NCT #: NCT06384547

VRDN-001-303

STRIVE

A randomized, controlled, safety and tolerability study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants with thyroid eye disease (TED)

Version 4.0, Amendment date: 06-May-2024

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Version 1.0, Original, date: 05-Jan-2024

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INVESTIGATOR'S AGREEMENT

Study Title

A randomized, controlled, safety and tolerability study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants 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 randomized, controlled, safety and tolerability study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants with thyroid eye disease (TED)

Version/Date: 4.0, 06-May-2024

Protocol Approver: [redacted]

[redacted]

Viridian Therapeutics, Inc.

[redacted]

Signature/Date: _____

Protocol Author: [redacted]

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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-001-303

Version Number and Date: Version 4.0, Amendment date: 06-May-2024

Study Title: A randomized, controlled, safety and tolerability study of VRDN-001, a humanized monoclonal antibody directed against the Insulin-like Growth Factor-1 receptor (IGF-1R), in participants with thyroid eye disease (TED)

Phase of Study: 3

Number of Participants (planned): Approximately 212 participants with TED

Number of Trial Sites: Approximately 70 sites globally

Objectives: To confirm the safety and tolerability of VRDN-001 when given as 5 intravenous (IV) infusions of 10 mg/kg or 3 mg/kg every three weeks in participants with TED of any duration.

Primary Safety Endpoint

- Treatment Emergent Adverse Event (TEAE) incidence rate through Week 15

Secondary Endpoints

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15
- Treatment Emergent Adverse Event (TEAE) incidence rate through Week 52

Exploratory Endpoints

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Weeks 24, 36 and 52
- Proptosis Responder defined as a reduction of at least 2 mm in study eye and no worsening of 2 mm or more in the fellow eye via exophthalmometer at Weeks 15, 24, 36 and 52
- Change from baseline in Clinical Activity Score (CAS) in the study eye at Weeks 15, 24, 36 and 52
- 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 Weeks 15, 24, 36 and 52
- 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 Weeks 15, 24, 36 and 52
- Gorman Subjective Diplopia Score change from baseline at Weeks 15, 24, 36 and 52
- Durability of Proptosis Response

Trial Rationale:

The overall safety data from the ongoing VRDN-001-101 study [redacted]

[redacted]

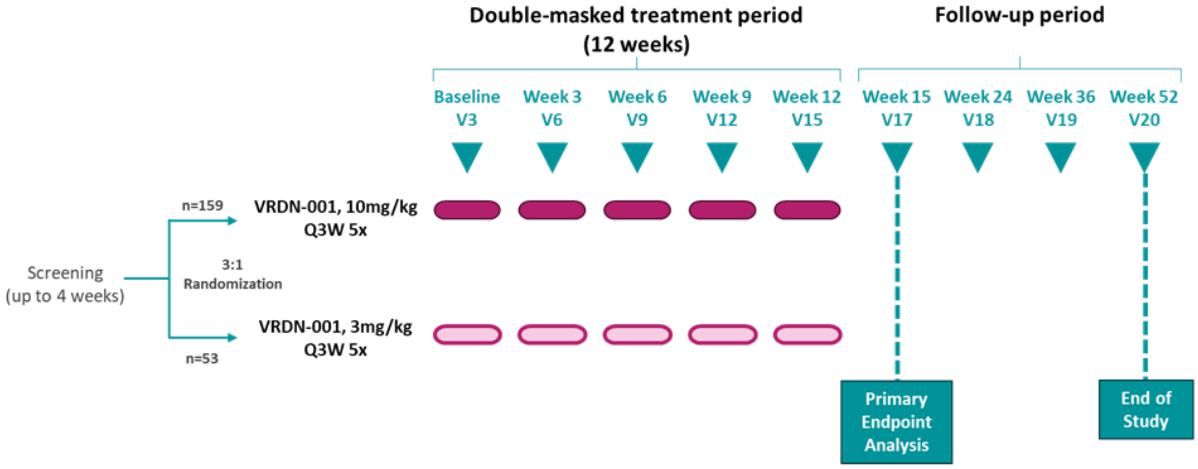
This study aims to confirm the safety and tolerability seen in the earlier VRDN-001 studies and provide additional safety data to satisfy health authority requirements in support of applications for marketing approval of VRDN-001 for TED.

Trial Design:

The study design will be a randomized, controlled and double-masked study. Participants and site personnel (except pharmacy personnel preparing the infusate) will be masked to treatment for the entire study duration. The sponsor will be masked to treatment up to the primary database lock which will be performed after all participants have received the 5 IV infusions and completed the Week 15 assessments or early discontinued. Approximately 212 participants with TED of any duration will be randomized to treatment with 5 IV infusions of either 10 mg/kg or 3 mg/kg VRDN-001 at 3-week intervals at a randomization ratio of 3:1 (approximately 159 participants at 10 mg/kg and 53 participants at 3 mg/kg).

The 3 to 1 randomization ratio of 10 mg/kg versus 3 mg/kg respectively has been selected to allow a majority of participants to receive the target therapeutic dose of 10 mg/kg while the remaining participants receive the lower control dose of 3 mg/kg. A controlled study design was selected based on US FDA recommendation for safety evaluation in the TED population. Additionally, inclusion of the lower dose control will advance the understanding of the safety and treatment effects of VRDN-001 at lower doses while also maintaining masking for thorough evaluation of safety and tolerability parameters of the target therapeutic dose of 10 mg/kg.

Study Design Schematic



Study procedures

The screening period for this study is 4 weeks. Participants may be rescreened at the investigator's discretion. The study procedures are described in the Schedule of Assessments

(SoA) in Appendix 1. Participants in both treatment arms will receive the same number of IV infusions administered at 3-week intervals to maintain masking.

Ocular assessments will be performed on both eyes. The study eye (for the purposes of efficacy assessments performed in this safety study) will be the most proptotic at the last assessment performed prior to the Day 1 IV infusion and if both eyes are equally proptotic then the eye with the worse visual acuity will be selected. If proptosis and visual acuity are equal in both eyes, then the right eye will be selected as the study eye for efficacy assessments.

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

The independent Data and Safety Monitoring Board (DSMB) will review safety and limited efficacy data at 6-month intervals during 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 is reviewed on an ongoing basis by the Sponsor and any concerns are immediately addressed and escalated to the independent DSMB, as needed.

Study Duration: This study is estimated to commence enrollment in the 1H2024. Each enrolled participant will be in the study for 52 weeks following the first dose. The end of the study will be when the last participant's last visit has occurred.

Inclusion Criteria:

Participants must:

1. Be able to understand the study procedures and the risks involved and must provide written informed consent before the first study-related activity
2. Be an adult male or female participant, ≥18 to ≤75 years of age
3. Have a clinical diagnosis of TED with or without proptosis and with any CAS (0 – 7) and in the opinion of the investigator may benefit from treatment
4. Not require immediate ophthalmological or orbital surgery in the study eye for any reason
5. VRDN-001 can be used with caution in participants with diabetes mellitus. Diabetic participants should be monitored by their endocrinologist, general practitioner or other appropriately trained personnel and have at study entry a glycated hemoglobin (HbA1c) of <8.5%
6. If female, have a negative serum pregnancy test at screening and further negative urine tests immediately before each dose of study medication and following the last dose of study medication as described in Appendix 1.
   If the participant is a women of childbearing potential (including those with <2 years since the onset of menopause or not surgically sterile by hysterectomy, bilateral salpingectomy or bilateral oophorectomy), 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 must agree to use a double-barrier method of contraception until

completing one-full cycle of hormonal contraception. An example of an acceptable double-barrier combination method is a condom with either a diaphragm or a sponge with spermicide
7. Be surgically sterile males for at least 6 weeks prior to the first dose of VRDN-001, 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
8. Be willing and able to comply with all the requirements of the protocol for the entire duration of the study

Exclusion Criteria
Participants must not:

1. Have received prior treatment with another anti-IGF-1R therapy
2. Have used systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study medication (topical steroids including eye drops or multivitamins that contain selenium are permitted). Also exclusionary is periocular (including intraorbital) or intraocular administration of corticosteroids within 3 months prior to the first dose of study medication or having received greater than 3 periocular or intraocular corticosteroid injections at any time
3. Have received other immunosuppressive agents, including rituximab, tocilizumab, secukimumab, satralizumab or anti-FcRn's for any condition (including TED) within 8 weeks prior to the first dose of study medication or have received intraorbital administration of other such immunosuppressive agents at any time
4. Have received any other therapy for TED within 8 weeks prior to the first dose of study medication (artificial tears are permitted)
5. Have received an investigational agent for any condition within 8 weeks prior to the first dose of study medication
6. Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future
7. Have corneal decompensation in the study eye unresponsive to medical management
8. Have had previous orbital irradiation or decompression surgery involving excision of fat for TED to the study eye's orbit
9. Have a pre-existing ophthalmic condition in the study eye which in the opinion of the Investigator, would confound interpretation of the study results
10. Have abnormal baseline audiometry Pure Tone Average (PTA) assessment or history of significant (as determined by the Investigator) ear pathology, relevant ear surgery or hearing loss
11. Have inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease)
12. Be a pregnant or lactating woman
13. Be an active alcoholic or illicit drug user or considered at high risk of relapse by the Investigator
14. Have a known hypersensitivity to any of the components of VRDN-001 or prior hypersensitivity to monoclonal antibodies (mAbs)
15. Have any condition, which in the opinion of the Investigator, would preclude inclusion in the study
16. Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2)

17. Have a positive test for active hepatitis B or hepatitis C infection
18. Have previously participated in this study or any study of VRDN-001 and received active treatment (VRDN-001)
19. 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
20. European Union participating sites only: Be committed to an institution by virtue of an order issued either by the judicial or the administrative authorities, per Article 34 Regulation (EU) No. 536/2014
21. Have received radioactive iodine (RAI) treatment for any condition within 8 weeks prior to the first dose of study medication

NOTE: Prior thyroidectomy or orbital decompression surgery limited to bone only are **NOT** exclusions. (If fat excision occurred with orbital decompression, patient is excluded, as noted in exclusions above.)

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 [redacted] mg/mL of antibody in 4.0 mL extractable volume in [redacted]R vials, frozen at -20 ± 5ºC and protected from light.

The pharmacist or other qualified medical professional with applicable certification or license per local laws who is trained and delegated by the principal investigator will prepare the IV infusion bags. This individual will dispense [redacted] mL bags of saline with VRDN-001 added, according to the Randomization and Trial Supply Management (RTSM) system with appropriate dispensing label. The volume of saline removed from the bags will equal the volume of VRDN-001 added. [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.

Statistical Methods:

As this study's primary objective is collection of safety and tolerability there will be no statistical testing. The primary safety, secondary and exploratory efficacy endpoints will be analyzed descriptively. The primary database lock will be performed after all participants have received the 5 IV infusions and completed the week 15 assessments or early discontinued. All participants will continue to be followed through 52 weeks from the first IV infusion.

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ADA	Anti-drug antibody
ADL	Activities of daily living
ALP	Alkaline phosphatase
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
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRO	Contract research organization
eCRF	Electronic case report form
CTFG	Clinical Trials Facilitation Group
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DSMB	Data and Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

Abbreviation or Specialist Term	Explanation
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GEE	Generalized estimated equation
GLM	General linear model
G protein	Guanine nucleotide-binding protein
HbA1c	Glycated hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
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
IV	Intravenous
LM	Laboratory Manual
mAb	Monoclonal antibody
[redacted]	[redacted]
MHRA	Medicines and Healthcare Products Regulatory Agency
MITT	Modified intent-to-treat
MTD	Maximum tolerated dose
NCT	National clinical trial
NOAEL	No observed adverse effect level
PTA	Pure Tone Average

Abbreviation or Specialist Term	Explanation
PD	Pharmacodynamic
PHI	Protected health information
PK	Pharmacokinetic
PM	Pharmacy Manual
PPM	Protocol Procedures Manual
QTcF	Corrected QT (interval between Q and T waves on the ECG) by Fredericia
RBM	Risk based monitoring
RSI	Reference Safety Information
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2\lambda z}$	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, 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). Commonly, 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, superficial vasculature, orbital fat, lids, 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 (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 approved by the FDA for the treatment of TED in the USA in 2020. 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 IV infusions over 24 weeks, administered at an IV infusion center, and is often accompanied by adverse events described in Section 1.6.2 below, and may include sensory neural hearing loss, exacerbation of inflammatory bowel disease and hyperglycemia.

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 IV 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 IV 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.

Positive preliminary safety and efficacy data from the [redacted] of the ongoing VRDN-001-101 study supports the continued clinical development of VRDN-001 in TED. 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] 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]) 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 central nervous system (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]

For the [redacted] repeat-dose toxicokinetic (TK) study (refer to Section 1.5.4), parameters were evaluated following [redacted] IV 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 IV 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 [redacted] mL/kg/hour). Half-lives were lower [redacted] days) and clearance values were higher [redacted] mL/kg/hour) in some 2 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 [redacted] mL/kg.

1.5.4. [redacted]

[redacted]

[redacted]

1.6. CLINICAL STUDIES OF ANTIBODIES TARGETING IGF-1R

1.6.1. Oncology Studies

Several mAbs directed against IGF-1R (R1507 [tepromumumab], 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 IB for VRDN-001.

1.6.2. TED Studies

Tepromumumab (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 IV 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, and headache, weight decreased, menstrual disorders and nail disorder. IV 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

[redacted]

[redacted]

1.8. RATIONALE FOR THE DOSE SELECTED FOR THIS STUDY

The dose level of VRDN-001 to be used in 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 to date 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 in >95% of the target patient population.

Participants will be randomized to receive either 5 IV infusions of the target therapeutic dose of 10 mg/kg VRDN-001 or 5 IV infusions of 3 mg/kg VRDN-001 (the low dose control arm). To maximize the number of participants receiving the target therapeutic dose of 10 mg/kg, randomization will be at a 3:1 ratio of 10 mg/kg versus 3 mg/kg respectively. A controlled study design was selected based on US FDA recommendation for safety evaluation in the TED population. Additionally, inclusion of the lower dose control will advance the understanding of the safety and treatment effects of VRDN-001 at lower doses while also maintaining masking for thorough evaluation of safety and tolerability parameters of the target therapeutic dose of 10 mg/kg.

1.8.1. Rationale for Dosing Regimen Selected For This Study

The rationale for selecting 5 IV infusions as the dosing regimen in this study is based on the objective of evaluating safety at the targeted dose (10 mg/kg) and regimen being evaluated in the pivotal studies (VRDN-001-101 and VRDN-001-301). The targeted regimen is based in part on published information for teprotumumab (Smith et al, 2017, Douglas et al, 2020) demonstrating that more than 90% of the proptosis response is observed following the first 5 IV infusions with minimal further improvement thereafter. [redacted] These results suggest that the required duration of treatment with VRDN-001 may be less than seen with teprotumumab.

1.8.2. [redacted]

[redacted]

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 of [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 the target patient population.

1.8.4. Clinical Pharmacokinetics

Preliminary non-compartmental analysis of the data from VRDN-001-101 in healthy volunteers indicates that VRDN-001 displayed [redacted]

[redacted]

1.9. RATIONALE FOR THIS CLINICAL TRIAL

The overall safety data from the ongoing VRDN-001-101 study in [redacted].

This study aims to confirm the safety and tolerability seen in the earlier VRDN-001 studies and provide additional safety data to satisfy health authority requirements in support of applications for marketing approval of VRDN-001 for TED.

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.

[redacted]

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. OBJECTIVE

To confirm the safety and tolerability of VRDN-001 when given as 5 IV infusions of 10 mg/kg or 3 mg/kg every 3 weeks in participants with TED of any duration.

2.2. PRIMARY SAFETY ENDPOINT

TEAE incidence rate through Week 15

2.3. SECONDARY ENDPOINTS

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 15
- TEAE incidence rate through Week 52

2.4. EXPLORATORY ENDPOINTS

- Change from baseline in proptosis in the study eye as measured by exophthalmometer at Week 24, 36 and 52
- Proptosis Responder defined as a reduction of at least 2 mm in study eye and no worsening of 2 mm or more in the fellow eye via exophthalmometer at Weeks 15, 24, 36 and 52
- Change from baseline in Clinical Activity Score (CAS) in the study eye at Weeks 15, 24, 36 and 52
- 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 Weeks 15, 24, 36 and 52
- 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 Weeks 15, 24, 36 and 52
- Gorman Subjective Diplopia Score change from baseline at Weeks 15, 24, 36 and 52
- Durability of Proptosis Response

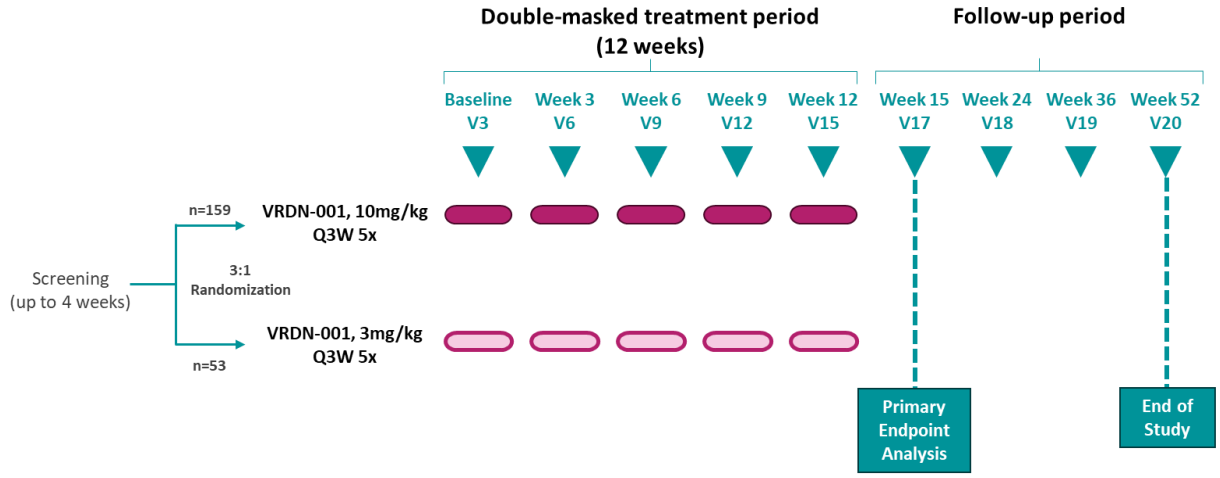
3. INVESTIGATIONAL PLAN

3.1. THE OVERALL STUDY DESIGN

The study design will be a randomized, controlled and double-masked study. Participants and site personnel (except pharmacy personnel preparing the infusate) will be masked to treatment for the entire study duration. The sponsor will be masked to treatment up to the primary database lock which will be performed after all participants have received the 5 IV infusions and completed the Week 15 assessments or early discontinued. Approximately 212 participants with TED of any duration will be randomized to treatment with 5 IV infusions of either 10 mg/kg or 3 mg/kg VRDN-001 at 3-week intervals at a randomization ratio of 3:1 (approximately 159 participants at 10 mg/kg and 53 participants at 3 mg/kg).

The 3 to 1 randomization ratio of 10 mg/kg versus 3 mg/kg respectively has been selected to allow a majority of participants to receive the target therapeutic dose of 10 mg/kg while the remaining participants receive the lower control dose of 3 mg/kg. A controlled study design was selected based on US FDA recommendation for safety evaluation in the TED population. Additionally, inclusion of the lower dose control will advance the understanding of the safety and treatment effects of VRDN-001 at lower doses while also maintaining masking for thorough evaluation of safety and tolerability parameters of the target therapeutic dose of 10 mg/kg.

Figure 1: Study Design Schematic



3.1.1. Overall Procedures

The screening period for this study is 4 weeks. Participants may be rescreened at the investigator's discretion. The study procedures are described in the Schedule of Assessments (SoA) in Appendix 1. Participants in both treatment arms will receive the same number of IV infusions administered at 3-week intervals to maintain masking.

Ocular assessments will be performed on both eyes. The study eye (for the purposes of efficacy assessments performed in this safety study) will be the most proptotic at the last assessment performed prior to the Day 1 IV infusion and if both eyes are equally proptotic then the eye with the worse visual acuity will be selected. If proptosis and visual acuity are equal in both eyes, then the right eye will be selected as the study eye for efficacy assessments.

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

The independent Data Safety Monitoring Board (DSMB) will review safety and limited efficacy data at 6-month intervals during 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

Approximately 212 participants with TED.

4.2. NUMBER AND LOCATION OF TRIAL SITES

Approximately 70 sites globally.

4.3. PARTICIPANT ELIGIBILITY CRITERIA

4.3.1. Participant Inclusion Criteria

Participants must:

1. Be able to understand the study procedures and the risks involved and must provide written informed consent before the first study-related activity
2. Be an adult male or female participant, ≥18 to ≤75 years of age
3. Have a clinical diagnosis of TED with or without proptosis and with any CAS (0 – 7) and in the opinion of the investigator may benefit from treatment
4. Not require immediate ophthalmological or orbital surgery in the study eye for any reason
5. VRDN-001 can be used with caution in participants with diabetes mellitus. Diabetic participants should be monitored by their general practitioners or other appropriately trained personnel and have at study entry a glycated hemoglobin (HbA1c) of <8.5%
6. If female, have a negative serum pregnancy test at screening and further negative urine tests immediately before each dose of study medication and following the last dose of study medication as described in Appendix 1.
   If the participant is a woman of childbearing potential (including those with <2 years since the onset of menopause or not surgically sterile by hysterectomy, bilateral salpingectomy or bilateral oophorectomy); 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 must agree 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
7. Be surgically sterile males for at least 6 weeks prior to the first dose of VRDN-001, 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
8. 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

Participants must not:

1. Have received prior treatment with another anti-IGF-1R therapy
2. Have used systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study medication (topical steroids including eye drops or multivitamins that contain selenium are permitted). Also exclusionary is periocular (including intraorbital) or intraocular administration of corticosteroids within 3 months prior to the first dose of study medication or having received greater than 3 periocular or intraocular corticosteroid injections at any time

3. Have received other immunosuppressive agents, including rituximab, tocilizumab, secukimumab, satralizumab or anti-FcRn's for any condition (including TED) within 8 weeks prior to the first dose of study medication or have received intraorbital administration of other such immunosuppressive agents at any time
4. Have received any other therapy for TED within 8 weeks prior to the first dose of study medication (artificial tears are permitted)
5. Have received an investigational agent for any condition within 8 weeks prior to the first dose of study medication
6. Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future
7. Have corneal decompensation in the study eye unresponsive to medical management
8. Have had previous orbital irradiation or decompression surgery involving excision of fat for TED to the study eye's orbit
9. Have a pre-existing ophthalmic condition in the study eye which in the opinion of the Investigator, would confound interpretation of the study results
10. Have abnormal baseline audiometry Pure Tone Average (PTA) assessment or history of significant (as determined by the Investigator) ear pathology, relevant ear surgery or hearing loss
11. Have inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease)
12. Be a pregnant or lactating woman
13. Be an active alcoholic or illicit drug user or considered at high risk of relapse by the Investigator
14. Have a known hypersensitivity to any of the components of VRDN-001 or prior hypersensitivity to monoclonal antibodies (mAbs)
15. Have any condition, which in the opinion of the Investigator, would preclude inclusion in the study
16. Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2)
17. Have a positive test for active hepatitis B or hepatitis C infection
18. Have previously participated in this study or any study of VRDN-001 and received active treatment (VRDN-001)
19. 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
20. European Union participating sites only: Be committed to an institution by virtue of an order issued either by the judicial or the administrative authorities, per Article 34 Regulation (EU) No. 536/2014
21. Have received radioactive iodine (RAI) treatment for any condition within 8 weeks prior to the first dose of study medication

NOTE: Prior thyroidectomy or orbital decompression surgery limited to bone only are NOT exclusions. (If fat excision occurred with orbital decompression, patient is excluded, as noted in exclusions above.)

4.4. CONTRACEPTION GUIDELINES

Women of childbearing potential (including those with <2 years since the onset of menopause or not surgically sterile by hysterectomy, bilateral salpingectomy or bilateral oophorectomy) must agree to take appropriate precautions to avoid pregnancy by using an acceptable method of contraception such as a condom and a second highly effective method of contraception, as described below, from screening up to and including 100 days after the last dose of study medication. Women who are believed to be postmenopausal with no menses for at least 2 years without alternative medical cause will have postmenopausal status confirmed with FSH testing at screening.

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, 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 male participants 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 tubal ligation at least 6 weeks prior to taking study treatment.

Note all female participants will have serum pregnancy tests completed at screening. Additionally, all female participants will complete a urine pregnancy test prior to each IV infusion and at designated timepoints in Appendix 1.

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 described in Appendix 1, 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, as applicable under national law, 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 an early termination visit for which a minimum of safety assessments will be offered when completion of all early termination assessments are not permitted by local health authorities and ECs/IRBs. For this study, the early termination visit should include assessments defined within the Week 15 visit (Visit 17) as indicated in the SoA in Appendix 1.

Study participants may also be temporarily or permanently discontinued from the study treatment as outlined in the protocol or if the investigator believes it is in the participant's best interest for any reason. Additional details related to individual participant study treatment discontinuation can be found in Section 9.7 Risk Mitigation and Toxicity Management Guidance and Section 9.8 Stopping Rules. Participants will also be discontinued from the study treatment if the treating physician identifies any signs of acute vision-threatening compressive optic neuropathy that requires surgical decompression.

In the event that a participant discontinues prematurely from the study because of a 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, where applicable as per national law: 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

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. CRITERIA FOR STUDY TERMINATION

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.

Circumstances that may warrant premature study termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Failure to enroll participants at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Plans to modify, suspend or discontinue the development of the study drug

In Germany, the study must also be terminated if:

- the approval of the responsible National Competent Authority (NCA) has been revoked

- the maximum sum insured cannot be adjusted

4.7. 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.

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

The CRF will clearly distinguish between reasons for non-adherence (that is, for not receiving 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 of antibody in 4.0 mL extractable volume in [redacted]R vials, frozen at -20 ± 5ºC and protected from light.

5.1.1. Administration of VRDN-001

The pharmacist or other qualified medical professional with applicable certification or license per local laws who is trained and delegated by the principal investigator will prepare the IV infusion bags. This individual will be unmasked to treatment and will dispense [redacted] mL bags of saline with VRDN-001 added, according to the Randomization and Trial Supply Management (RTSM) system assignment with appropriate dispensing label. The volume of saline removed from the bags will equal the volume of VRDN-001 added. [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 in a secure area frozen at -20 ± 5ºC and protected from light (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 IV infusion visit, any medication including selenium supplements, systemic, topical (including eye drops), periocular (including intraorbital) and intraocular corticosteroids, other immunosuppressive agents or any other therapy for the treatment of TED that is administered to the participants 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 IV 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, periocular (including intraorbital) and intraocular steroids (topical steroids including eye drops are allowed), any other anti-IGF-1R therapy, insulin receptor inhibitors, anti-TSHR monoclonal antibodies, any immunomodulating therapies including rituximab, tocilizumab, secukimumab, satralizumab or anti-FcRn's 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 data to ensure the achievement of the target level of data capture.

6.1. CONDUCT OF STUDY

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 without undue influence including that of a financial nature. 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 informed consent form must be maintained within the participant's study records.

The Principal 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 an Investigator is 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 must also be documented in the participant's source documentation.

Participants should be 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 SoA in Appendix 1 describes the procedures that will be performed at each visit.

7. OPHTHALMIC ASSESSMENTS

All ophthalmological assessments will be performed on both eyes at the visits specified in Appendix 1. Detailed descriptions of the assessments outlined in this section are described in the accompanying Protocol Procedures Manual (PPM).

7.1. 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 average of 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 who completes the baseline assessment (defined as the last assessment prior to the first infusion) must perform the measurement throughout; the same exophthalmometer should be used throughout the course of the study for an individual participant**. **Additionally, the base setting at screening on the exophthalmometer must be recorded and available to the**

physician at each clinical encounter, and the same base setting used for each subsequent measurement.

7.2. 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,
- 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 who completes the baseline assessment (defined as the last assessment prior to the first infusion) must perform the assessment for an individual participant throughout the course of the study.**

7.3. 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),
- continuous diplopia in the primary or reading position (constant, scored as 3).

The same assessor who completes the baseline assessment (defined as the last assessment prior to the first infusion) 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.

7.4. 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.

7.5. 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.

7.6. FUNDOSCOPY

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

7.7. 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. When applicable 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 the SoA in Appendix 1.

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 the SoA in Appendix 1. 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 in Appendix 1. A symptoms-directed physical examination will be performed at every study IV 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 abnormalities that may be 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 Appendix 1.

8.5. [redacted]

[redacted]

8.6. LABORATORY ASSESSMENTS

Clinical laboratory tests will include 12-hour fasting (nothing by mouth but water) serum chemistry, lipid panel, hematology, HbA1c, coagulation panel, infectious disease testing (HIV 1/2, Hepatitis B and Hepatitis C [at Screening visit]) and urinalysis as denoted in Appendix 1. HbA1c will be collected at the Screening, Week 12 (Day 85), Week 24, 36 and Week 52 Visits. Serum and urine pregnancy tests in **all females** will be performed as described in Appendix 1. Blood collection for FSH levels will be performed at the Screening visit for women who are believed to be postmenopausal with no menses for at least 2 years without alternative medical

cause to confirm postmenopausal status. All laboratory samples will be collected as described in the SoA in Appendix 1. Additional tests may be performed at any time during the study as considered necessary by the Investigator.

The analytes and blood collection, sample processing and shipment to the central laboratory facility are detailed in the study Laboratory Manual. Blood and urine samples for safety will be analyzed at a central laboratory facility.

In addition, blood samples for PK analyses and ADA will be shipped via the central laboratory facility but analyzed by different vendors. The timing of sample collection is described in Appendix 1.

Urinalysis by routine urine dipstick analyses will be performed at the site, and a microscopic analysis performed by the central laboratory only if any abnormalities are found during the on-site dipstick analyses. All laboratory reports must be reviewed, signed and dated and clinical significance of abnormal values documented 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) Eosinophil (Absolute/Percent) Monocyte (absolute/Percent) Hb HbA1c Hct Lymphocyte (Absolute/Percent) Red Cell Distribution Width MCV Neutrophil (Absolute/Percent) Platelets RBC WBC MCH MCHC	Albumin ALT ALP AST Amylase Bilirubin, Direct and Total BUN Calcium Carbon dioxide (Bicarbonate) Chloride Cholesterol CK Total (or CPK) Creatinine serum GGT Glucose (Fasting) HDL LDH LDL Lipase Magnesium Phosphorus Potassium Sodium Total Protein Triglycerides Uric Acid	Appearance Bilirubin Blood Color Glucose Ketones Leucocyte Esterase Nitrite pH Protein Specific gravity Urobilinogen **Microscopic (if dipstick abnormal):** Bacteria Crystals (Calcium Oxalate, Triphosphate & Uric Acid) Epithelial Cells (Renal Tubular, Squamous & Transitional) Casts (Granular, Hyaline, Waxy, RBC & WBC) RBC WBC Yeast
Coagulation: PT/INR & aPTT		
Infectious diseases: HIV 1/2, Hepatitis B and Hepatitis C		
Other: FSH: Women who are believed to be postmenopausal with no menses for at least 2 years without alternative medical cause will have postmenopausal status confirmed with FSH testing at screening.		
Pregnancy test: A serum pregnancy test will be performed at screening and urine test prior to each IV infusion and at designated timepoints in Appendix 1 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, 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 IV infusion.

The study medical monitor will review SAEs and AEs on an ongoing basis during the treatment phase of the study.

9.1. DATA SAFETY AND MONITORING BOARD

An independent DSMB will oversee the safety of the study and review safety and limited efficacy data from 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 IV 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 will be evaluated as to whether they are expected or unexpected, and related to VRDN-001, the IV 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 RSI section of the IB.

Relatedness

The Investigator will determine the assessment of the causal relationship of the AE/adverse reaction to the study drug. The following terms for assessment of the causality to study drug 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 drug or procedure interrupted
- Study drug or procedure discontinued
- Other (i.e., missed or delayed dosing)

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 the 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 site 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.

Sponsor contact information and additional contact information for the Contract Research Organization (CRO) are provided in the PPM.

Viridian and any delegated CRO are responsible for reporting of suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities and principal investigators in 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 IV 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 participant will have the final decision on type of treatment at the time of an event.

IV infusion associated adverse events

Monoclonal antibodies may cause IV 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 IV infusion and are usually associated with the first IV infusion. The incidence and severity typically decrease with subsequent IV infusions.

For the first 3 IV infusions in the study, participants should be monitored during the IV infusion and for at least 60 minutes after completion of the IV infusion including vital signs monitored within 2 hours pre-IV infusion, 30 (±15) minutes after the start of IV infusion and again at 1 hour (±15 minutes) after completion of the IV infusion and the IV infusion site examined 5 to 10 minutes and then again at 30 (±10) minutes after the start of each IV infusion for local tolerance. For subsequent IV infusions (the 4th dose and 5th dose), participants who have not previously experienced an IV infusion reaction should be monitored during the IV infusion and for at least 30 minutes after the IV infusion including vital signs monitored within 2 hours pre-IV infusion, 30 (±15) minutes after the start of IV infusion and again 30 (±15) minutes after completion of the IV infusion and the IV infusion site examined 5 to 10 minutes and then again at 30 (±10) minutes after the start of each IV 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 IV infusions. Participants who exhibit immediate hypersensitivity reactions or IV

infusion-associate reactions during an IV infusion of VRDN-001 should have the IV infusion interrupted or the IV 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 IV 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 IV 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 IV infusions of VRDN-001 in those who have experienced IV 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 (paracetamol) 500 mg, or with the site's own standard of care regimen for prophylaxis of anaphylaxis. In addition, all future IV infusions should be administered over a minimum of 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 IV infusions should be pre-medicated with the above medications (diphenhydramine, ranitidine, dexamethasone, and/or acetaminophen [paracetamol]). Participants who experience a worsening delayed-type hypersensitivity reaction following repeated IV 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) IV infusion related reaction (IRR) occurs, or recurrent Grade 3 IRR occurs, 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 1. 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 ≥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 teprotumumab, [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. **For cases of new onset glucose intolerance/diabetes mellitus in whom glycemic control cannot be achieved by oral hypoglycemic agents or insulin and hospitalization is indicated, study drug must be interrupted until participant has attained a fasting glucose < 160 mg/dL**. If glycemic control has not been achieved prior to completion of five infusions and prior to Week 15, study drug must be permanently discontinued.

Muscle Spasms

If muscle spasms occur during or after the VRDN-001 IV 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 IV infusions has 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]. Clinical data and real-world experience with Teprotumumab, [redacted] has indicated that hearing impairment, if it occurs, usually presents after the 3rd or 4th IV infusion (Sears 2022). **Study drug must be interrupted if there is new onset of severe or higher grade hearing result on Pure Tone Average (PTA) or worsening from baseline of PTA by two grades or more, either of which is confirmed by a repeat audiometry assessment and also associated with hearing symptoms (e.g., tinnitus, hypoacusis) and additionally does not recover (or return to baseline) within approximately 3 weeks (i.e., prior to the next infusion)**. If the audiometry assessment and symptoms do not recover/resolve or return to baseline prior to the completion of five infusions and prior to Week 15, study drug must be permanently discontinued. The participant may 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. If possible, avoid medications known to cause diarrhea such as laxatives and magnesium. **If new onset IBD is confirmed by biopsy or clinically diagnosed by a gastroenterologist, the study drug must be permanently discontinued for the participant**.

9.8. STOPPING RULES

In addition to those circumstances outlined in Section 9.7, if a participant experiences an SAE with a severity ≥ 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 ≥ 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 the 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 ≥ 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 primary database lock will be performed after all participants have received the 5 IV infusions and completed the week 15 assessments or early discontinued. All participants will continue to be followed through 52 weeks from the first IV infusion.

10.1. STATISTICAL METHODOLOGY

10.1.1. Randomization

The participants will be randomized using permuted blocks (3:1 to 10 mg/kg versus 3 mg/kg). Participants and site personnel (except pharmacy personnel preparing the infusate) will be masked to treatment up to the completion of the study or early discontinued. The sponsor will be masked to treatment up to the primary database lock which will be performed after all participants have received the 5 IV infusions and completed the Week 15 assessments or early discontinued. The masking requirements are discussed in Section 10.1.2 and full details of the masking and unmasking procedures will be included in the PPM.

Randomization codes are created by the RTSM vendor before the beginning of the study, maintained by the RTSM vendor throughout the study, and only designated unmasked personnel and system administrators have access to the randomization codes.

10.1.2. Study Masking

Masking will be maintained by the use of IV infusions that appear identical between the two doses of VRDN-001. Additionally, all participants will receive the same number of IV infusions and the total IV infusion volume will remain constant (e.g., the volume of saline removed from the bags will equal the volume of VRDN-001 added) to maintain masking.

Participants and site personnel (except pharmacy personnel preparing the infusate) will be masked to treatment up to the completion of the study or early discontinued. The sponsor will be masked to treatment up to the primary database lock which will be performed after all participants have received the 5 IV infusions and completed the Week 15 assessments or early discontinued.

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 their unmasked CRO team (unmasked CRA) or unmasked Clinical Supply Manager whose contact details are provided in the study contact sheet.

A complete list of all unmasked personnel will be maintained.

10.1.3. Procedure for Unmasking Participants

An appropriate user (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 study. An emergency participant code break by the masked investigator in case of an urgent situation may be performed without prior notification to a monitor or the sponsor.

The designated user will need to complete an acknowledgment of the unmasking transaction prior to the information being displayed.

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

Additionally, once the transaction has been completed successfully, the RTSM system will generate an email with a PDF attachment and send to all designated individuals. The RTSM system generates an email upon successful unmasking, with the transaction details included in the content of that email (not a PDF). The vendor generates both a masked and unmasked email for each unmasking transaction. These emails may be saved to PDF once received via email.

10.1.4. Description of Populations for Analysis

Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population will include all participants, irrespective of whether study medication was administered or not. This dataset will be used to report participant disposition and as the primary analysis population for the efficacy endpoints.

Modified Intent-to-Treat (MITT) Population

The Modified Intent-to-Treat (MITT) population will include all participants who received at least 1 IV infusion of study medication. This dataset will be used to report efficacy endpoints for secondary and exploratory endpoints.

Safety Population

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

10.2. SAMPLE SIZE

The sample size of this study was not based on formal statistical calculations but for obtaining sufficient patient exposure and safety data.

10.3. ENDPOINTS

A description of endpoints for this study can be found in Section 2 of this protocol.

10.4. ANALYSIS OF EFFICACY

Efficacy endpoint will be summarized descriptively. For continuous endpoints descriptive statistics will include N, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized as counts and percentages of participants in each category.

All visits the endpoint is collected will be summarized unless it is a post-baseline unscheduled visit in which this data will be listed.

The statistical analysis plan will document how missing data will be handled.

10.5. ANALYSIS OF SAFETY

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 and 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.

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

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.

All other safety assessments will be analyzed by timepoint and change from baseline as appropriate. An out of normal range summary may be performed for laboratory and ECG measurements.

Audiometry will be summarized by result based on pure tone average. The last assessment associated with a visit will be utilized in this analysis.

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.

11. DATA HANDLING AND RECORDKEEPING

11.1. DATA PROTECTION AND DATA COLLECTION

Data Protection

All parties will comply with all applicable laws, including laws, regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants personal data will be stored at the study site in encrypted, electronic, and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff will have access. The study site will implement appropriate, technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has a fact occurred, and, if so, providing breach notifications as required by law and to the sponsor.

To protect the rights and freedoms of participants, with regard to the processing of personal data, participants must be informed of his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant. The participant will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by the single, participant-specific code. The study site will maintain a confidential list of participants, who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. The participant identification code list is an essential document and as such should be maintained according to the ICH GCP guidelines.

Pseudonymized study data will be transferred by the CRO to the Sponsor in the United States. The sponsor will protect the confidentiality of participant's personal data, consistent with a clinical study agreement and applicable privacy laws.

Data Collection and Case Report Forms

Clinical data management will be performed in accordance with CRO's applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data and documented in the Data Management Plan. Description of the use of computerized system is documented in the Data Management Plan.

An eCRF will be used for this study. The data will be entered in the eCRF in a timely manner on an ongoing basis. The eCRF is the primary data collection instrument for the trial. The Principal Investigator is responsible for ensuring that data are properly recorded in each participant's eCRF and related documents. 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 participant'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.

Data management personnel will review data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the electronic data capture (EDC) system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to data.

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 personally sign and date the participant eCRF casebook in accordance with the procedure described in the eCRF completion guidelines indicating that the data on the eCRF have been assessed and to ensure that the observations and findings are correct and complete once all data for that participant is final.

The database will be declared locked once the data have been verified for completeness and accuracy, and after instruction from the Sponsor. Authorization is required prior to making any database changes to locked data by written agreement from Sponsor.

For EDC studies, after the final study database lock, the investigator will receive electronic copies of the participant data for archiving at the investigational site.

A separate Data Management Plan will be prepared to describe the data management process.

For data handled by the CRO, eCRF data and some or all of the study-related data will be managed and stored electronically in the CRO's database system. Validated data will subsequently be transferred to the sponsor or its representatives for data management and analysis.

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 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 that 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 studies conducted within the EU the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law. Record retention requirements must be in accordance with local regulations. 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 this study.

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 applicable site personnel and participant signatures, 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 participant'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 their authorization.

In the event that a participant revokes authorization to collect or use their 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 participant's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality will include a unique trial identification number to 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 participant'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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Appendix 1: Schedule of Assessments

Visit/Telephone Call	V1	V2	V3	V4/ C1[a]	V5	V6	V7/ C2[a]	V8	V9	V10/ C3[a]	V11	V12	V13/ C4[a]	V14	V15	V16/ C5[a]	V17[m]	V18	V19	V20
Study Day/Week	**D-28 To D-2**	**D -1**	**D1**	**D2**	**D21**	**D22**	**D23**	**D42**	**D43**	**D44**	**D63**	**D64**	**D65**	**D84**	**D85**	**D86**	**D106 (W15)**	**D168 (W24)**	**W36**	**W52**
Visit Window					**+/- 3 Days**													**+/- 7 Days**		
Informed consent/Eligibility	X		X[b]																	
Randomization			X																	
Demographics, tobacco use and medical history	X																			
Physical exam	X	X[c,d]				X[e]			X[e]			X[e]			X[e]		X[e]	X[e]	X[e]	X[e]
ECG	X	X[c,d]															X			
Vital signs[n]	X		X[f]			X[f]			X[f]			X[f]			X[f]		X	X	X	X
Examination of IV infusion site [g]			X			X			X			X			X					
Pregnancy test [h]	X		X			X			X			X			X		X	X		
FSH[o]	X																			
HIV 1/2, Hepatitis B/C	X																			
Laboratory assessments [i]	X		X[j]			X			X			X			X		X	X	X	X
Urinalysis [p]	X		X[j]			X			X			X			X		X	X	X	X
Blood samples for ADA and PK [k]			X			X			X			X			X		X	X		
Exophthalmometry	X	X[c]															X	X	X	X
Slit lamp biomicroscopy	X	X[c,d]			X[c]			X[c]			X[c]			X[c]			X	X	X	X
IOP	X	X[c,d]			X[c]			X[c]			X[c]			X[c]			X	X	X	X
Visual Acuity	X	X[c,d]			X[c]			X[c]			X[c]			X[c]			X	X	X	X
Fundoscopy	X	X[c,d]			X[c]			X[c]			X[c]			X[c]			X	X	X	X
Gorman Subjective Diplopia score	X	X[c]															X	X	X	X
CAS	X	X[c]															X	X	X	X
Audiometry[q]	X	X[c,d]			X[c]			X[c]			X[c]			X[c]			X	X	X	X
Breakfast [l]			X			X			X			X			X					
Study IV infusion			X			X			X			X			X					
Telephone call to participant[a]				X			X			X			X			X				
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Con med review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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 IV infusion clinic the previous day.
[b] Eligibility must be re-confirmed prior to enrollment on Day 1.
[c] Assessment will be performed either the day before or on the day of, but prior to each IV infusion.
[d] 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: Physical exam, ECG, Audiometry, VA, fundoscopy, biomicroscopy, and IOP.
[e] Symptoms-directed physical examination will be conducted at all study IV infusion visits, and at any study visit if clinically indicated.
[f] Vital signs monitored within 2 hours pre-IV infusion, 30 (±15) minutes after the start of IV infusions and again at 1 hour (±15 minutes) after completion of the IV infusions for the first 3 IV infusions and within 2 hours pre-IV infusion, 30 (±15) minutes after the start of IV infusions and again at 30 (±15) minutes after completion of the IV infusions for the 4th and 5th IV infusion for participants who have previously not experienced an IV infusion reaction. Additional vital signs will be monitored if IV 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 IV infusions.
[g] The IV infusion site will be examined 5 to 10 minutes and then again at 30 (±10) minutes after the start of each IV infusion for local tolerance on IV infusion days.
[h] Pregnancy test for **all females** will be serum at the Screening Visit and urine prior to each subsequent IV infusion and on Week 15 and Week 24 visits.
[i] Blood samples for laboratory assessments for safety must be collected in the 12-hour fasting state (nothing by mouth but water) and prior to IV infusion when sampled on IV infusion days. HbA1c testing will be performed at the Screening Visit, Week 12 (Day 85), Week 24, Week 36 and Week 52.
[j] 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 and urinalysis.
[k] On IV infusion days participants will have blood samples drawn for PK and ADA levels before the IV infusion. PK and ADA blood samples will also be taken at Week 15 and Week 24.
[l] Breakfast will be provided after completion of the fasting blood draws, when required.
[m] Participants who discontinue early from the trial whenever possible should return for an early termination visit for which a minimum of safety assessments will be offered when completion of all early termination assessments are not permitted by local health authorities and ECs/IRBs. For this study, the early termination visit should include assessments defined within the Week 15 visit (Visit 17).
[n] Height will be measured only at Screening. Weight will be measured prior to assigning study drug in the RTSM on IV infusion visits and at all visits where vital signs are collected.
[o] Women who are believed to be postmenopausal with no menses for at least 2 years without alternative medical cause will have postmenopausal status confirmed with FSH testing at screening.
[p] Routine urine dipstick analyses will be performed at the site, and a microscopic analysis performed by the central laboratory only if any abnormalities are found during the on-site dipstick analyses.
[q] 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