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

Kimberly Cockerham, MD

Senta Clinic, San Diego, CA

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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.
- All data from the active TED phase 2 proof-of-concept study are as of data cutoff of December 19, 2022.
- All data from the chronic TED phase 2 proof-of-concept study are as of data cutoff of May 30, 2023.
- Presenting author: **Kimberly Cockerham** is a clinical research investigator for Viridian Therapeutics, Inc. and consultant for Horizon Therapeutics.
- Coauthors: **Roger E. Turbin, Navdeep Nijhawan, Rosa Tang, Michael T. Yen, Chantal Boisvert, David Kaufman, Andrea Kossler, Wendy W. Lee, Michael Yoon, Shoaib Ugradar,** and **Raymond S. Douglas** have consulted for, conducted studies funded by, or received honoraria for services provided to Viridian Therapeutics, Inc. **Vahe Bedian** and **Barrett Katz** are employees of Viridian Therapeutics, Inc.
- The authors would like to thank the study investigators, research teams, and study participants who make this research possible.

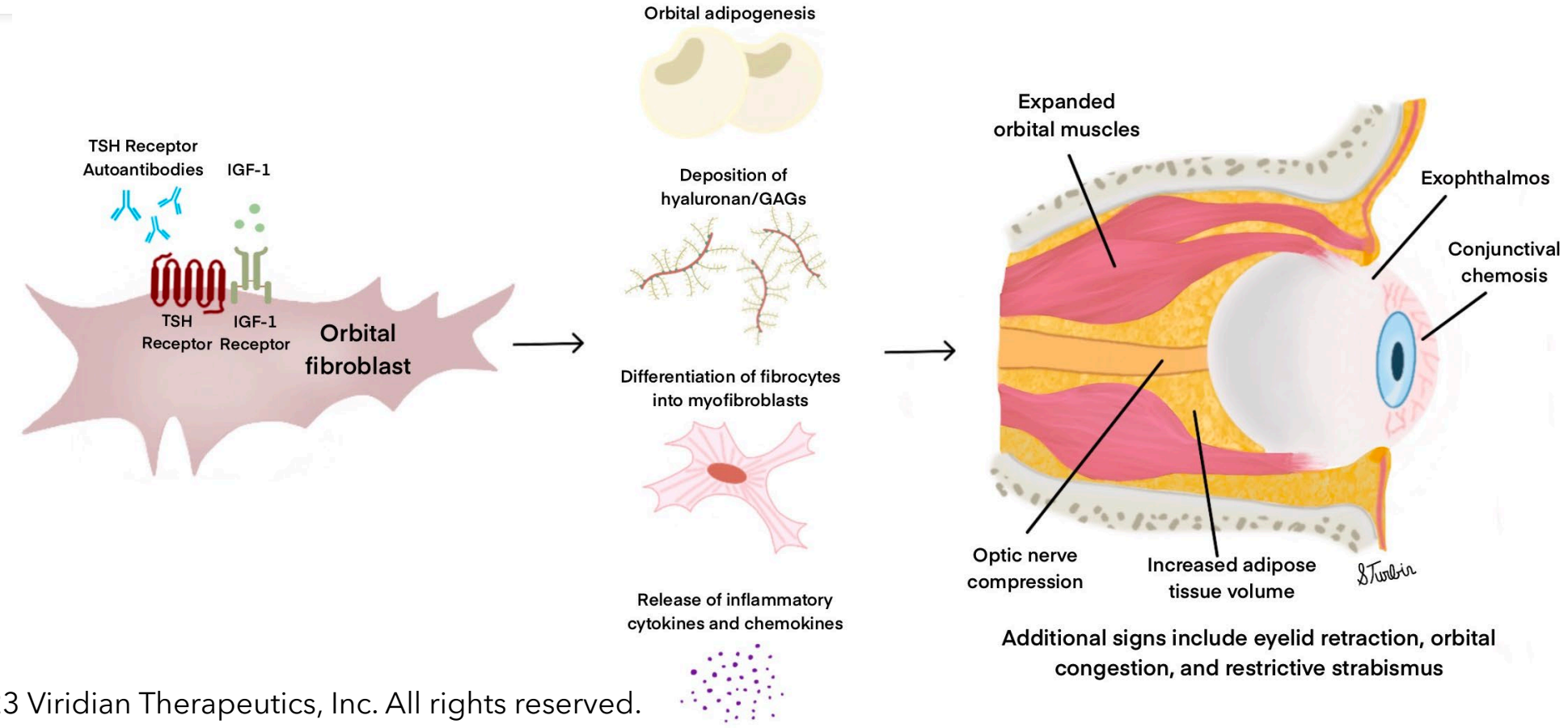
Learning objectives

To better understand:

- Thyroid eye disease (TED) pathophysiology
- **VRDN-001** preclinical data on distinct binding and antagonism
- **VRDN-001** phase 2 proof-of-concept (POC) study results

Thyroid eye disease (TED) pathophysiology

TED: Stimulation of TSHR/IGF-1R signaling complex results in inflammation and tissue expansion in the fixed bony orbit



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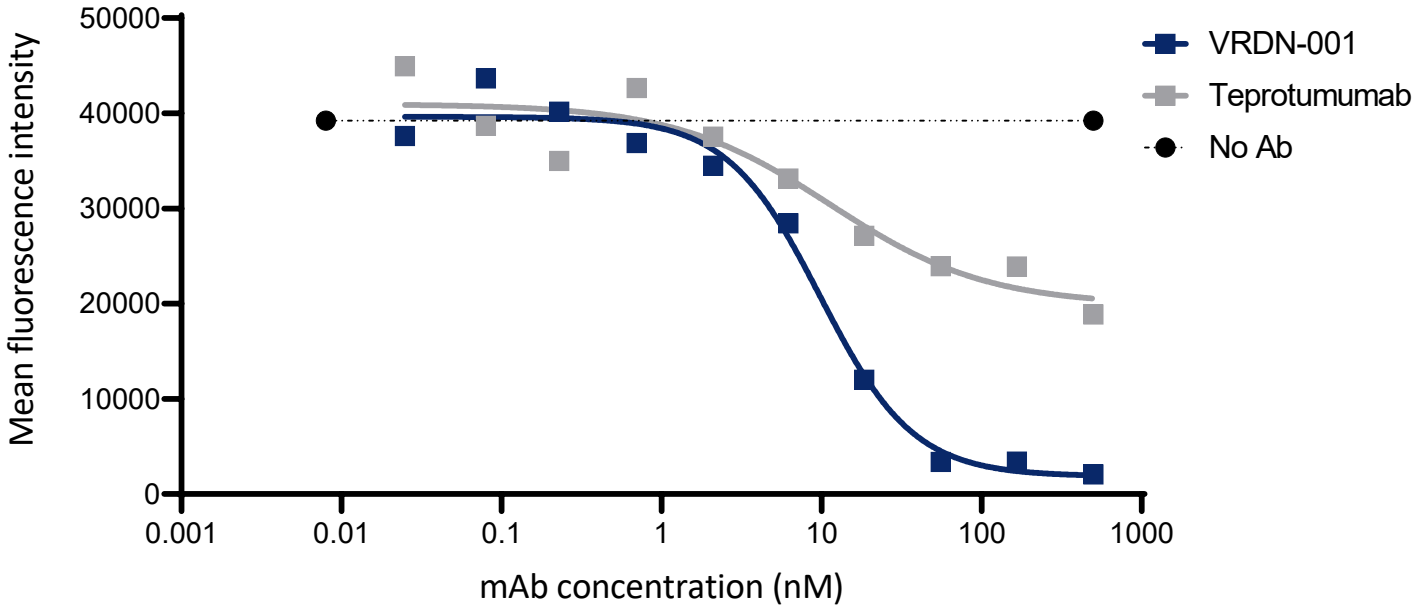
VRDN-001 preclinical data: distinct binding & antagonist properties

Inhibition of IGF-1 binding to IGF-1 receptor

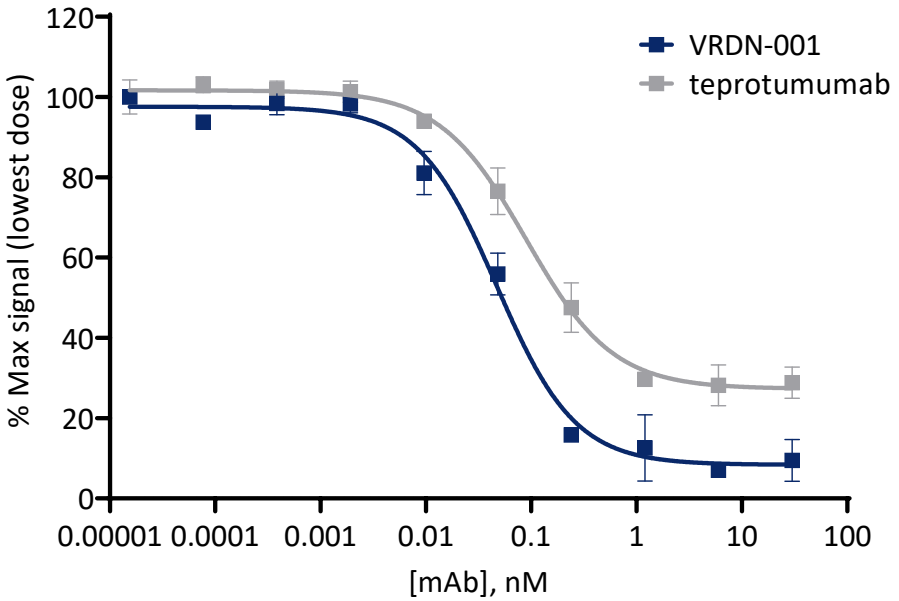
30 nM biotinylated IGF-1 binding to FreeStyle™ 293-F Cells



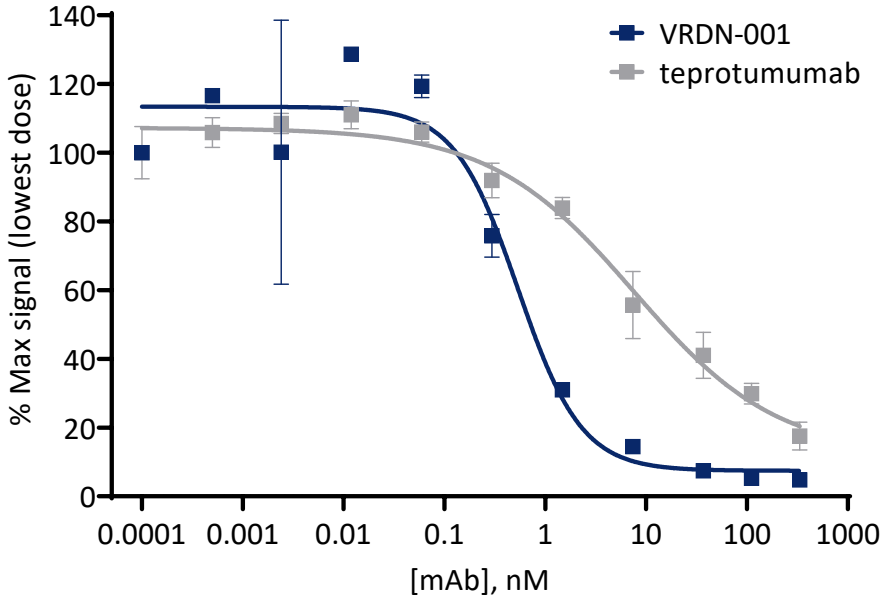
- **VRDN-001** gives near-complete inhibition at ≥50 nM
- Teprotumumab gives partial inhibition (does not exceed ~50% up to 300 nM)

VRDN-001 fully antagonizes markers of IGF-1 receptor signaling

Proximal signaling
(inhibition of IGF-1R phosphorylation)



Distal signaling
(inhibition of AKT phosphorylation)



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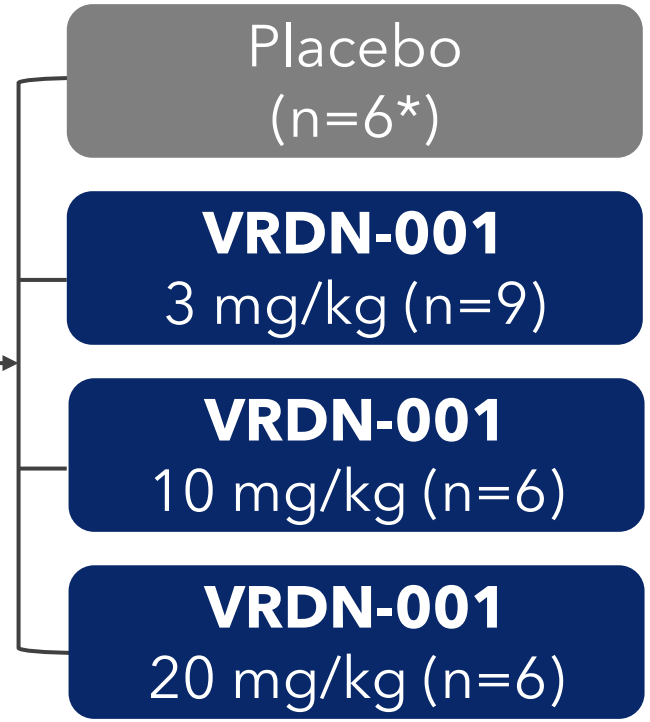
VRDN-001 phase 2 proof-of-concept study in *active* TED

POC randomized, double-masked trial tested 3 different doses in active TED

Patients received 2 infusions 3 weeks apart

Patients with active TED:
- Clinical activity score (CAS) of ≥4
- Onset of signs/symptoms within prior 12 months



*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 characteristics

	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

Summary of VRDN-001 outcome measures

Preliminary data after 2 infusions (6 weeks)

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

*Includes only patients who had diplopia present at baseline. Diplopia was present at baseline in 13 out of 21 drug-treated patients (mean Gorman score of 2.2); 4 in 10 mg/kg cohort, 4 in 20 mg/kg cohort, and 5 in 3 mg/kg cohort.

Overall responder rate: % of patients with ≥2-mm reduction in proptosis and ≥2-point reduction in CAS

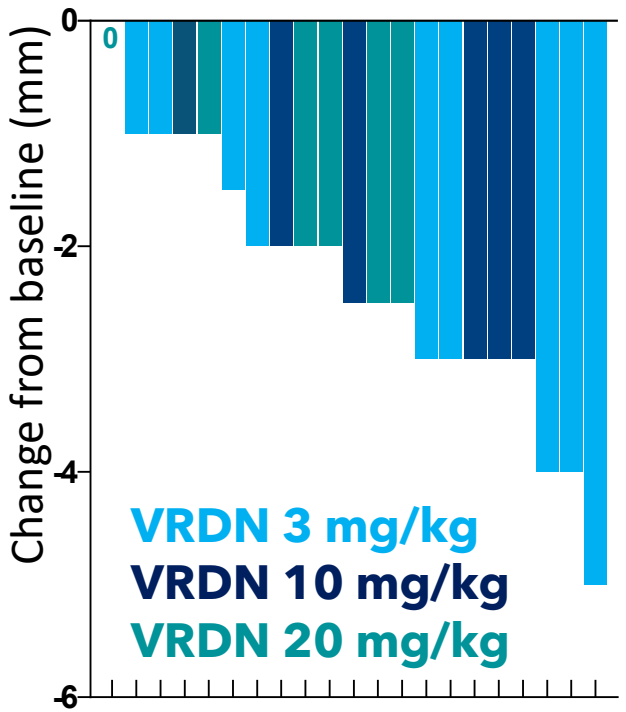
Proptosis responder rate: % of patients with ≥2-mm reduction in proptosis measured by exophthalmometry

Clinical activity score (CAS): a composite 0-7 scale scoring signs and symptoms of TED

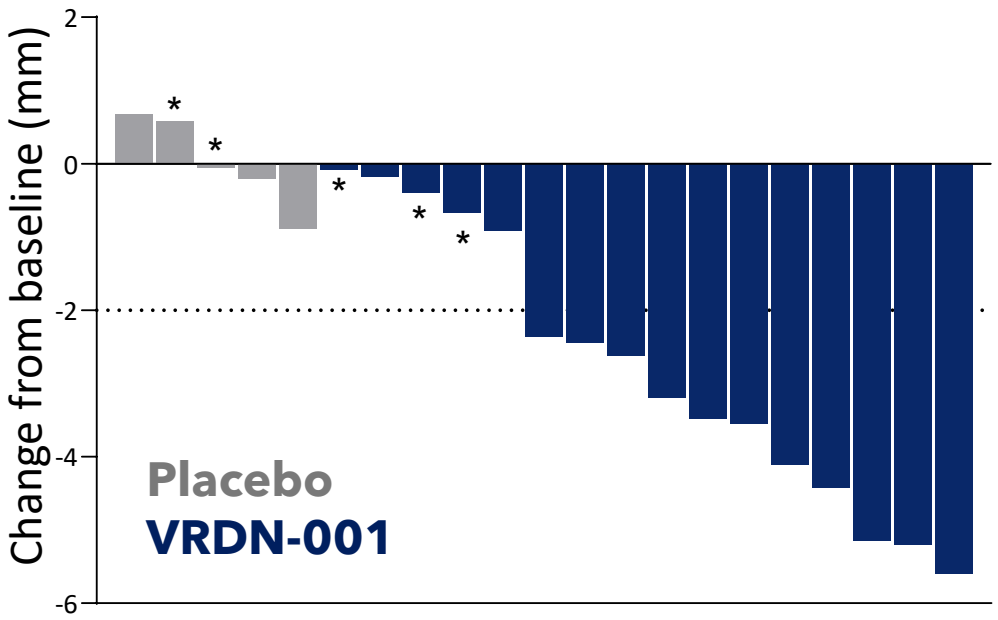
Proptosis reductions by exophthalmometer and MRI/CT

Preliminary data after 2 infusions (6 weeks)

Individual Hertel proptosis change (all VRDN-001 patients)

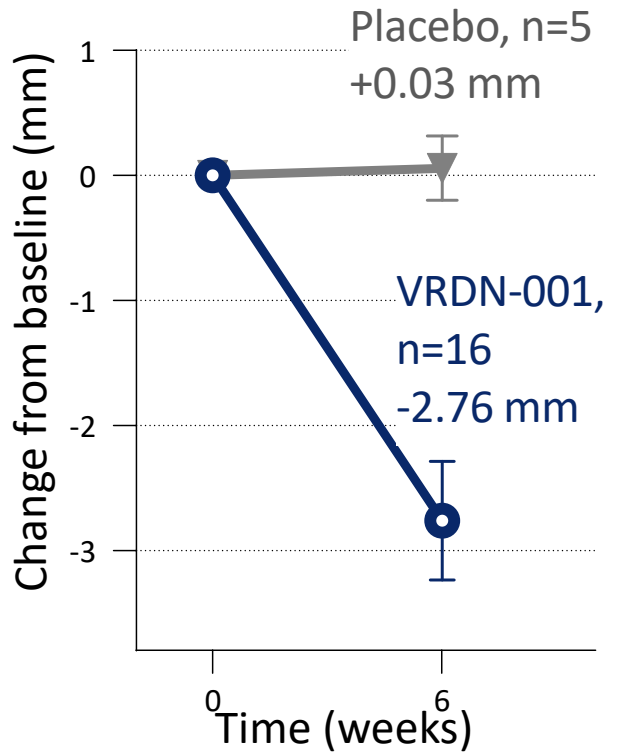


Individual MRI/CT proptosis change (all patients with scans**)



*2 placebo patients and 3 VRDN-001 patients were proptosis responders by Hertel exophthalmometer, but response was not confirmed by MRI/CT.

Mean MRI/CT proptosis change (all patients with scans**)



**Masked, centrally reviewed MRI/CT data were available for 5 of 5 placebo patients and 16 of 21 VRDN-001 patients. All MRI/CT images were reviewed centrally by 2 independent, masked readers.

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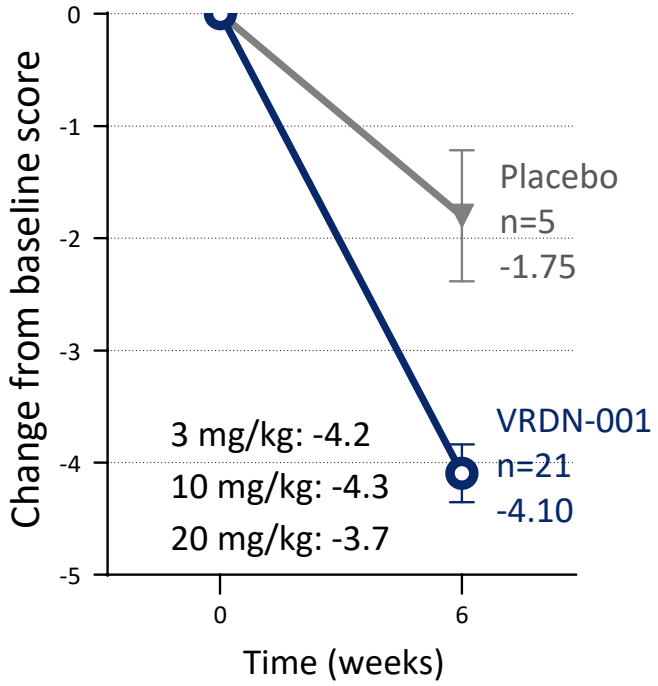
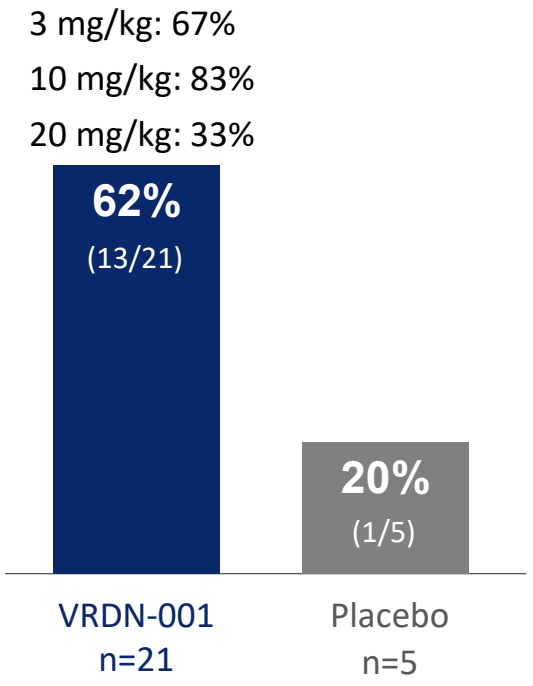
Improvement in CAS

Preliminary data after 2 infusions (6 weeks)

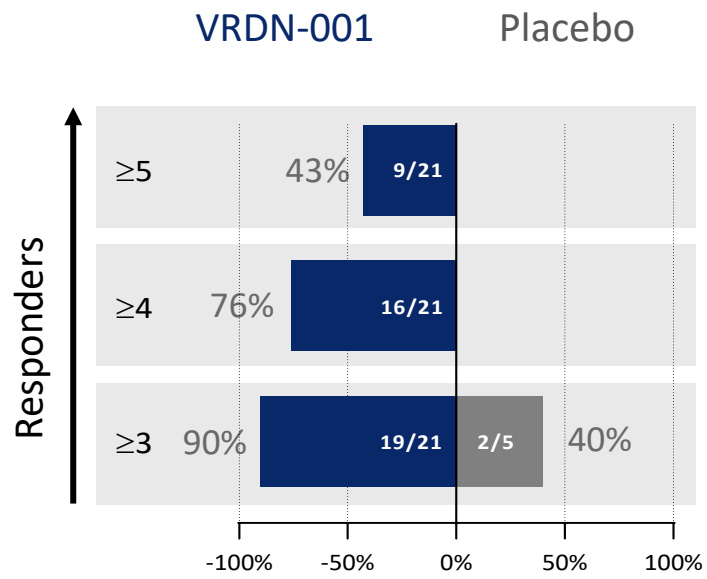
Mean change in CAS (from baseline to Week 6)



CAS of 0 or 1 at Week 6



Reduction in CAS (from baseline to Week 6)



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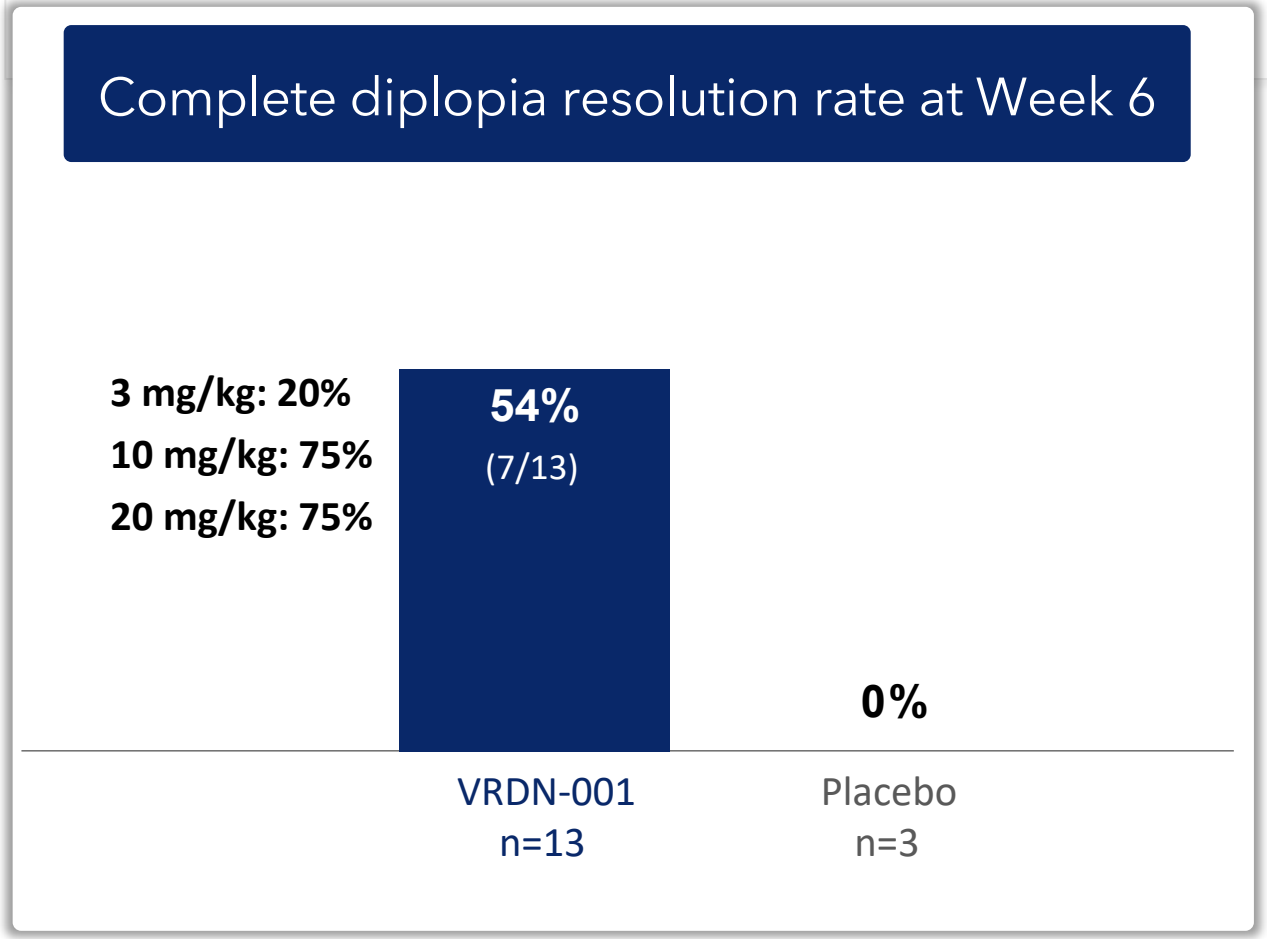
Complete diplopia resolution by Gorman score

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).

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Safety profile

Preliminary data

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

Most AEs were mild and self-limiting

Hyperglycemia events were in known diabetics

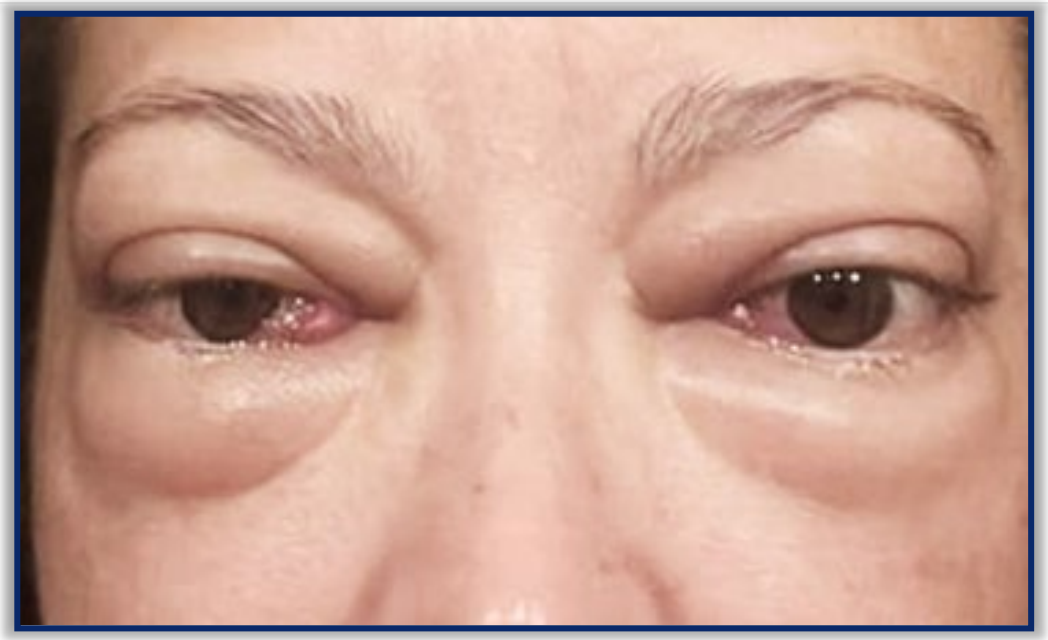
Adverse Reactions	**VRDN-001** 3 mg/kg (n=9), n	**VRDN-001** 10 mg/kg (n=6), n	**VRDN-001** 20 mg/kg (n=6), n	Placebo (n=6), n
Muscle spasms	2	2	2**	-
Nausea	2	-	-	-
Alopecia	-	-	-	1
Diarrhea	1	2**	1*	-
Fatigue	-	1	-	3
Hyperglycemia	1	-	1*	-
Hearing impairment	1	1	-	-
Dysgeusia	-	-	1	-
Headache	2	1	1	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 (n=2) resolved without intervention in both cases.

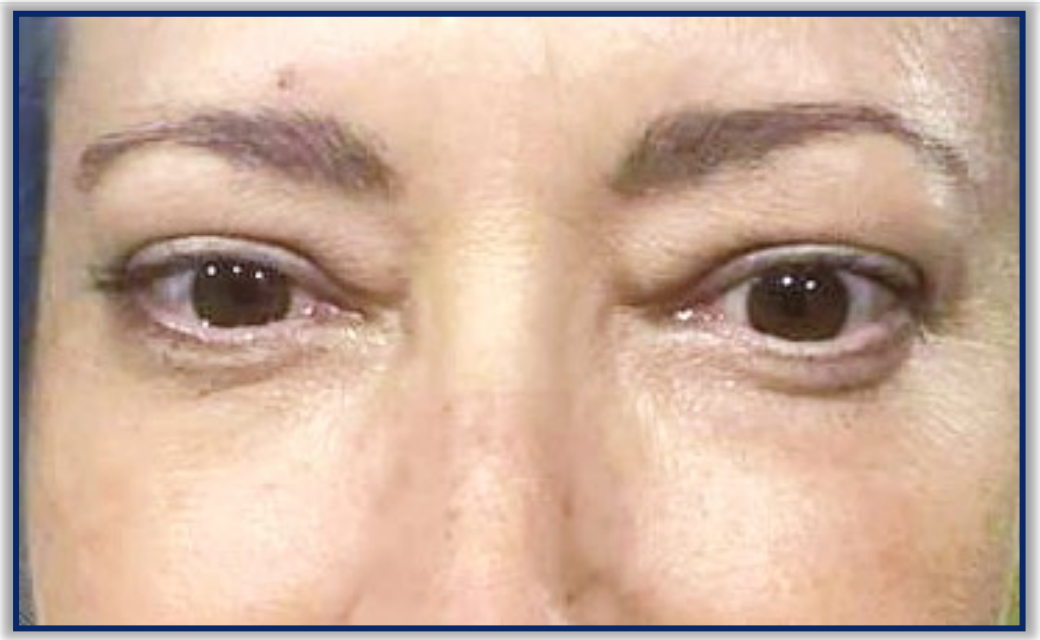
1st patient example

Baseline at Week 0



2 days before first infusion of VRDN-001

Week 6

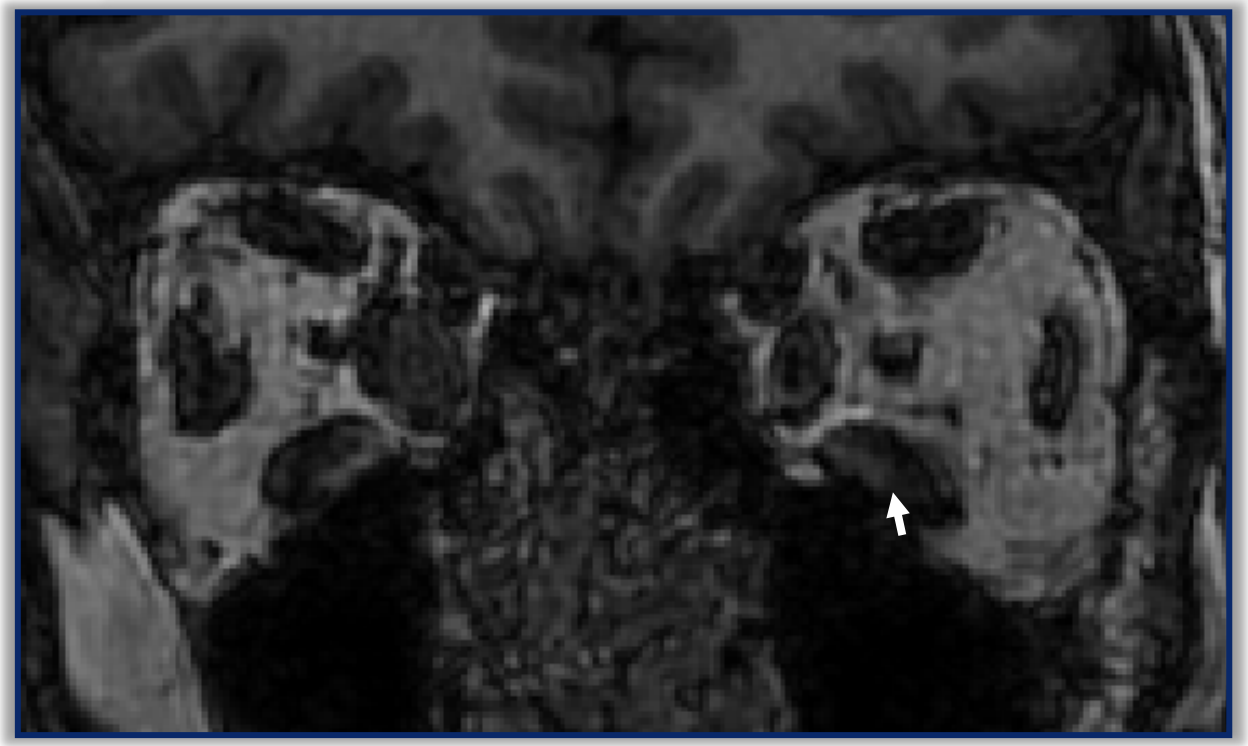


2 days following second infusion of VRDN-001

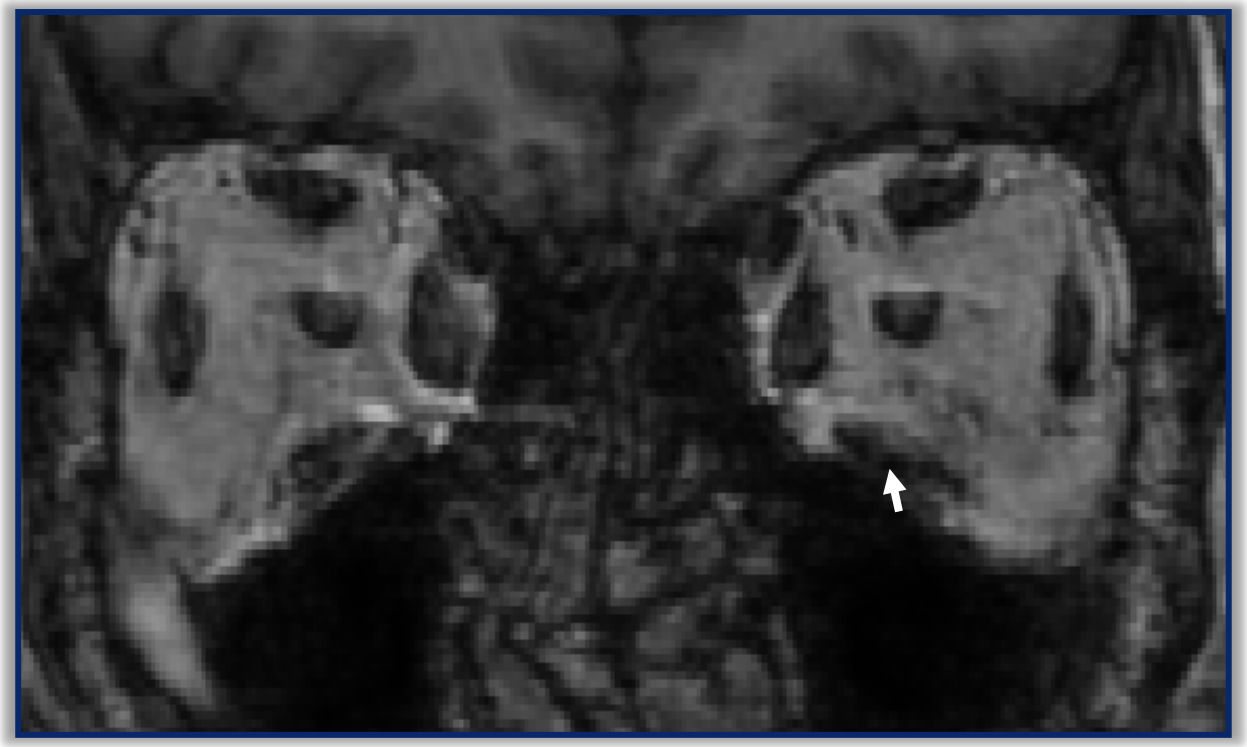
Patient photos taken by patient used with patient and investigator permission. Patient received 2 infusions in the study; in extended follow-up off treatment, TED signs/symptoms have returned for this patient.

2nd patient example

Baseline (Week 0)



After 2 VRDN-001 infusions (Week 6)



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

Update: Chronic TED

VRDN-001 phase 2 POC study in *chronic* TED

Preliminary data

- 12 patients with a mean duration of TED of 7.8 years were treated with 2 infusions of **VRDN-001**
- Outcome measures at 6 weeks demonstrated clinical activity of both 3 and 10 mg/kg doses

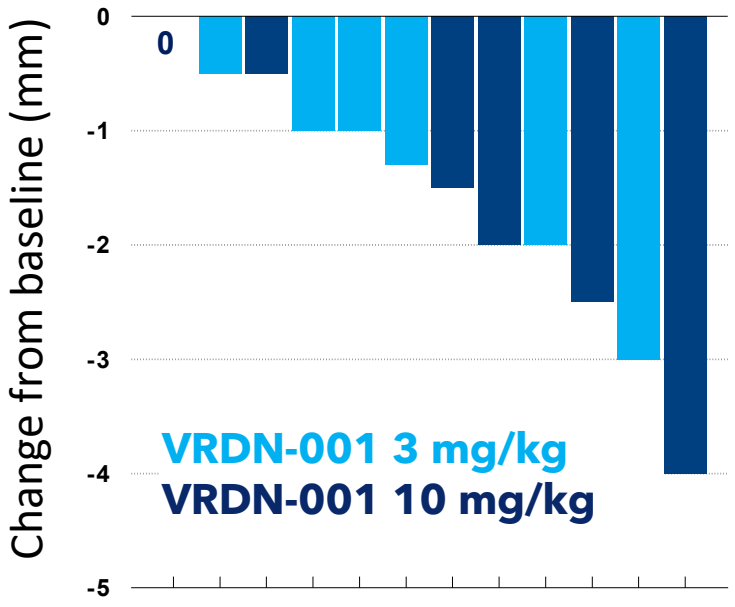
Week 6	Proptosis responder rate	Proptosis mean change by Hertel	Proptosis mean change by MRI/CT*	CAS score of 0 or 1**	CAS mean change**	Diplopia complete resolution***
VRDN-001, n=12	**42%**	**-1.6 mm**	**-2.0 mm**	**40%**	**-2.3**	**0%**
10 mg/kg, n=6	**50%**	**-1.8 mm**	**-1.5 mm**	**50%**	**-2.8**	**0%**
3 mg/kg, n=6	33%	-1.5 mm	-2.6 mm	33%	-2.0	0%

Proptosis responder rate: % of patients with ≥2-mm reduction in proptosis measured by exophthalmometry
Clinical activity score (CAS): a composite 0-7 scale scoring signs and symptoms of TED
*MRI/CT available for 4 of 6 VRDN-001 10 mg/kg treated patients, 4 of 6 VRDN-001 3 mg/kg treated patients,. **2 patients with CAS of 0 at baseline excluded from calculation. ***Includes only patients who had diplopia present at baseline. Diplopia was present at baseline in 5 of 12 VRDN-001 treated patients (mean Gorman score of 2.2); 2 in 3 mg/kg cohort, and 3 in 10 mg/kg cohort.

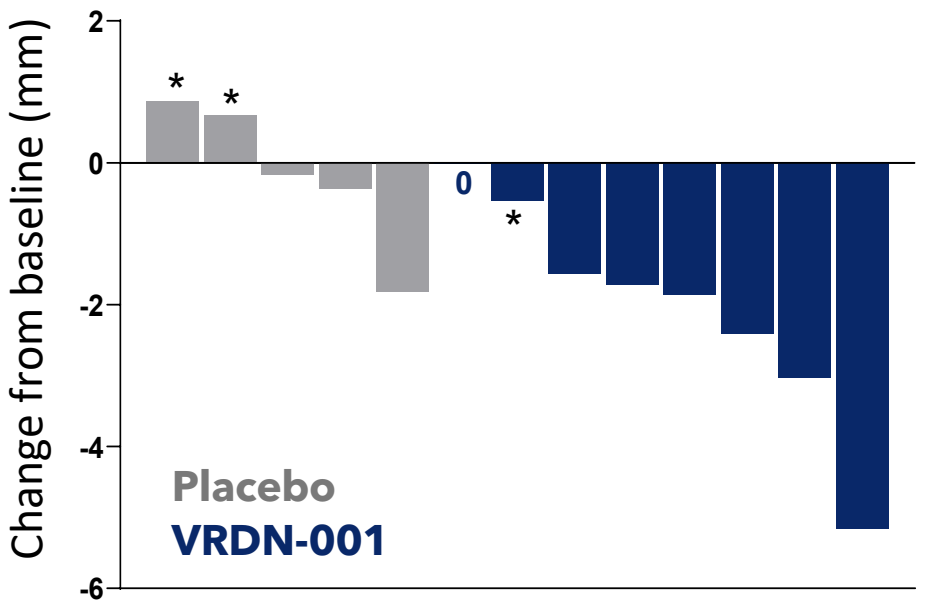
Proptosis reductions by exophthalmometer and MRI/CT

Preliminary data after 2 infusions (6 weeks)

Individual Hertel proptosis change (all VRDN-001 patients)

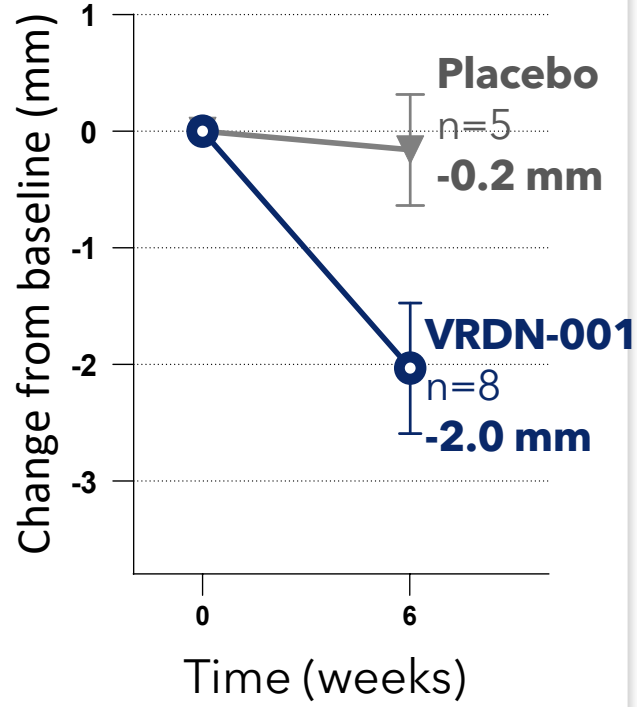


Individual MRI/CT proptosis change (all patients with scans**)



*2 placebo and 1 VRDN-001 treated patients were responders by exophthalmometer, but response was not confirmed by MRI/CT.

Mean MRI/CT proptosis change (all patients with scans**)



**Masked, centrally reviewed MRI/CT data were available for 5 of 5 placebo patients and 8 of 12 VRDN-001 patients. All MRI/CT images were reviewed centrally by 2 independent, masked readers.

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VRDN-001 phase 2 POC study in *chronic* TED

Preliminary data

- **VRDN-001** was well tolerated with a similar safety profile to that observed in active TED
- No serious adverse events (SAEs); no hearing impairment or hyperglycemia events

Adverse events occurring in ≥10% of patients	**VRDN-001** 3 & 10 mg/kg (n=13*)	Placebo (n=5)
Back pain	2 (15%)	0 (0%)
Muscle spasms	2 (15%)	0 (0%)
Headache	1 (8%)	2 (40%)
Ear discomfort	0 (0%)	1 (20%)
Fatigue	0 (0%)	1 (20%)
Flatulence	0 (0%)	1 (20%)
Pruritus	0 (0%)	1 (20%)

Preliminary data are as of data cutoff of May 30, 2023.

*Though not evaluable at Week 6 for clinical activity, the 7th patient randomized in the 3 mg/kg cohort who discontinued the trial prior to Week 6 due to leaving the country for a family emergency was followed for safety until their discontinuation.

Conclusions

- **VRDN-001** shows distinct binding and antagonist properties
- Preliminary results of the phase 2 proof-of-concept studies showed 2 IV infusions of **VRDN-001** were well tolerated and led to meaningful improvements in symptoms of both active and chronic 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
  - Non-responders at week 15 (treated and placebo) will be able to enter a separate phase 3 clinical trial to receive open-label VRDN-001.

Kimberly Cockerham, MD
CockerhamMD@gmail.com
C: 650-804-9270
Sentaclinic.com

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The authors would like to thank the patients who participated in these clinical trials

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