatment of an AE must be recorded on the concomitant medication eCRF.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Relationship to study treatment
- Outcome
- Treatment or action taken.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used.

If more than one distinct AE occurs, each event should be recorded separately. However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the eCRF rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension → fainting and fall to floor → head trauma → neck pain

The primary event is orthostatic hypotension and the sequelae are fainting, fall, head trauma and neck pain.

9.5. CLASSIFICATION OF ADVERSE EVENTS BY INTENSITY/SEVERITY

Severity

All AEs should be graded by Investigators using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 ([Appendix 3](#)). If the AE is not specifically listed in the CTC toxicity criteria, use the following grades:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)

Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs.

Expectedness

All AEs considered related to VRDN-001/Placebo will be evaluated as to whether they are expected or unexpected, and related to VRDN-001/Placebo, the infusion procedure, and/or more than one of these. Expectedness will be determined by the Sponsor.

Expected (anticipated): An AE is expected when the nature, severity, or degree of incidence was previously described in the Reference Safety Information (RSI) section of the IB.

Unexpected (unanticipated): An AE is unexpected when the nature, severity, or degree of incidence was not previously described in the Reference Safety Information (RSI) section of the IB.

Relatedness

The Investigator will determine the assessment of the causal relationship of the AE/adverse reaction to the study product. The following terms for assessment of the causality to study product or study procedures are to be used:

Not related

Related

Outcome

The clinical outcome of an AE will be characterized as follows:

- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Death
- Unknown/Lost to follow-up

Action Taken with Study Drug or Procedure

- None
- Study product or procedure interrupted
- Study product or procedure discontinued

9.6. SERIOUS ADVERSE EVENT REPORTING

SAEs must be reported to the Sponsor as soon as possible and no later than 24 hours after the Investigator first learns of the event, or sooner if required by local regulations (e.g., immediately in Germany). The SAE form is to be completed and submitted per delivery method specified in the PPM. For initial reports, Investigators should record all case details that can be gathered within the reporting timeframe. Relevant follow-up information should be submitted to the Sponsor as soon as it becomes available and/or upon request and no later than 24 hours after the Investigator first learns of the relevant follow-up information, or sooner if required by local regulations. For some events, the Sponsor or designee or the medical monitor may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the participant's subsequent medical course must be submitted to the Sponsor until the event has resolved or, in case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained.

SAE reporting timelines should be followed when reporting a pregnancy or symptomatic overdose. Additionally, pregnancy should be reported from the time of consent through 100 days after the last study treatment in this study.

The SAE report should be sent per the delivery method specified in the PPM.

You may also contact Safety personnel at the phone number specified in the PPM.

Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Sponsor within 24 hours of the change in seriousness criteria, or sooner if required by local regulations; these reports should be submitted per the delivery method specified in the PPM.

If the site personnel need to speak to the Sponsor's representative, please use the following contact information:

Medical monitor contact email mailbox: [REDACTED]

Sponsor contact information and additional contact information for the Contract Research Organization [CRO] are provided in the accompanying PPM.

Viridian and any delegated CRO are responsible for reporting of suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities and principal investigators in Australia, Canada, Turkey, European Union, United Kingdom, United States and any other countries that may participate in this trial using expedited timelines according to ICH-GCP requirements. Furthermore, all other SAEs will be reported as part of annual reporting requirements or more frequently as line listings per local health authorities and EC/IRB requirements.

9.7. RISK MITIGATION AND TOXICITY MANAGEMENT GUIDANCE

Risk mitigation and toxicity management guidance for VRDN-001 infusion and treatment, based on findings with teprotumumab, an anti-IGF-1R monoclonal antibody approved in the US for treatment of TED, include the following. Note that the physician treating each patient will have the final decision on the type of treatment at the time of an event.

Infusion associated adverse events

Monoclonal antibodies may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea and/or vomiting. Such reactions, which may be indistinguishable from anaphylactic reactions, typically occur during or shortly after the infusion and are usually associated with the first infusion. The incidence and severity typically decrease with subsequent infusions.

For the first 3 infusions in the pivotal part of the study [REDACTED], participants should be monitored during the infusion and for at least 60 minutes after completion of the infusion including vital signs monitored within 2 hours pre-infusion, 30 (± 15) minutes after the start of infusion and again at 1 hour (± 15 minutes) after completion of the infusion and the infusion site examined 5 to 10 minutes and then again at 30 (± 10) minutes after the start of each infusion for local tolerance. For subsequent infusions (the 4th dose and 5th dose), participants who have not previously experienced an infusion reaction should be monitored during the infusion and for at least 30 minutes after the infusion including vital signs monitored within 2 hours pre-infusion, 30 (± 15) minutes after the start of infusion and again 30 (± 15) minutes after completion of the infusion and the infusion site examined 5 to 10 minutes and then again at 30 (± 10) minutes after the start of each infusion for local tolerance. For participants enrolled in the Czech Republic, local regulation requires that participants be monitored by the investigator for 2 hours following all infusions. Participants who exhibit immediate hypersensitivity reactions or infusion-associated reactions during an infusion of VRDN-001 should have the infusion interrupted or the infusion rate slowed. Symptomatic

treatment (e.g., antipyretics, antihistamines and/or corticosteroids, oxygen, beta agonists, IV fluids, epinephrine and atropine as needed, resuscitation as needed) should be administered to the participant. Following an immediate hypersensitivity reaction, or infusion-associated reaction, vital signs (temperature, blood pressure, pulse and respiratory rate) should be determined every 5 minutes until stable, and then every 15 minutes for 2 additional determinations. The infusion may be restarted after complete resolution of symptoms except in case of participants who experience an anaphylactic reaction; these participants should be discontinued from treatment.

In general, the decision to keep a participant on study treatment with VRDN-001 should take into consideration potential risks and benefits to the participant. Prior to all future infusions of VRDN-001 in those who have experienced infusion-associated reactions, these participants should be pre-medicated with IV diphenhydramine 1 to 1.25 mg/kg (maximum: 50 mg), IV ranitidine 50 mg, IV dexamethasone 0.4 mg/kg (maximum: 20 mg), and/or acetaminophen 500 mg, or with the site's own standard of care regimen for prophylaxis of anaphylaxis. In addition, all future infusions should be administered over at a minimum 90 minutes. Participants who experience delayed-type hypersensitivity reactions (e.g., skin rash) may remain on treatment at the discretion of the Investigator, and prior to all future infusions should be pre-medicated with the above medications (diphenhydramine, ranitidine, dexamethasone, and/or acetaminophen). Participants who experience a worsening delayed-type hypersensitivity reaction following repeated infusions of VRDN-001 or who have other signs of serum-sickness (e.g., delayed fever, myalgias, arthralgias) may be discontinued from treatment after discussion with the Investigator and Sponsor.

If a Grade 4 (life-threatening) infusion related reaction (IRR) occurs, or recurrent Grade 3 IRR occur, then study drug must be permanently discontinued and no further rechallenge may occur.

Hyperglycemia

Fasting glucose and HbA1c levels (after 12-hour fast) will be tested at baseline and at additional study visits as described in [Appendix 1C](#). Participants with known controlled diabetes mellitus are allowed to participate in studies with VRDN-001 when meeting the inclusion and exclusion criteria for the study. Investigators are encouraged to adjust their participants' diabetes management to maintain participants' HbA1c levels at < 8.5%. In the event a participant's HbA1c level rises to $\geq 8.5\%$ while in the study, the participant should have their hyperglycemia treated with glycemic control medications and Investigator should determine the risk versus benefit for each participant to remain on treatment. Hyperglycemia should be promptly investigated and managed and has, based upon the experience with Tepezza, [REDACTED]

[REDACTED] been short lived and readily managed.

Participants with recurrent hyperglycemia, defined as a fasting glucose level of moderate intensity (glucose >160 – 250 mg/dL), will require evaluation for diabetes mellitus (e.g., fasting glucose, glucose tolerance, and HbA1c tests) and appropriate medical management and glycemic control at the discretion of the Investigator.

Muscle Spasms

If muscle spasms occur during or after the VRDN-001 infusion, avoid medications known to cause muscle spasms or muscle toxicity such as diuretics or statins and evaluate for other causes

of muscle spasm such as electrolyte abnormalities and dehydration. Treatment with muscle relaxants may be considered, particularly if spasms last for longer than 1 week. Treatment with oral Magnesium 400 mg 1-2 days prior to subsequent infusions have been reported to be of potential benefit in limiting muscle spasms, and may be administered at the discretion of the clinical center physician and Investigator.

Hearing Impairment

Air conduction audiometry [REDACTED]

[REDACTED]. Clinical data and real world experience with teprotumumab, [REDACTED], has indicated that hearing impairment, if it occurs, usually presents after the 3rd or 4th infusion (Sears 2022). If significant hearing impairment is detected, the participant will be referred to an Audiologist and/or an Ear, Nose and Throat physician for further evaluation and treatment. In general, the decision to keep a participant on study treatment with VRDN-001 should take into consideration potential risks and benefits to the participant.

Diarrhea

If diarrhea occurs and is progressive and persistent, or has features of Inflammatory Bowel Disease (IBD) such as bloody stools or abdominal pain, the participant should undergo prompt evaluation to exclude IBD or other serious conditions. Discontinue the participant from treatment if IBD worsens. If possible, avoid medications known to cause diarrhea such as laxatives and magnesium.

9.8. STOPPING RULES

If a participant experiences an SAE with a severity $\geq$ Grade 3 on the CTCAE scale ([Appendix 3](#)) which is considered by the investigator to be related to the study drug, then that participant will be immediately withdrawn from treatment and followed until the event has resolved, returned to baseline, or in case of permanent impairment, until the condition stabilizes.

If 2 or more participants experience an SAE with a severity $\geq$ Grade 3 on the CTCAE scale, which is considered by the investigator(s) to be related to the study drug, then the DSMB will be immediately informed to make their assessment on the relationship to study drug and make a sponsor recommendation to either continue or discontinue the study treatment for all participants.

9.9. PROCEDURE FOR COMMUNICATING SAFETY EVENTS WITH ALL PARTICIPATING SITES

All sites will be informed electronically of the recommendations of DSMB within 48 hours of receipt from the DSMB Chair when significant safety issues are identified. Furthermore, all sites will be informed within the same timeframe specified by the specific country regulatory agency

or EC/IRB of any SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) with a severity $\geq$ Grade 3 on the CTCAE scale.

10. STATISTICS

All statistical considerations and analyses will be fully described in the statistical analysis plan (SAP), which will be finalized prior to database lock.

The [REDACTED] and pivotal parts will be analyzed separately, and results will not be pooled in any way. [REDACTED].

10.1. STATISTICAL METHODOLOGY

10.1.1. Randomization

[REDACTED]. Participants in the pivotal portion of this study (THRIVE) were either randomized (1:1:1) to 5 infusions or 8 infusions versus placebo (as per protocol version 6.0 or earlier [including all version 6 country specific amendments (e.g., v6.1, v6.2, etc.)]) or randomized (2:1) to 5 infusions versus placebo [REDACTED] each administered as IV infusions at 3-week intervals.

Randomization codes are created and maintained throughout the study by the RTSM vendor with access given only to designated unmasked personnel.

If a participant discontinues the study early, a replacement participant may be enrolled at the discretion of the sponsor on a case-by-case basis. Replacement participants will be randomized to the same treatment as the original participant.

10.1.2. Study Masking

Masking will be maintained by the use of placebo (saline) infusions that appear identical to VRDN-001 infusions. [REDACTED]

Both participants and site personnel (except pharmacy personnel preparing the infusate) will be masked to treatment through the primary endpoint assessment at a minimum and through Week 52 where allowed by local health authorities. The Sponsor will also be masked to treatment for the pivotal portion of the study, save for selected sponsor designees who will have no direct contact with any study operations, [REDACTED].

During the site initiation visit, all sites will be informed of the masking requirements and will be asked to document on the Delegation of Authority Log who will be masked or unmasked and what their specific roles and responsibilities will be. It is the responsibility of the Investigator to ensure that the masking requirements of the participant's treatment assignment are adhered to.

To avoid any possible unmasking, if the unmasked Pharmacy personnel have any questions regarding the study drug dosing preparation, they should contact the unmasked Clinical Supply Manager whose contact details are provided in the PPM.

10.1.3. Procedure for Unmasking Participants

An appropriate user (i.e., Investigator, Safety Officer, RTSM system administrator) will be able to perform a participant code break in the RTSM system after treatment allocation throughout the duration of the randomized treatment phase. An emergency subject code break by the masked investigator in case of an urgent situation may be performed without prior notification to a monitor or the sponsor.

Once the participant code break action is completed, a Confirmation Screen is displayed with the participant code break information. This page will no longer be available once the user has left it.

Additionally, once the transaction has been completed successfully, the ID-Net system will generate an email with a PDF attachment and send to all designated individuals.

10.1.4. Description of Populations for Analysis

Pivotal cohorts (THRIVE):

Intent-to-Treat (ITT) 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 baseline characteristics.

Modified Intent-to-Treat (MITT) Population

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

Safety Population

The Safety population will comprise all participants who receive at least one dose of study medication. This dataset will be employed to analyze the safety endpoints. Participants will be analyzed according to the study medication received for all safety analyses.

Per-Protocol (PP) Population

The Per-Protocol (PP) population will comprise participants in the MITT population who did not have any selected major protocol violations. This population will only be utilized as a sensitivity analysis for the primary and key secondary efficacy endpoints.

10.2. SAMPLE SIZE

The pivotal portion of the study has a power of greater than 90% power to test the 5 infusion 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 ([Smith 2017](#); [Douglas 2020 Appendices 1A, 1B and 1C](#)). 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 minus the penalty. The study consists of approximately 90 participants, randomized with allocation ratio of 2:1 over the 5 infusion 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%.

The sponsor may decide to enroll replacement participants in the event participants drop out prior to evaluation of the primary endpoint, in order to restore the power of the study.

10.3. ENDPOINTS

A description of endpoints for this study can be found in [Section 2](#) of this protocol.

10.4. ANALYSIS OF ENDPOINTS

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.

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum), while categorical variables will be summarized as counts and percentages of participants in each category. Results will be presented by study arm and combined as appropriate.

Pivotal cohorts (THRIVE):

For the pivotal portion of the study, 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 a statistical penalty for data reviews. The p-value for the primary analysis will be documented prior to the primary analysis Week 15 database lock. A gated testing methodology will be utilized to control Type 1 error. The primary population will be tested for the primary and key secondary endpoints in the order specified in the SAP.

The primary analysis for timepoints earlier than 3 weeks post the fifth infusion (i.e., Week 15) will be the combined 5 infusion and 8 infusion treatment arms compared to placebo.

10.4.1. Primary Efficacy Endpoint**Pivotal cohorts (THRIVE):**

For the pivotal cohorts, the primary analysis of efficacy will be a comparison of the Proptosis Responder rate as measured by exophthalmometer at 3 weeks post the 5th infusion (i.e., Week 15). For this analysis all participants who were randomized to the 5 infusion and 8 infusion treatment arms will be combined and tested against placebo.

Proptosis Responder Rate and Overall Responder Rate will be evaluated at different post-baseline visits throughout the trial, the longitudinal data will be analyzed using a logistic regression model for correlated observations fitted by the generalized estimating equation (GEE) approach. The risk difference will be estimated as the difference of the average model-based response probabilities at 15 weeks. The reported treatment effect will not be the overall risk difference across multiple visits. The GEE-modeling is not a likelihood-based approach and, therefore, it provides valid estimates if the data are missing completely at random (MCAR), i.e., if the probability of missingness depends neither on observable outcomes, nor on the unobservable ones. All model specifications will be detailed in the SAP.

Sensitivity analyses will be performed to assess the robustness of the proptosis response and overall response. These sensitivity analyses will be described in the SAP.

10.4.2. Secondary/Exploratory Efficacy Endpoints

Pivotal cohorts (THRIVE):

Endpoints similar to the primary endpoints (i.e., clinical activity responder rate, diplopia responder rate, diplopia resolution rate, clinical activity score of 0 or 1 rate) will be analyzed in the same way as the primary endpoints.

Changes from baseline will be estimated and compared between treatment arms using a general linear model for correlated data. All model specifications will be detailed in the SAP.

10.4.3. Efficacy Analysis for Fellow/Other Eye

All efficacy endpoints are defined for the study/most proptotic eye. Given the systemic nature of the study treatment, the outcomes for the fellow/other eye will also be evaluated for efficacy and safety. To this end, all analyses for primary and secondary efficacy endpoints will be repeated for the fellow/other eye.

10.5. ANALYSIS OF SAFETY

Safety analyses will be reported for [REDACTED] and THRIVE separately.

Safety assessments will be made at all study visits and both safety and tolerability will be evaluated by assessing the incidence of AEs and the incidence of SAEs.

AEs, SAEs, and other findings will be summarized by presenting the percentages of participants with each event for each treatment group. When relevant, the time course of AEs will be presented.

Safety analyses will summarize participants by the treatment received.

The safety analysis will summarize ocular treatment-emergent AEs (TEAEs) for all treated participants using discrete summaries at the participant- and event-level by system organ class and preferred term. A TEAE will be defined as occurring on or after the day that treatment is initiated. Non-ocular TEAEs will be summarized using discrete summaries at the participant- and event-level by system organ class and preferred term. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity or toxicity grade. Additionally, TEAEs will be summarized by treatment schedule as deemed necessary to better understand the safety profile.

Vital signs, laboratory, audiometry and ECG measurements will be analyzed by timepoint and change from baseline. An out of normal range summary may be performed for safety measurements as appropriate. Clinically meaningful abnormalities will be recorded as AEs.

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum), while categorical variables will be summarized as counts and percentages of participants in each category. Results will be presented by study arm as appropriate.

11. DATA HANDLING AND RECORDKEEPING

11.1. DATA COLLECTION

The eCRF is the primary data collection instrument for the trial. All eCRFs will be kept current to enable the monitor to review the participants' status throughout the course of the trial. In order to maintain confidentiality, only the study number, and participant number will identify the participant on the eCRF. All data requested on the eCRF must be supported by and be consistent with the subject's source documentation.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the participant's eCRF data are obtained.

All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Principal Investigator will sign and date the participant eCRF casebook indicating that the data on the eCRF have been assessed, once all data for that participant is final.

11.2. STUDY MONITORING

The Investigator will permit monitoring, quality audits, and inspections by the government regulatory authorities, and the Sponsor or its representative(s) of all trial related documents (e.g., source documents, regulatory documents, data collection instruments, eCRFs).

Study Monitors hired or contracted by the Sponsor will be responsible for monitoring the study sites and study activities. They will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on participant enrollment and on study site performance. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of eCRFs
- Dispensing, storage, and accountability of investigational product
- Source data verification
- AE and SAE reporting
- Essential documents contained within the regulatory binder

For source data verification (i.e., comparison of eCRF entries with participant records), data will be reviewed using a Risk Based Monitoring (RBM) approach. RBM consists of a strategic, risk-based monitoring implementation where the level of assigned risk informs the intensity and method of the study monitoring required. Additionally, 100% Source Document Review (SDR) (i.e., review of Source Documentation to check on quality, protocol and Good Clinical Practice compliance, staff involvement and other areas not associated with an eCRF page) will occur on all enrolled participants.

Member(s) of the Sponsor or their designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's participant population, facilities, and equipment, and to familiarize the Investigator with the protocol.

A member of the Sponsor or their designee in the role of Study Monitor will subsequently meet with the Investigator after a participant has initiated the study in order to ensure the participants are being properly selected, adequate supplies for the study have been provided and the assignment of medication is properly recorded. In addition, the Study Monitor will verify the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Investigator's regulatory documents, source documents, Informed Consent Forms, and eCRFs of study participants.

On site or remote interim monitoring visits and telephone consultations will be performed by the Study Monitor as necessary, to ensure the proper progress and documentation of the study.

Due to the changing circumstances as a result of the Coronavirus (COVID-19) Pandemic, impact to clinical trial oversight, particularly on-site monitoring, remains at risk. In order to ensure proper oversight of investigator sites, alternative methods of monitoring will be implemented. Details of the alternative monitoring procedures will be provided in the clinical monitoring plan (CMP).

11.3. STUDY DOCUMENTATION AND RETENTION OF RECORDS

All study-related correspondence, participant records, consent forms, record of the distribution and use of all study medication and copies of CRFs should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. For Canadian sites, record retention requirements in accordance with local regulations will be followed. It is the responsibility of the Sponsor or designee to inform the Investigator/institution as to when these documents no longer need to be retained.

It is the responsibility of the Investigator to allow access to the study records by the sponsor, its designee or regulatory agencies as requested.

If the responsible Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor or designee must be notified in writing of the name and address of the new custodian.

The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

11.4. AUDITS AND INSPECTIONS

Authorized representatives of Viridian, or designee, a regulatory authority, an Independent Ethics Committee (EC), or an Institutional Review Board (IRB) may visit any sites to perform audits or inspections, including source data verification. The purpose of an audit or inspection is

to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Viridian immediately if contacted by a regulatory agency about an inspection. In the event quality issues are identified by auditors or inspectors at the site, the PI is responsible for addressing quality issues.

11.5. QUALITY CONTROL AND QUALITY ASSURANCE

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the Study Monitor. The Investigator will allow the Sponsor or designee to inspect all CRFs; participant records (source documents); signed consent forms; records of study medication receipt, storage, preparation, and disposition; and regulatory files related to this study. All data captured by the electronic data capture (EDC) system will be transferred through an electronic interface into a study database for management, analysis, and reporting. Upon completion of data collection, the database will receive a quality control check by the Sponsor or the Statistics and Data Management vendor for this study to ensure acceptable accuracy and completeness. In the event quality issues are identified at the site, the PI is responsible for addressing quality issues.

11.6. AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor (or its representative) and signature authorized prior to implementation. The written amendment must be reviewed and approved by the Sponsor and submitted for the review and approval by the appropriate IRBs/ECs.

The amendment will be submitted formally to regulatory authorities by the Sponsor or its representative as applicable.

12. ETHICS

12.1. IRB/EC REVIEW

The study protocol, participant information and consent form, the IB, questionnaires or written instructions to be given to the participant, available safety information, participant recruitment procedures (e.g., study website), information about payments and compensation available to the participants and documentation evidencing the Investigator's qualifications should be submitted to the IRB/EC for review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment. The Investigator must submit and, where necessary, obtain IRB/EC and/or Sponsor approval for all subsequent protocol amendments and changes to the ICF or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB/EC of protocol

deviations or SAEs occurring at the site and other AE reports received from the Sponsor in accordance with local procedures.

Safety updates for VRDN-001 will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB/EC.

12.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with the protocol, principles set forth in the Declaration of Helsinki (October 2013), ICH Guideline E6(R2) for GCP (March 2018), Canadian Food and Drug Regulations, Standard Operating Procedures (SOPs) of the Sponsor and any vendors participating in the conduct of the study, and the U.S. Code of Federal Regulations (CFR) Title 21, parts 50, 54, 56, and 312.

[Appendix 2](#) provides more detail about the Sponsor's commitments to clinical research and to 2

12.3. WRITTEN INFORMED CONSENT

Informed consent is a process by which a participant voluntarily confirms their willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated ICF.

The ICF will be submitted for approval to the IRB/EC that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the national regulatory body, as well as local county authority or state regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an ICF. A notation that written informed consent has been obtained will be made in the participant's medical record. A copy of the ICF, to include the participant's signature, will be provided by the Investigator to the participant.

12.4. PARTICIPANT CONFIDENTIALITY

All ICFs must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended ICF is reviewed and approved by the Sponsor or Sponsor designee prior to submission to the governing IRB/IEC and that it is read, signed and dated by all participants subsequently enrolled in the study as well as those currently enrolled in the study if directed by the IRB/IEC.

Confidentiality of participant's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a participant must sign an authorization from the trial that they have been informed of the following:

- What Protected Health Information (PHI) will be collected from participants in this trial;

- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the subject's medical records, but the participant will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date;
- The rights of a research participant to revoke his or her authorization.

In the event that a participant revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines, it is a requirement that the Investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality will include a unique trial number and initials will identify participants on the eCRF, or other documents submitted to the Sponsor. This information will be used in the database for participant identification. Participant names or addresses will not be entered on the eCRF or in the database. No material bearing a subject's name will be kept on file by the Sponsor. Participants will be informed of their rights within the ICF.

12.5. DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The Investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the Investigator of the results of the trial conducted at his/her research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the Investigator shall have the right to publish his/her results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection.

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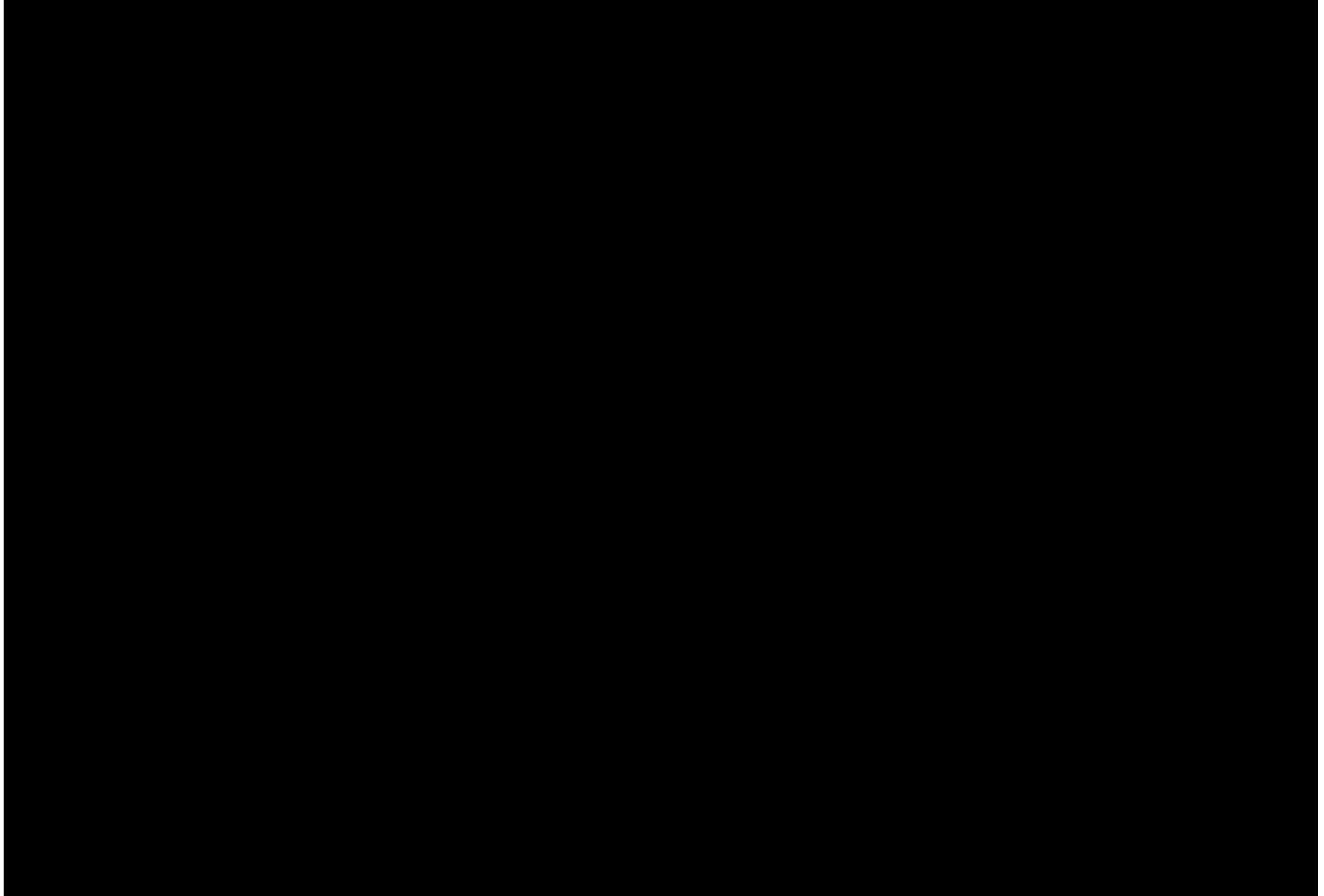
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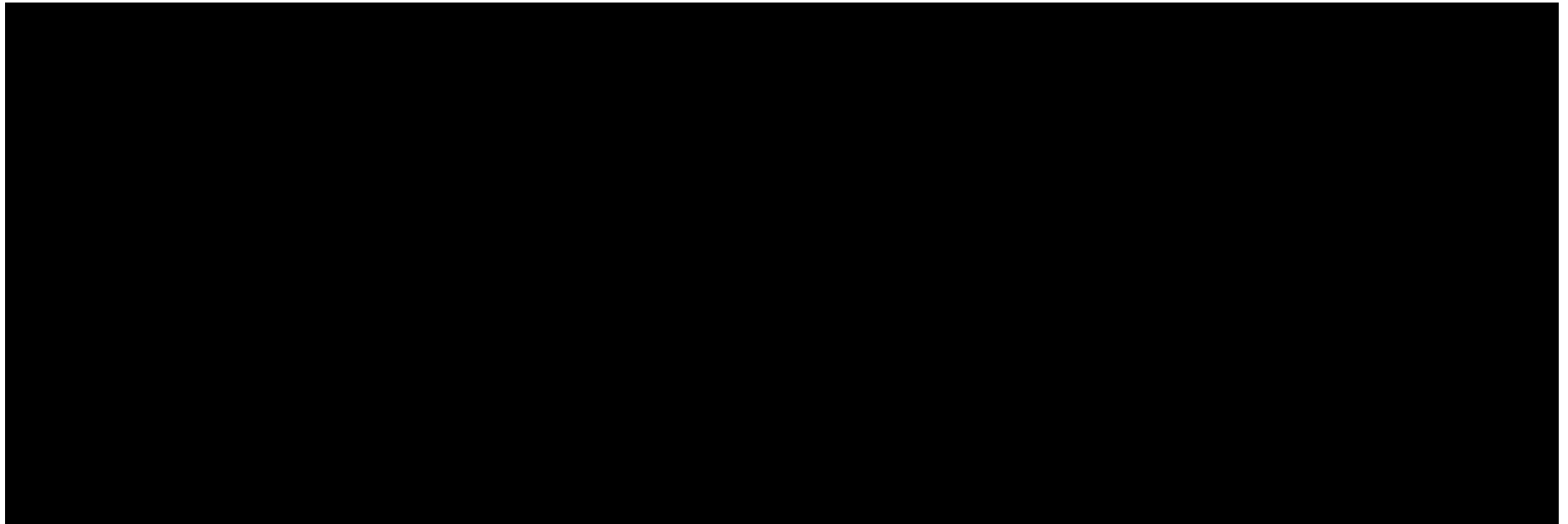
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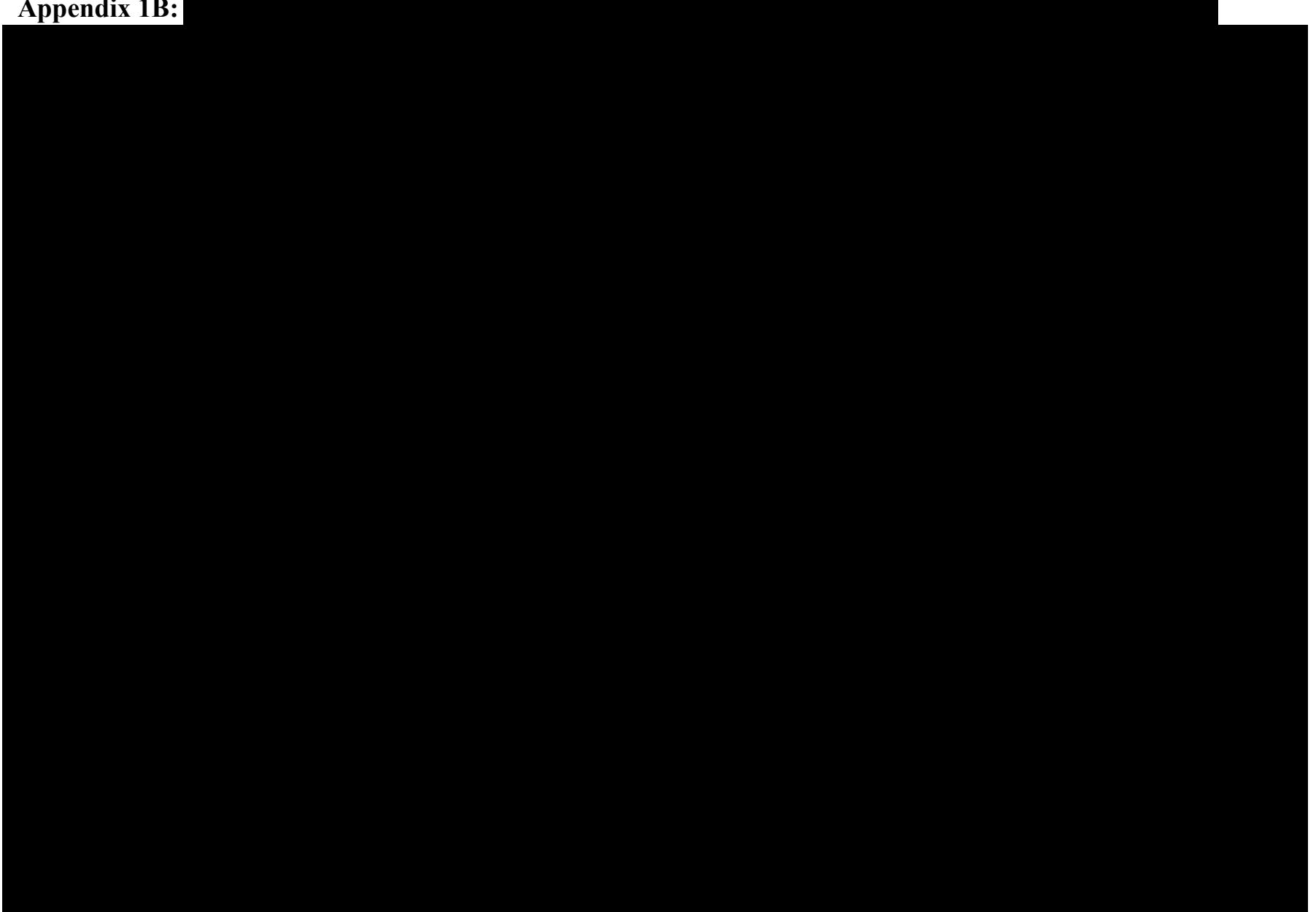
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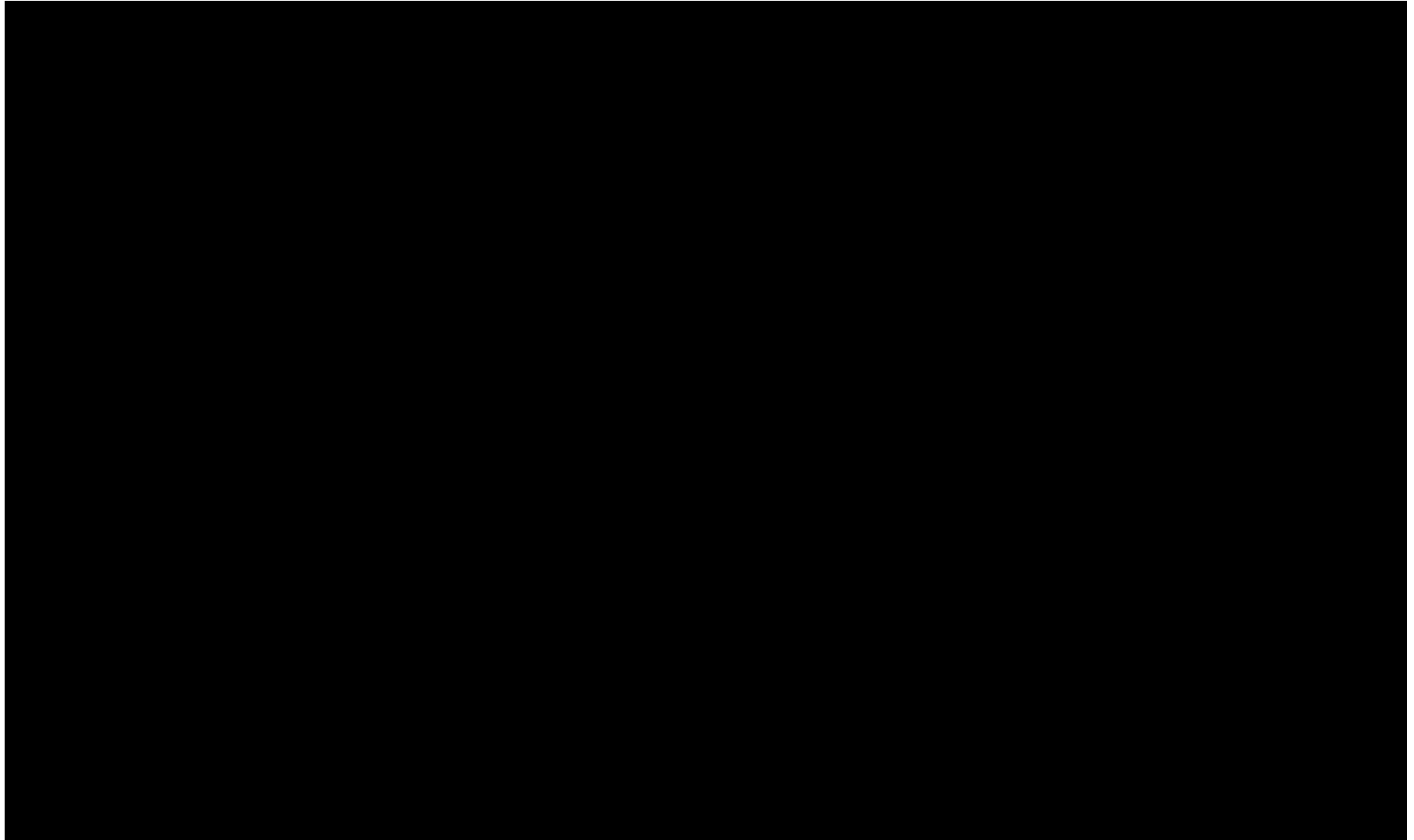
Appendix 1A:





Appendix 1B:





Appendix 1C: Schedule of Assessments for the Active TED Participants in the Pivotal Study (THRIVE)

Visit/Telephone Call	V1	V2	V3	V4/C1 ^a	V5	V6	V7	V8	V9	V10/C2 ^a
Study Day	Day-28 to Day-2	D-1	D1	D2	D4±1 days	D8±1 days	D15±3 days	D21±3 days	D22±3 days	D23±3 days
Informed consent/Eligibility	X		X ^m							
Randomization			X							
Demographics, tobacco use and medical history	X									
Physical exam	X	X ^{l,p}	X ^k						X ^k	
ECG	X	X ^{l,p}								
Vital signs ^s	X		X ^g						X ^g	
Examination of injection site ^h			X						X	
Pregnancy test ^b	X		X						X	
FSH (post-menopausal female)	X									
HIV 1/2, Hepatitis B/C	X									
Laboratory assessments ^c	X		X ^q			X			X	
Blood samples for PK			X ^d	X	X	X	X		X ^e	
Blood samples for IGF-1			X ^e	X	X	X	X		X ^e	
Blood samples for ADA			X ^e						X ^e	
Exophthalmometry	X	X ^l						X ^l		
Orbital MRI/CT ^f			X							
Slit lamp biomicroscopy	X	X ^{l,p}						X ^l		
IOP	X	X ^{l,p}						X ^l		
Visual Acuity ^r	X	X ^{l,p}						X ^l		
Fundoscopy	X	X ^{l,p}						X ^l		
Lid Retraction	X	X ^l						X ^l		
Gorman Subjective Diplopia score	X	X ^l						X ^l		
CAS	X	X ^l						X ^l		
GO-QoL ⁿ	X	X ^l						X ^l		
EQ-5D-5L ⁿ	X	X ^l						X ^l		
Audiometry ^t	X	X ^{l,p}						X ^l		
Breakfast ^j			X						X	
Study infusion			X						X	
Telephone call to participant				X						X
AE review ^o	X ⁱ	X	X	X	X	X	X	X	X	X
Con/Prior med review ^o	X	X	X	X	X	X	X	X	X	X

Visit/Telephone Call	V11	V12	V13/C3 ^a	V14	V15	V16/C4 ^a	V17	V18	V19	V20	V21
Study Day	D42±3 days	D43±3 days	D44±3 days	D63±3 days	D64±3 days	D65±3 days	D67±3 days	D71±3 days	D78±3 days	D84±3 days	D85±3 days
Physical exam		X ^k			X ^k						X ^k
ECG											
Vital signs ^s		X ^g			X ^g						X ^g
Examination of injection site ^h		X			X						X
Pregnancy test ^b		X			X						X
Laboratory assessments ^c		X			X			X			X
Blood samples for PK		X ^e			X ^d	X	X	X	X		X ^e
Blood samples for IGF-1		X ^e			X ^e	X	X	X	X		X ^e
Blood samples for ADA		X ^e			X ^e						X ^e
Exophthalmometry	X ^l			X ^l						X ^l	
Orbital MRI/CT ^f											
Slit lamp biomicroscopy	X ^l			X ^l						X ^l	
IOP	X ^l			X ^l						X ^l	
Visual Acuity ^r	X ^l			X ^l						X ^l	
Fundoscopy	X ^l			X ^l						X ^l	
Lid Retraction	X ^l			X ^l						X ^l	
Gorman Subjective Diplopia score	X ^l			X ^l						X ^l	
CAS	X ^l			X ^l						X ^l	
GO-QoL ⁿ	X ^l			X ^l						X ^l	
EQ-5D-5L ⁿ	X ^l			X ^l						X ^l	
Audiometry ^t	X ^l			X ^l						X ^l	
Breakfast ^j		X			X						X
Study infusion		X			X						X
Telephone call to participant			X			X					
AE review ^{i,o}	X	X	X	X	X	X	X	X	X	X	X
Con med review ^o	X	X	X	X	X	X	X	X	X	X	X

Visit/Telephone Call	V22/ C5 ^a	V23	V24	V25	V26	V27
Study Day/Week	D86±3 days	D106±3 days (W15)	D127±3 days (W18)	D168±7 days (W24)	W36±7 days	W52±7 days
Physical exam		X ^k		X ^k	X ^k	X ^k
ECG		X				
Vital signs ^s		X		X	X	X
Pregnancy test ^b		X		X		
Laboratory assessments ^c		X		X	X	X
Blood samples for PK		X	X	X		
Blood samples for IGF-1		X	X	X		
Blood samples for ADA		X		X		
Exophthalmometry		X		X	X	X
Orbital MRI/CT ^f		X		X	X	X
Slit lamp biomicroscopy		X		X	X	X
IOP		X		X	X	X
Visual Acuity ^r		X		X	X	X
Fundoscopy		X		X	X	X
Lid Retraction		X		X	X	X
Gorman Subjective Diplopia score		X		X	X	X
CAS		X		X	X	X
GO-QoL ⁿ		X		X	X	X
EQ-5D-5L ⁿ		X		X	X	X
Audiometry ^t		X		X	X	X
Telephone call to participant	X					
AE review ^o	X	X	X	X	X	X
Con med review ^o	X	X	X	X	X	X

^a Participants will be called by one of the study site personnel to confirm the participant's wellbeing and whether there have been any changes to or new AEs or concomitant medications since their discharge from the infusion clinic the previous day.

^b Pregnancy test will be serum at the Screening Visit and urine prior to each subsequent infusion and on Week 15 and Week 24 Visits for all females.

^c Blood samples for laboratory assessments for safety must be collected in the fasting state and prior to infusion when sampled on infusion days. HbA1c testing will be performed at the Screening Visit, Week 12 (Day 85), Week 24, Week 36 and Week 52.

^d Participants will have blood samples drawn by an indwelling venous cannula (inserted in the opposite forearm to the infusion arm) on the 1st and 4th infusion days for PK pre-infusion, 5 to 10 minutes before the end of infusion and at 2 hours (±15 minutes) and 4 hours (±15 minutes) after the end of infusion.

^e On infusion days participants will have blood samples drawn for PK, ADA and IGF-1 levels before the infusion.

^f Orbital MRI/CT (CT is permitted where allowed per local health authorities) will be scheduled within 7 days prior to the infusion on Day 1, and within ±7 days of the visits at Weeks 15, 24, 36 and 52. It is recommended that the same imaging modality that is used at Day 1 be used throughout the study for an individual patient.

- ^g Vital signs monitored within 2 hours pre-infusion, 30 (± 15) minutes after the start of infusion and again at 1 hour (± 15 minutes) after completion of the infusion for the first three infusions and within 2 hours pre-infusion, 30 (± 15) minutes after the start of infusion and again 30 (± 15) minutes after completion of the infusion for the 4th and 5th infusions. Additional vital signs will be monitored if infusion-associated AEs occur (see [Section 9.7](#) for details) or as required by local health authorities. For participants enrolled in the Czech Republic, local regulation requires that participants be monitored by the investigator for 2 hours following all infusions.
- ^h The infusion site will be examined 5 to 10 minutes and then again at 30 (± 10) minutes after the start of each infusion for local tolerance.
- ⁱ AEs and SAEs are required to be recorded from the time of consent.
- ^j Breakfast provided after completion of the fasting blood draws, when required.
- ^k Symptoms-directed physical examination will be conducted at all study infusion visits, and at any other time throughout the trial if clinically indicated.
- ^l Assessment will be performed either the day before or on the day of, but prior to each infusion.
- ^m Eligibility must be re-confirmed prior to randomization on Day 1.
- ⁿ The GO-QoL and EQ-5D-5L must be performed prior to all other study assessments at all applicable study visits.
- ^o For all study visits where laboratory sample collection is performed at home/office-based as allowed per protocol (V4-7, V16-19, and V24), adverse event and concomitant medication information will not be obtained.
- ^p If the Day -1 Visit occurs no more than 6 days after the Screening Visit, the following assessments are not required to be repeated at the Day -1 Visit: Audiometry, Physical exam, ECG, VA, fundoscopy, biomicroscopy, and IOP.
- ^q If the Day 1 Visit occurs no more than 7 days after the Screening Visit, the following assessments are not required to be repeated at the Day 1 Visit: Laboratory assessments.
- ^r This assessment should be conducted prior to dilation of the eyes.
- ^s Height will be measured only at Screening. Weight will be measured prior to assigning study drug in the RTSM on infusion visits and at all visits where vital signs are collected.
- ^t If there is an abnormal audiometric result that is a change (worsening) in the PTA grade from baseline in either ear, a repeat test is required to confirm the abnormal finding.

Appendix 2: Sponsor's Commitments

The Sponsor is committed to:

1. Complying with all applicable health authority regulations governing the conduct of clinical research studies, including the U.S. Food and Drug Administration.
2. Protecting the rights, health, safety and welfare of study participants.
3. Informing the clinical Investigators of any new information about the study which may affect the health, safety or welfare of the participants, or may influence their decision to continue participation in the study.
4. Providing the clinical Investigators with the study protocol, and access to electronic CRFs on which to document the study evaluation variables for each participant entered into the study.
5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
6. Ensuring equity of consideration among all Investigators in multicenter studies in all matters of publications, meeting presentations, etc.
7. Certifying that IRB/EC approval of the protocol and Investigator's Agreement will be completed prior to treatment at an investigational site.

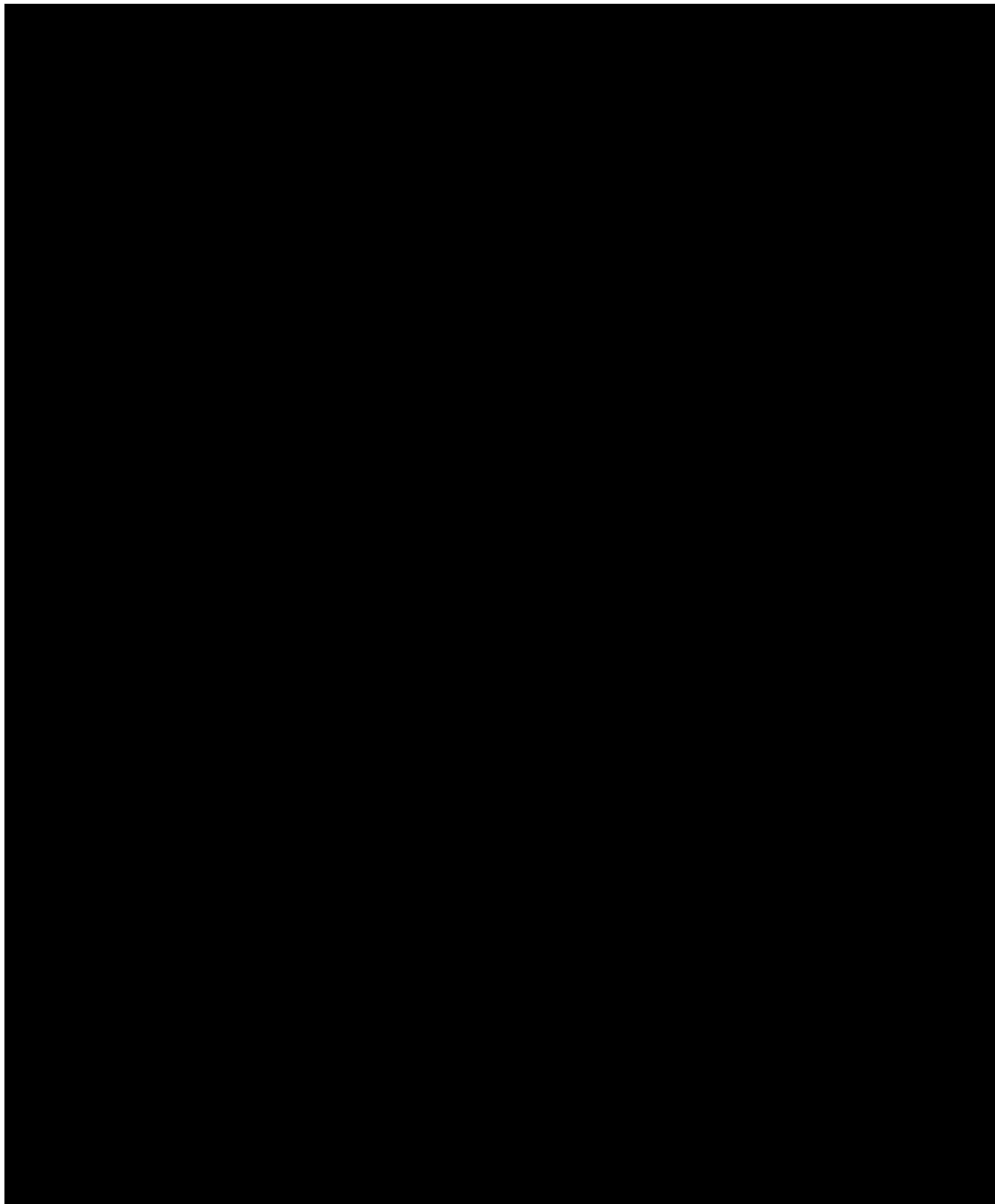
Appendix 3: Common Terminology Criteria for Adverse Events

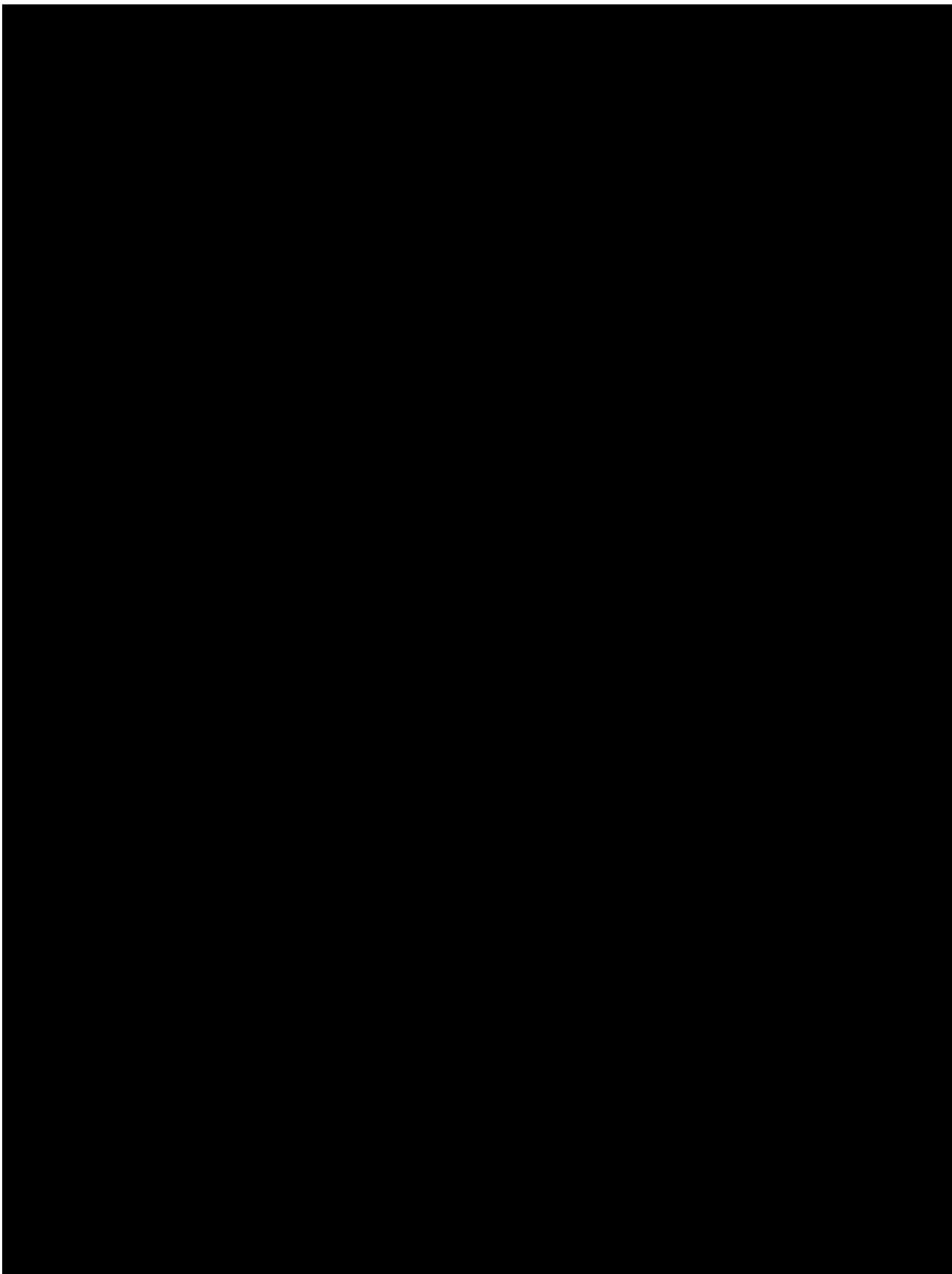
Refer to CTCAE, Version 5.0, published November 27, 2017. Online resources are available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60 and include the following documents provided in different formats:

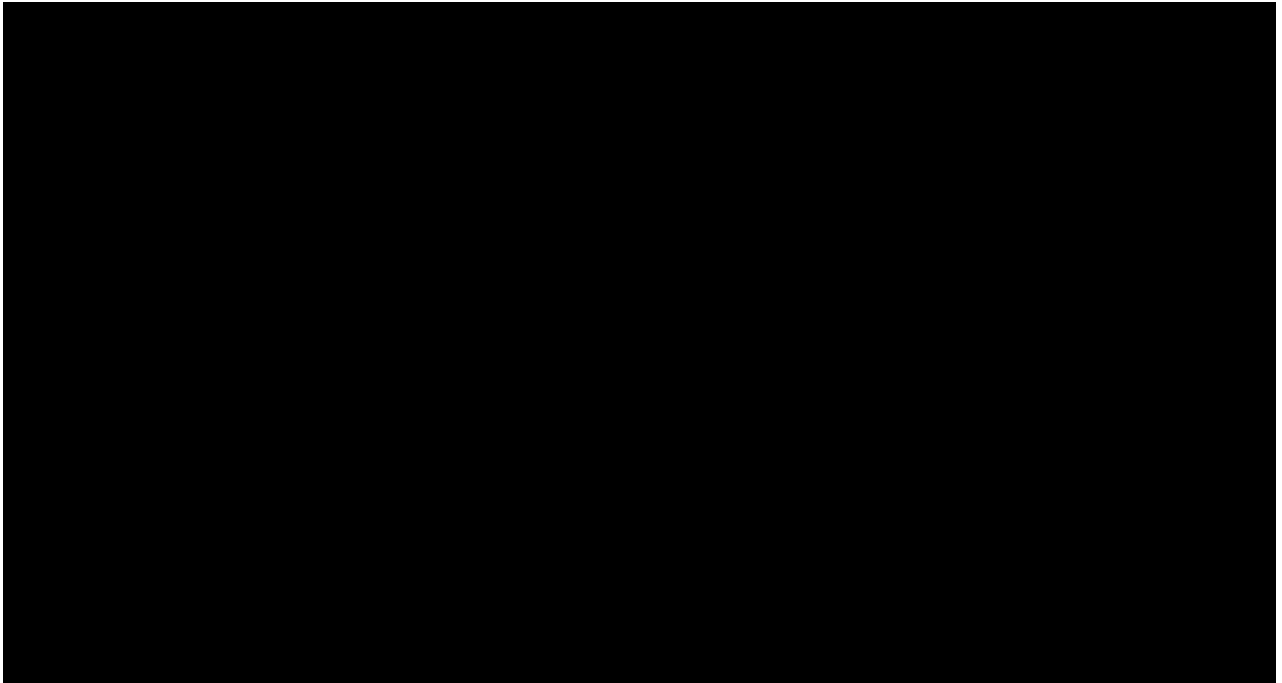
The file named “CTCAE_5.0_QuickReference_5x7.pdf” provides the most recent release of core terminology and is available as a PDF document in traditional small booklet format.

The file name “CTCAE_5.0_QuickReference_8.5x11.pdf” provides the most recent release of core terminology and is available as a PDF document in letter-sized format.

Appendix 4: [REDACTED]







Appendix 5:

