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VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor for Thyroid Eye Disease (TED): In Vitro Pharmacology and Clinical Phase 1/2 Results

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Disclosures

- These studies were sponsored by Viridian Therapeutics, Inc. All data are proprietary.
- **VRDN-001** is an investigational therapy not approved in any country. All authors met the ICMJE authorship criteria and had full access to relevant data
  - **Andrea Kossler: Viridian (R), Horizon Therapeutics (R, C), Sling Therapeutics (R). Immunovant (C), Genetech (C), Argenx (C), Acelyrin (C)**
  - Navdeep Nijhawan: Viridian Therapeutics (R)
  - Kimberly Cockerham: Horizon Therapeutics (R, S), Viridian Pharmaceuticals (S), Immunovant (C, R) consultant/advisor
  - Roger E. Turbin: Viridian Therapeutics (R), Horizon (C)
  - Rosa Tang: Viridian (R, C) Horizon, Serono (S), Alexion (C)
  - Pawel Wiczling Viridian (C)
  - Chantal Boisvert: Viridian (R), OVID Therapeutics (R)
  - Wendy W. Lee: Viridian (R)
  - Michael T. Yen: Viridian (R), Ipsen Innovations (C), and Sling Therapeutics (C)
  - David Kaufman: Viridian (R)
  - Michael Yoon: Viridian (R)
  - Madhura Tamhankar: Viridian (R), Horizon Therapeutics (R), UptoDate (C)
  - Vahe Bedian: Viridian employee
  - Barrett Katz: Viridian employee

Learning objectives

- Review Thyroid eye disease (TED) pathophysiology
- Introduce VRDN-001 and explain distinct antagonist properties
- Overview VRDN-001 phase 2 proof-of-concept (POC) study in ***active*** TED

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Thyroid Eye Disease (TED) Pathophysiology

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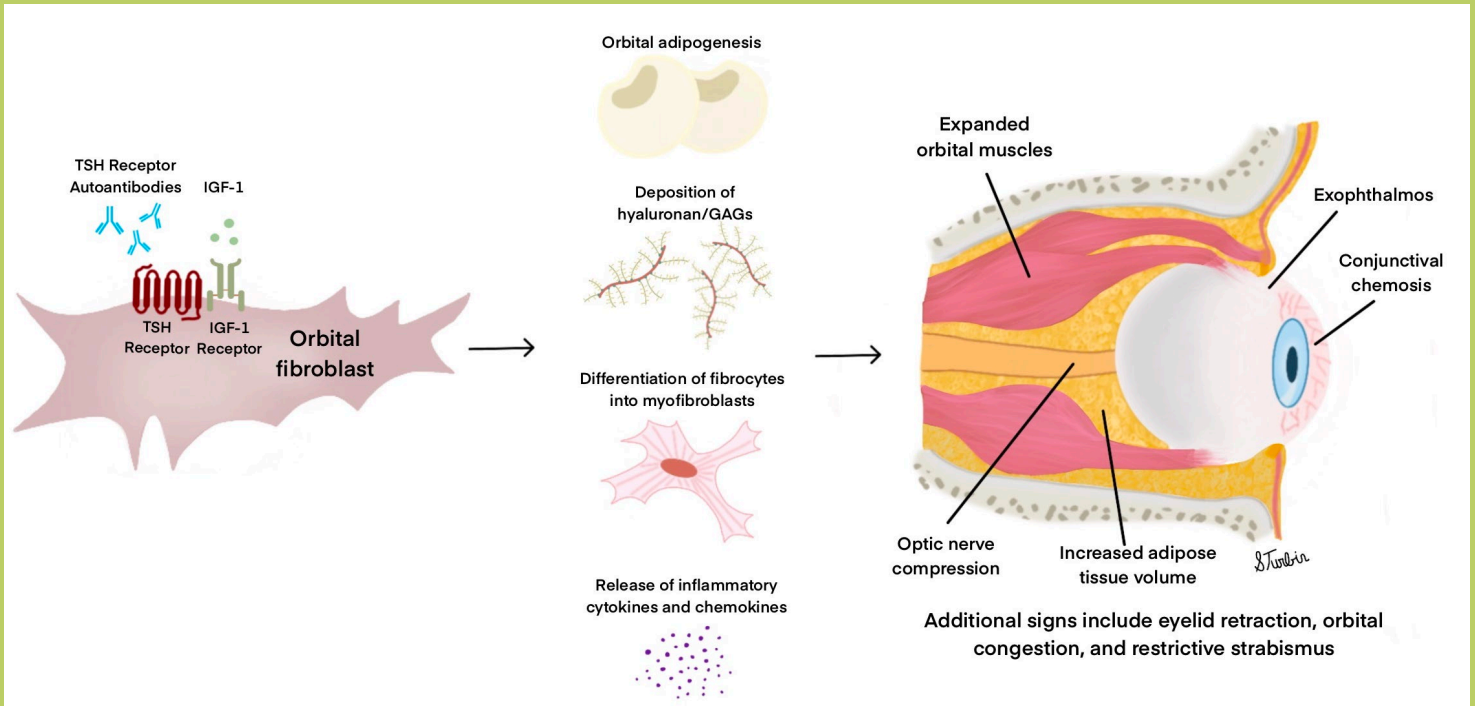
TED Pathophysiology

- Autoantibody stimulation of the TSHR/IGF-1R signaling complex results in:
  - Adipogenesis
  - Deposition of hyaluronan, GAG, & cytokines
  - Myofibroblast proliferation
- Tissue expansion in a fixed bony orbit



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VRDN-001 Pharmacology Data: Distinct Binding & Antagonist Properties

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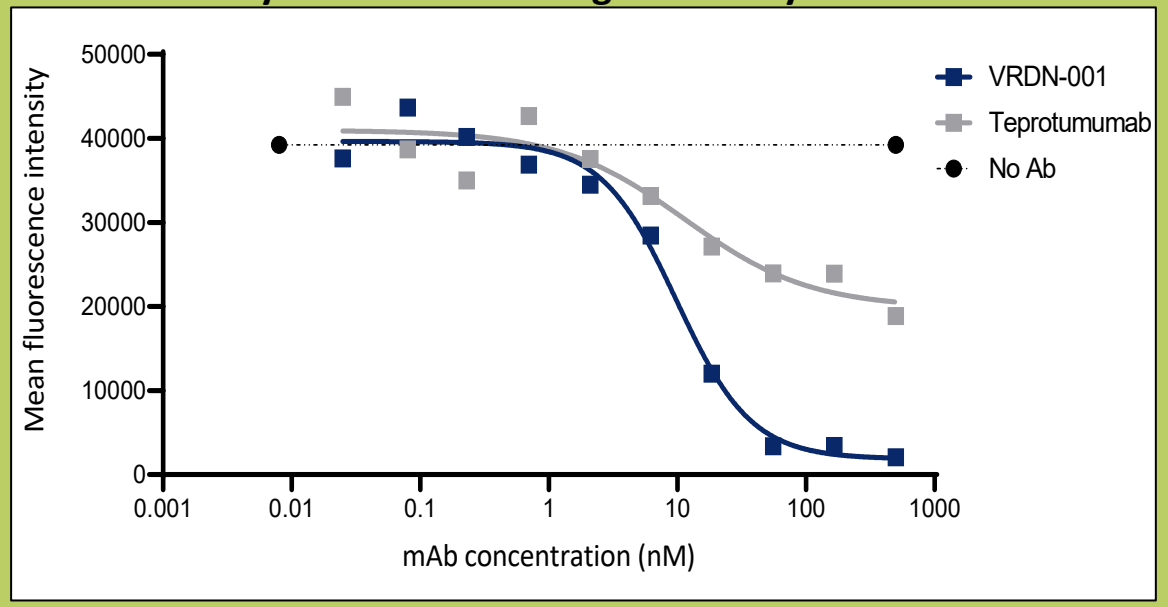
VRDN-001, full antagonist antibody to IGF-1R, for treatment of TED

30 nM biotinylated IGF-1 binding to FreeStyle™ 293-F Cells



- **VRDN-001** gives near-complete inhibition at ≥50 nM
- Teprotumumab gives partial inhibition, does not exceed ~50% up to 300 nM

- **VRDN-001** is a monoclonal antagonist antibody against the IGF-1 receptor
- In preclinical studies, **VRDN-001**:
  - Provided near complete inhibition of IGF-1 ligand binding to IGF-1R*
  - Provided full antagonism of IGF-1R proximal and distal signaling*

*Zhao Y et al. Late Breaking Highlighted Poster 132. *Thyroid.* 2022;32(1).

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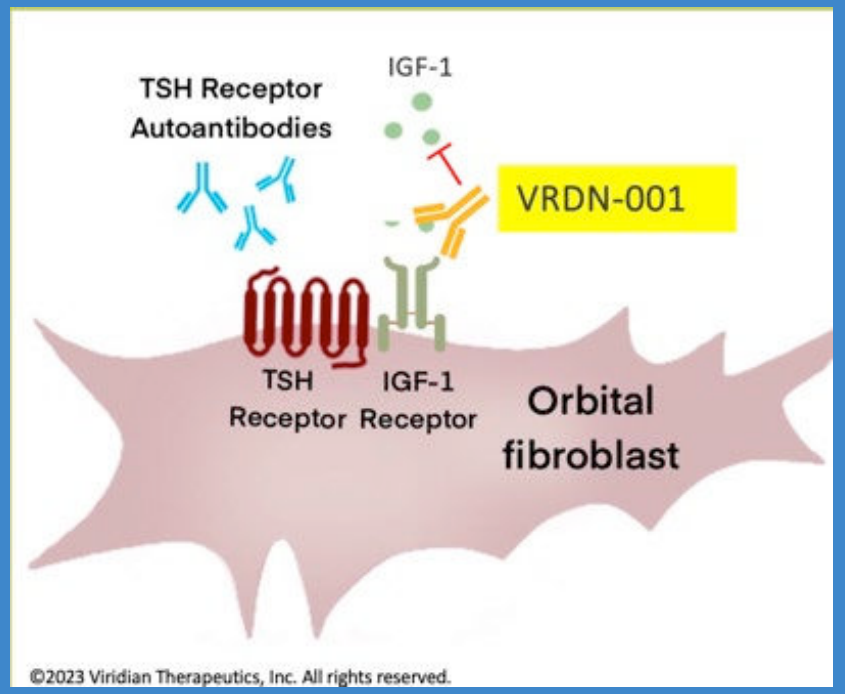
Proof-of-Concept Study: VRDN-001 Phase 2 Results in *Active* TED



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Proof-of-concept randomized, double-masked trial tested 3 different doses in active TED

Patients received 2 infusions 3 weeks apart

Active moderate-severe TED Patients:

- Clinical activity score (CAS) of ≥4
- Onset of signs/symptoms within prior 12 months
- No history of inflammatory bowel disease or significant ear pathology/impairment
- No history of optic neuropathy or IGF-1R inhibition.
- No prior immunosuppressive agents (60 days)

→

- Placebo (n=6*)
- **VRDN-001** 3 mg/kg (n=9)
- **VRDN-001** 10 mg/kg (n=6)
- **VRDN-001** 20 mg/kg (n=6)

*One patient in the placebo arm discontinued the study before Week 6 and thus is not included in the efficacy analysis but is included in the safety analysis.

Baseline patient demographic and exam results

	VRDN-001 (3, 10, and 20 mg/kg)	Placebo
n	21	5
Proptosis, mean (SEM)	23.7 (0.7)	22.8 (2)
CAS, mean (SEM)	5.4 (0.2)	5.0 (0.5)
Diplopia, n (%)	13 (62%)	3 (60%)
Gorman diplopia score, mean (SEM)	1.3 (0.3)	1.6 (0.7)
Months since onset of TED signs/symptoms, mean (SEM)	7.4 (0.8)	7.0 (2.0)
Age, mean years (SEM)	47 (3.3)	44.2 (4.3)
Female, n (%)	19 (90%)	3 (60%)

SEM = Standard error of the mean

Proptosis Responder Rate

Preliminary data after 2 infusions (6 weeks)

Hertel: 71% proptosis responder rate

Magnetic Resonance Imaging

- Exploratory measure of proptosis (more precise than Hertel)
- 3D reconstruction algorithm used
- Centrally read by 2 independent masked reviewers

Week 6	Placebo	All VRDN-001
Hertel proptosis responder rate	**40% (2/5)**	**71% (15/21)**
MRI proptosis responder rate	0% (0/5)	69% (11/16)

- 5 of 5 placebo patients and 16 of 21 VRDN-001 patients
- Proptosis responder rate: % of patients with ≥2-mm reduction in proptosis

Summary of VRDN-001 outcome measures

Preliminary data after 2 infusions (6 weeks)

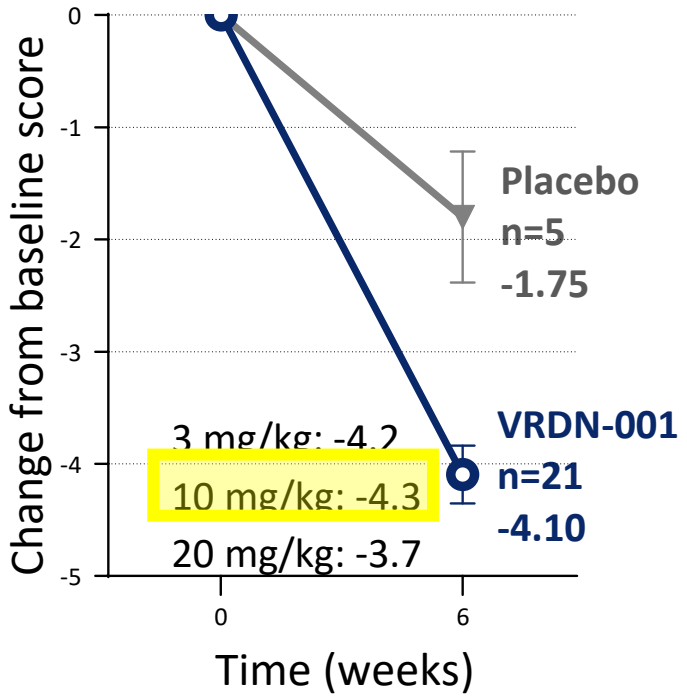
Week 6	Proptosis responder rate	Proptosis mean change by Hertel	Overall responder rate	CAS mean change	CAS score of 0 or 1	Diplopia complete resolution*
All VRDN-001, n=21	**71%**	**-2.3 mm**	**67%**	**-4.1**	**62%**	**54%**
3 mg/kg, n=9	67%	-2.7 mm	56%	-4.2	67%	20%
10 mg/kg, n=6	83%	-2.4 mm	83%	-4.3	83%	75%
20 mg/kg, n=6	67%	-1.7 mm	67%	-3.7	33%	75%

*Includes only patients who had diplopia at baseline (13/21 in treatment groups: 4 in 10 mg/kg cohort, 4 in 20 mg/kg cohort, and 5 in 3 mg/kg cohort). Mean Gorman score: 2.2

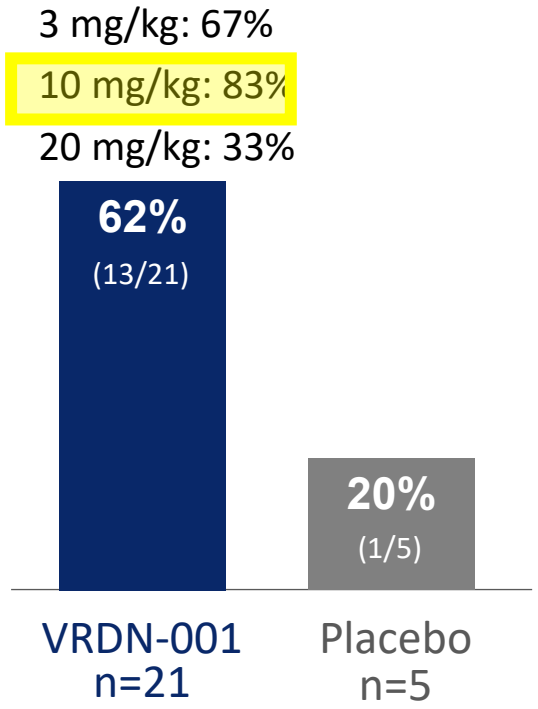
Improvement in CAS

Preliminary data after 2 infusions (6 weeks)

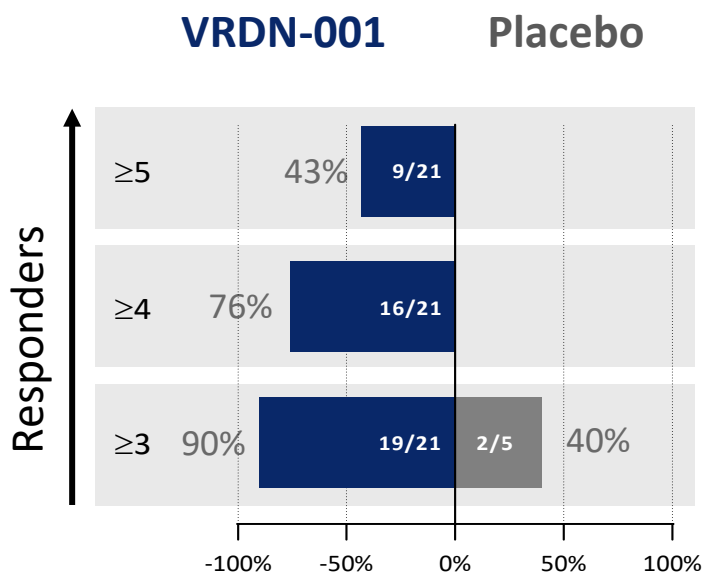
Mean change in CAS (from baseline to Week 6)



CAS of 0 or 1 at Week 6

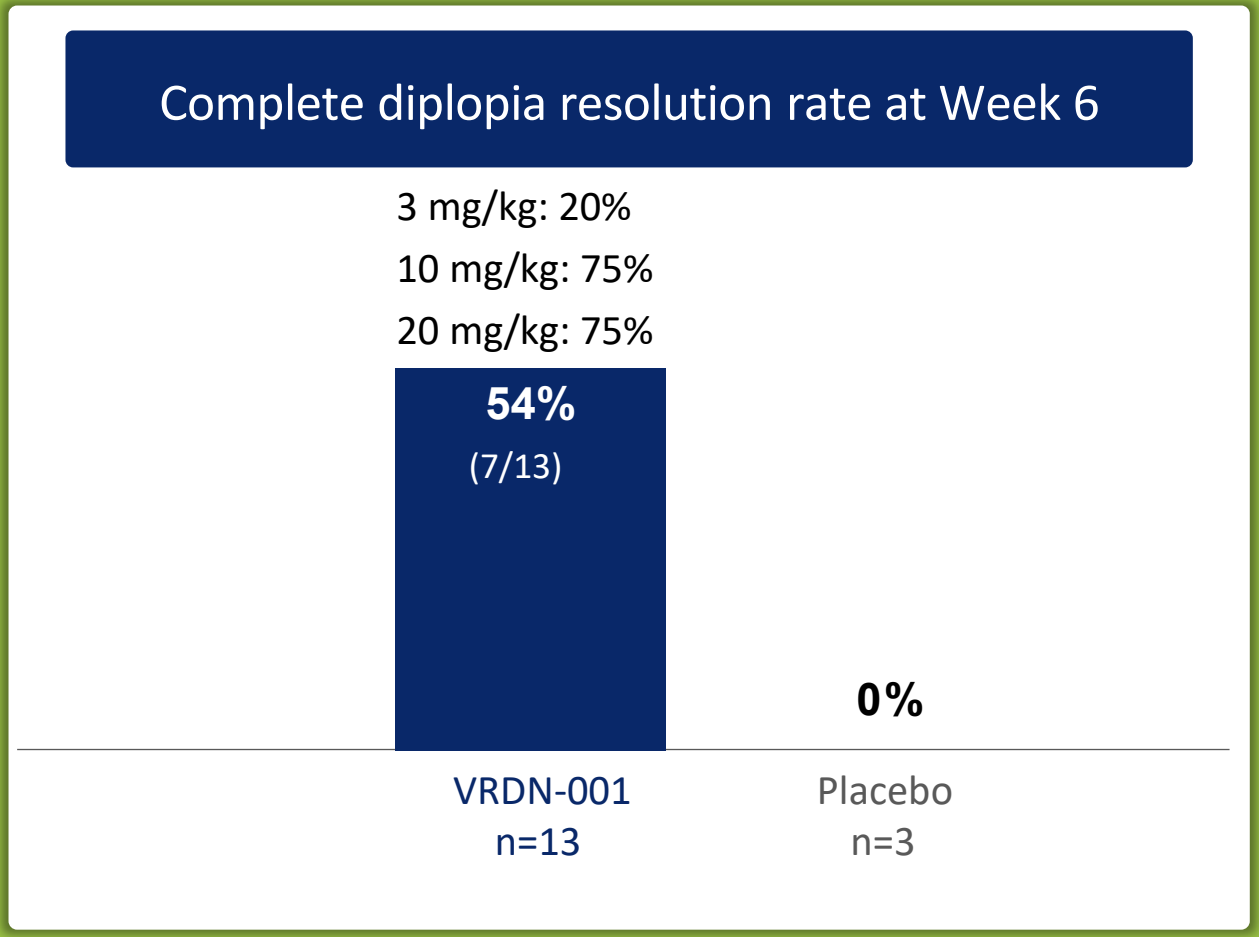


Reduction in CAS (from baseline to Week 6)



Complete diplopia resolution by Gorman score

Preliminary data after 2 infusions (6 weeks)



Diplopia resolution rate defined as % of patients with diplopia at baseline whose diplopia completely resolved

Diplopia was present at baseline in 13 out of 21 drug-treated patients (mean Gorman score of 2.2) and 3 out of 5 placebo patients (mean Gorman score of 2.8).

Safety profile

Preliminary data

No serious adverse events (SAEs), infusion reactions, or discontinuations

Follow-Up: At least 6 weeks

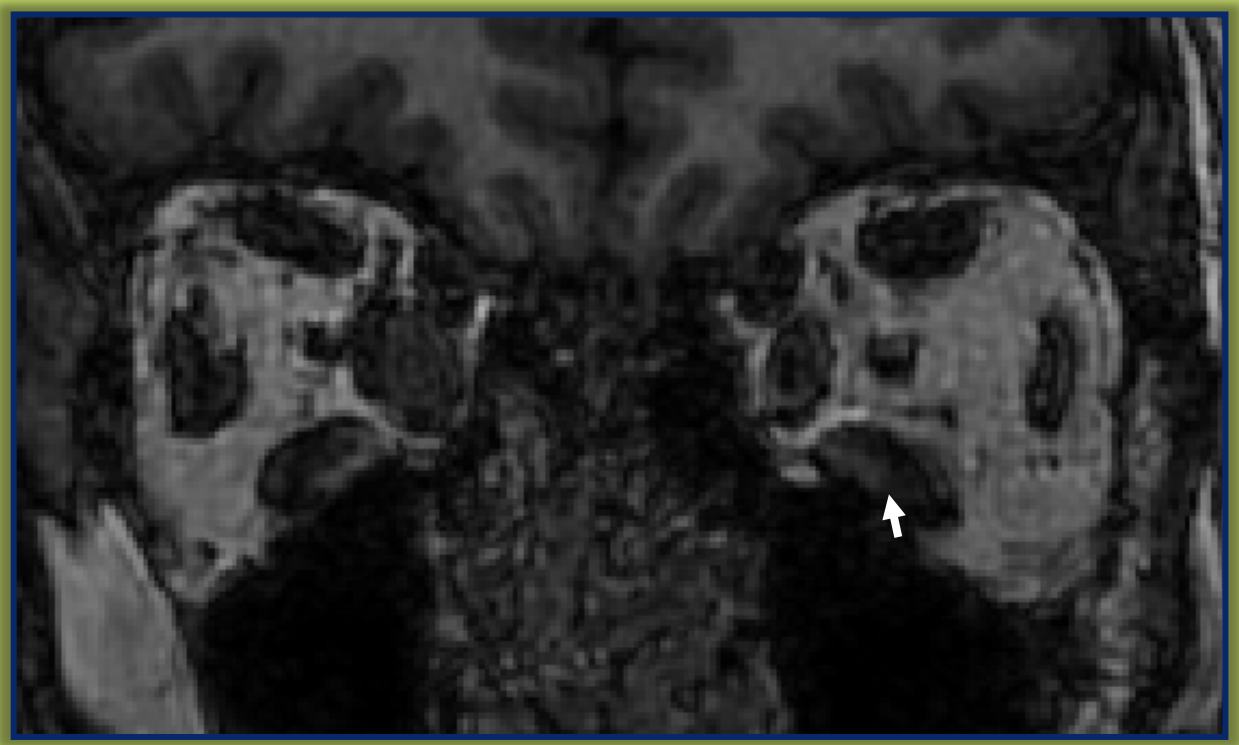
Adverse Reactions	VRDN-001 3 mg/kg (n=9), n	VRDN-001 10 mg/kg (n=6), n	VRDN-001 20 mg/kg (n=6), n	Placebo (n=6), n
Muscle spasms	2	2	2**	-
Nausea	2	-	-	-
Alopecia	-	-	-	1
Diarrhea	1	2**	1*	-
Fatigue	-	1	-	3
Hyperglycemia	1	-	1*	-
Hearing impairment	1	1	-	-
Dysgeusia	-	-	1	-
Headache	2	1	1	2**
Dry skin	1	-	1	-
Infusion reactions	-	-	-	-

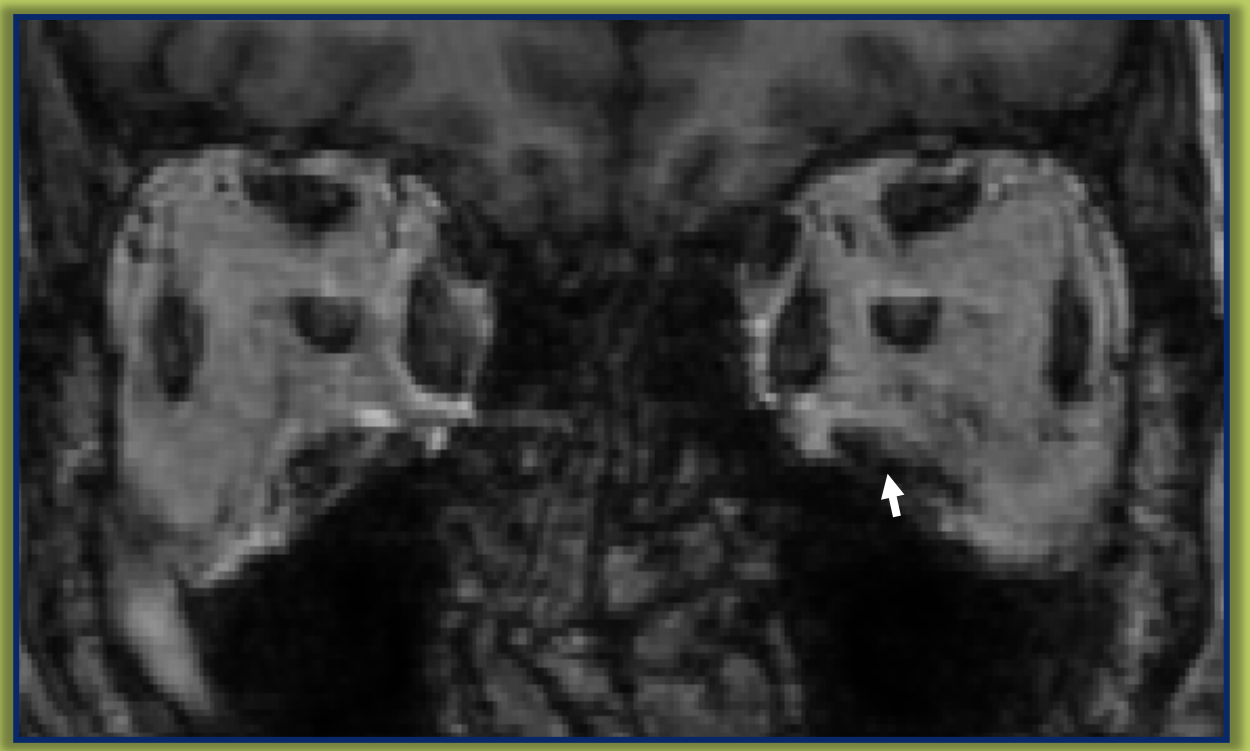
*Deemed unrelated to study drug by the masked investigators.
**1 patient deemed related and 1 patient deemed unrelated to study drug by the masked investigators.

Data are as of data cutoff of December 19, 2022. Other AE that occurred in more than 1 patient and deemed related to study drug by masked investigators was acne (n=2). Instances were mild and did not require intervention. Muscle spasms were mild and did not require intervention; hearing impairment AEs were hypoacusis and tinnitus with return to normal audiometry at follow-up in both cases. Both patients with hyperglycemia were diabetic at baseline; in 1 case glucose variability was determined by masked PI to be unrelated to drug.

Patient #1

After 2 **VRDN-001** infusions (Week 6)





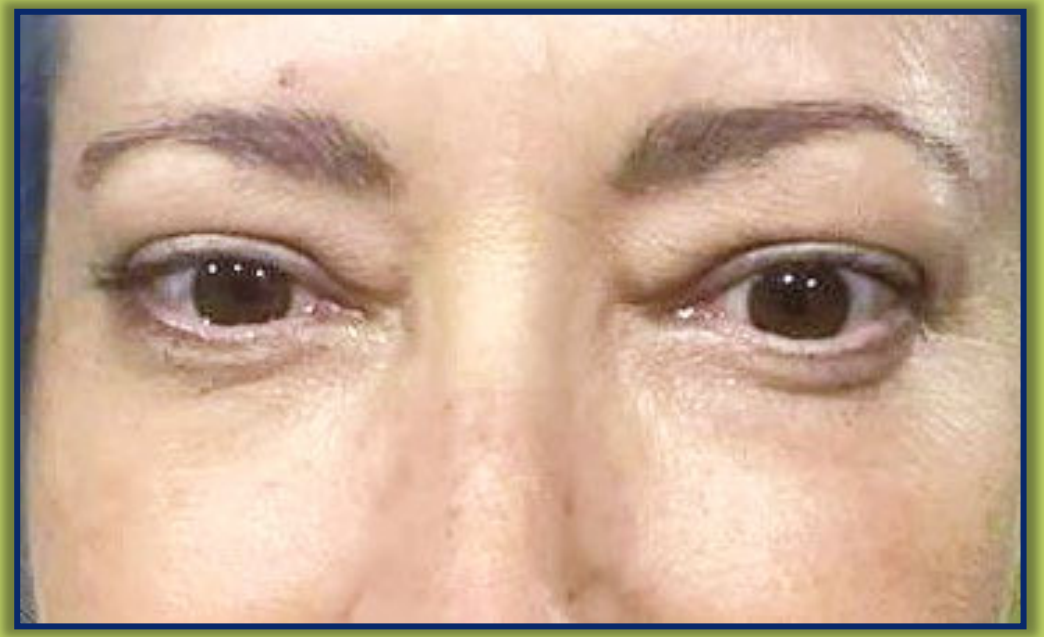
White arrows highlight reduction in size of the inferior rectus muscle.

Patient #2

Baseline at Week 0

2 days before first infusion of **VRDN-001**

Week 6



2 days following second infusion of **VRDN-001**

Patient photos taken by patient used with patient and investigator permission. Patient received 2 infusions in the study; in extended follow-up off treatment, TED symptoms have returned for this patient.

Conclusions

- **VRDN-001** shows distinct binding and antagonist properties to other IGF-1R inhibitors
- Preliminary phase 2 POC results show 2 IV infusions of **VRDN-001** were well tolerated and led to meaningful improvements in symptoms of TED
- The safety and efficacy of **VRDN-001** will be further assessed in the ongoing THRIVE (active TED, NCT05176639) and planned THRIVE-2 (chronic TED, NCT06021054) phase 3 clinical trials

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Thank you!

Questions?

VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor for Thyroid Eye Disease (TED): In Vitro Pharmacology and Clinical Phase 1/2 Results

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