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

Raymond S. Douglas[1], Roger E. Turbin[2], Kimberly Cockerham[3], Navdeep Nijhawan[4], Rosa Tang[5], Michael T. Yen[6], Chantal Boisvert[7], David Kaufman[8], Andrea Kossler[9], Wendy W. Lee[10], Michael Yoon[11], Shoaib Ugradar[12], Vahe Bedian[13], Barrett Katz[13]

1. Cedars-Sinai Medical Center, Los Angeles, CA. **2.** Rutgers New Jersey Medical School, Newark, NJ. **3.** Senta Clinic, San Diego, CA. **4.** Oshawa Clinic, Oshawa, ON, Canada. **5.** Eye Wellness Center-Neuro-Eye Clinical Trials, Inc., Bellaire, TX. **6.** Baylor College of Medicine, Alkek Eye Center, Houston, TX. **7.** Duke Eye Center, Durham, NC. **8.** Michigan State University, East Lansing, MI. **9.** Stanford University Ophthalmology at Byers Eye Institute, Stanford, CA. **10.** Bascom Palmer Eye Institute, Miami, FL. **11.** Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA. **12.** UCLA Stein Eye Institute, Los Angeles, CA. **13.** Viridian Therapeutics, Inc., Waltham, MA.

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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: Raymond S. Douglas is a consultant and clinical research investigator for Horizon Therapeutics and Viridian Therapeutics, Inc.
- Coauthors: Roger E. Turbin, Kimberly Cockerham, Navdeep Nijhawan, Rosa Tang, Michael T. Yen, Chantal Boisvert, David Kaufman, Andrea Kossler, Wendy W. Lee, Michael Yoon, and Shoaib Ugradar 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.
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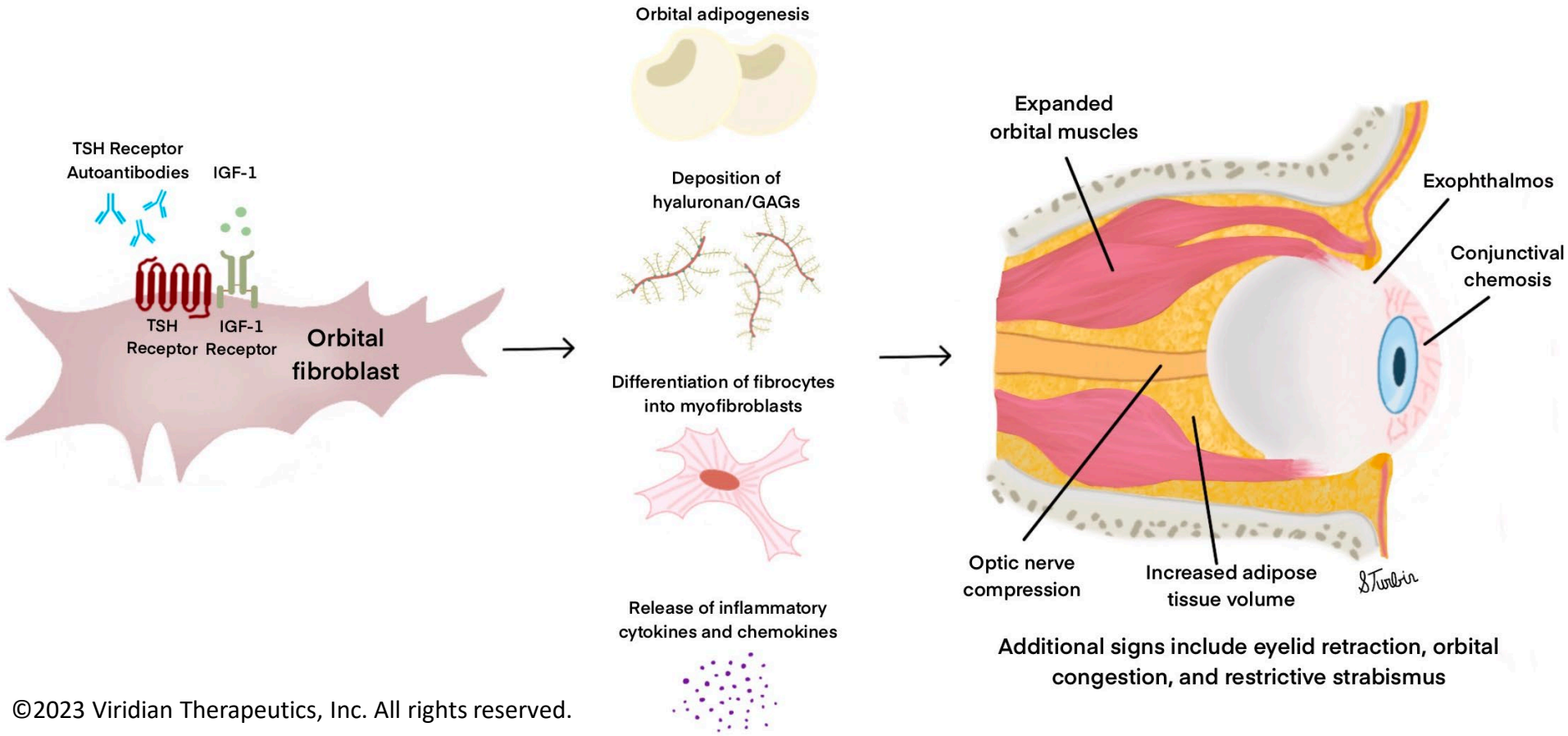
Learning objectives

Better understand:

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

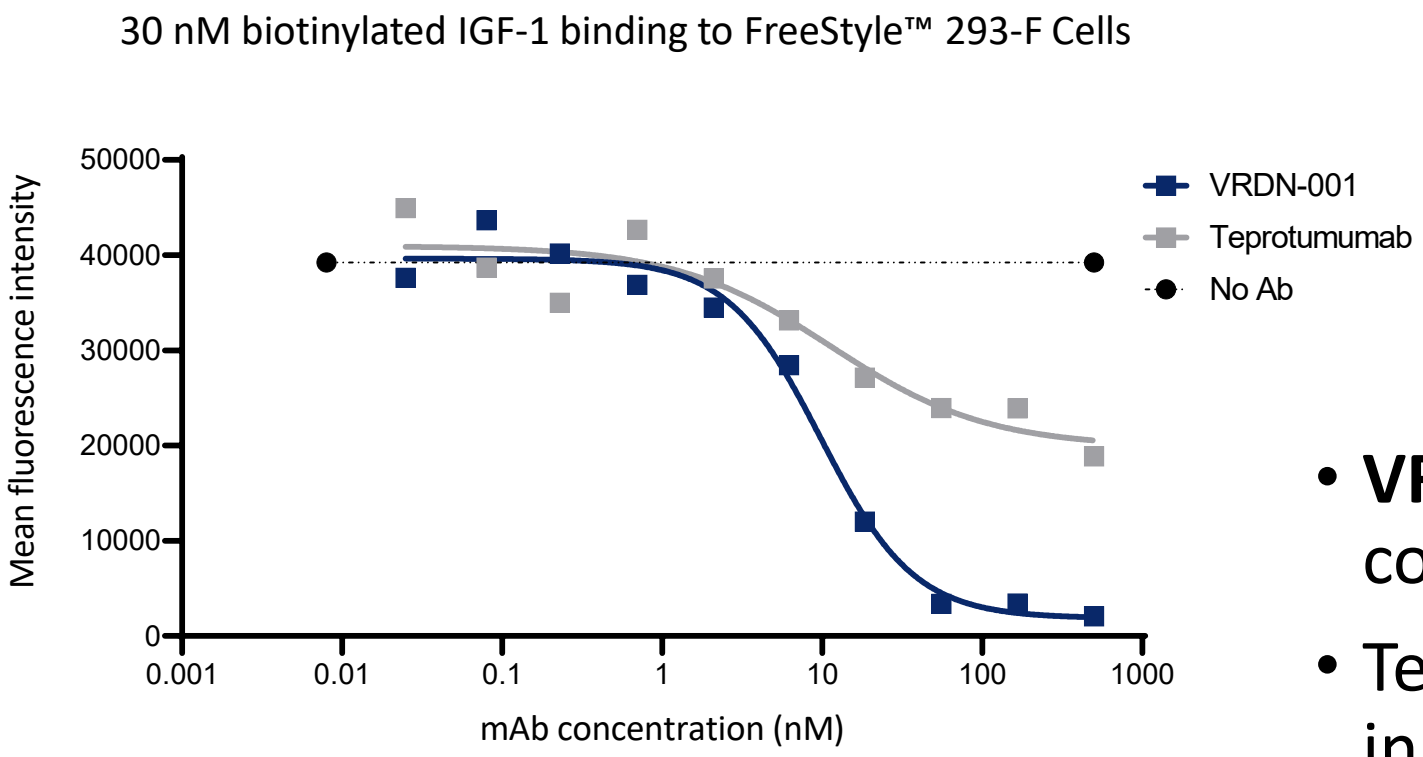
Thyroid eye disease (TED) pathophysiology

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



VRDN-001 preclinical data: distinct binding & antagonist properties

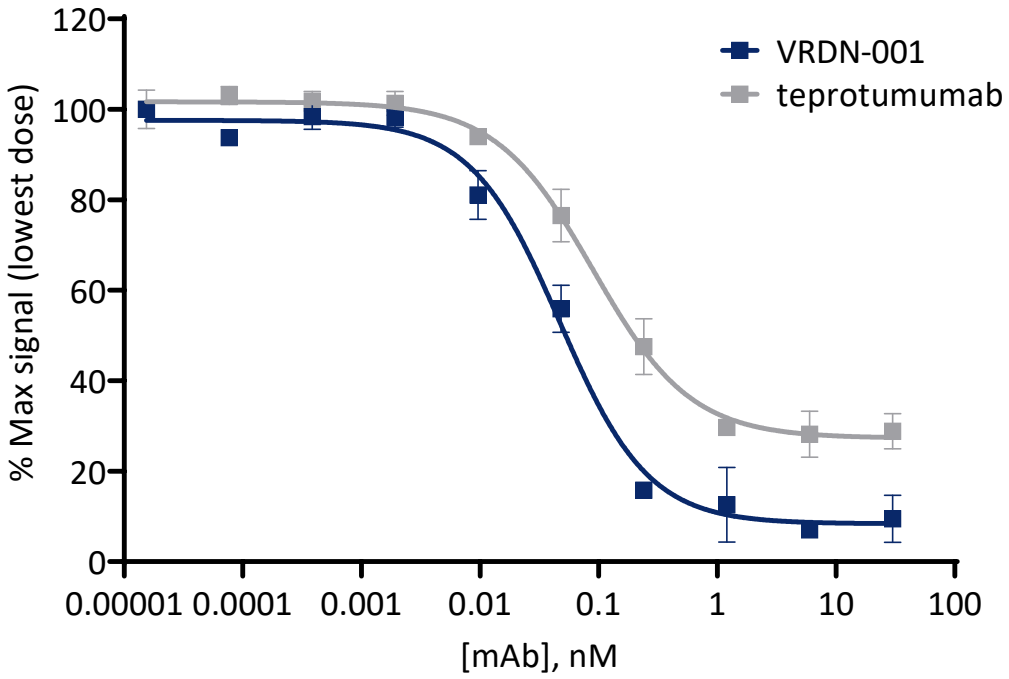
Inhibition of IGF-1 binding to IGF-1 receptor



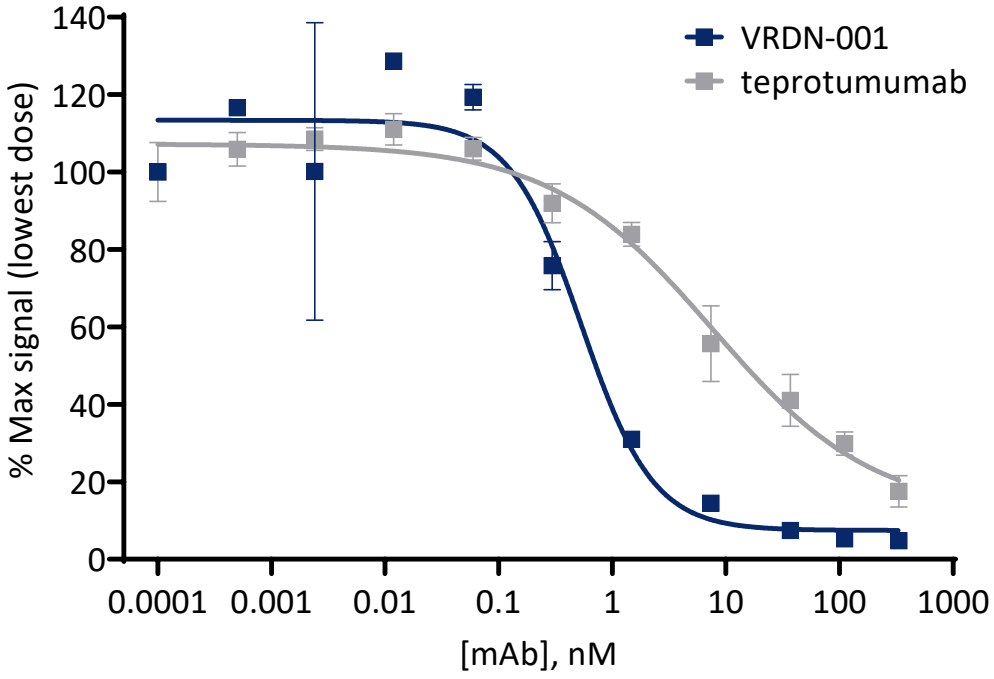
- **VRDN-001** gives near-complete inhibition at ≥50 nM
- Teprotumumab gives partial inhibition, does not exceed ~50% up to 300 nM

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

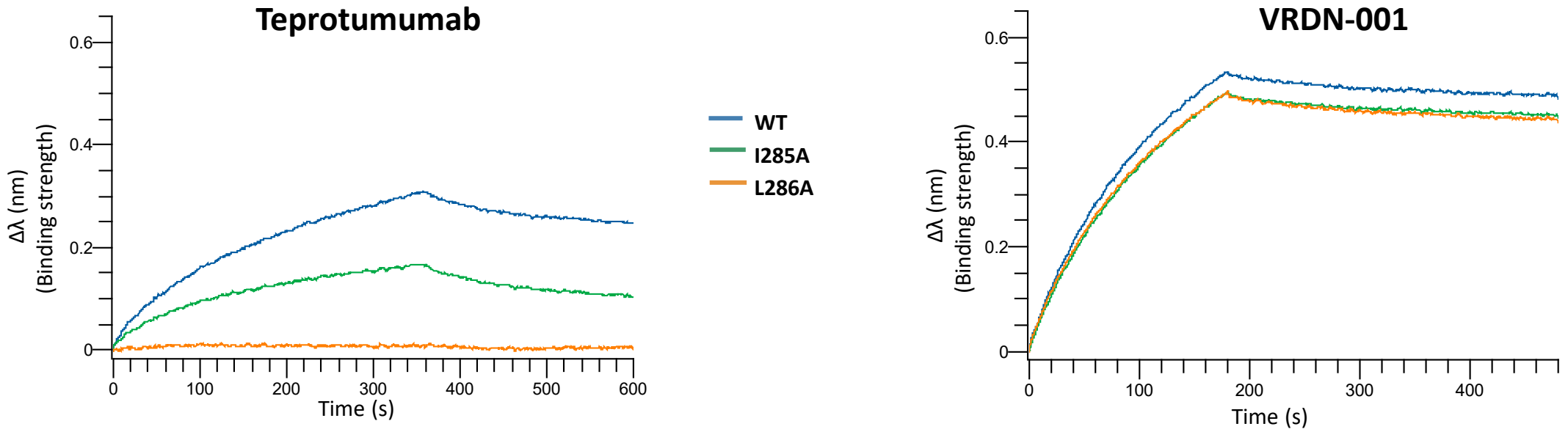
Proximal signaling
(inhibition of IGF-1R phosphorylation)



Distal signaling
(inhibition of AKT phosphorylation)



VRDN-001 and teprotumumab have distinct IGF-1 receptor epitopes



In the presence of IGF-1R mutations (I285A and L286A):

- Teprotumumab binding is reduced or eliminated
- **VRDN-001** binding remains the same

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

Proof-of-concept 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

- 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 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)

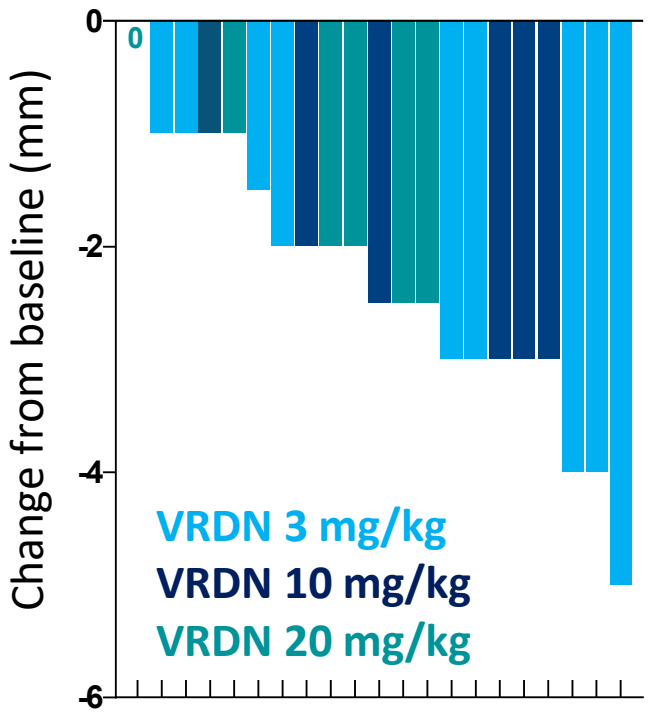
Week 6	Overall responder rate	Proptosis responder rate	Proptosis mean change by Hertel	CAS score of 0 or 1	CAS mean change	Diplopia complete resolution*
All VRDN-001, n=21	**67%**	**71%**	**-2.3 mm**	**62%**	**-4.1**	**54%**
3 mg/kg, n=9	56%	67%	-2.7 mm	67%	-4.2	20%
10 mg/kg, n=6	83%	83%	-2.4 mm	83%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

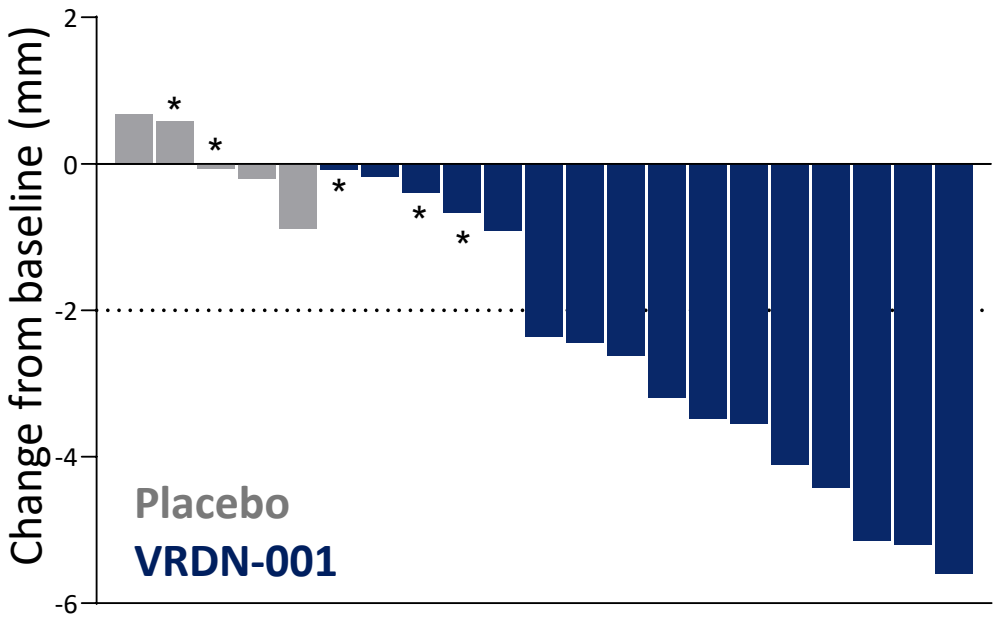
Proptosis reductions by exophthalmometer and MRI/CT

Preliminary data after 2 infusions (6 weeks)

Individual Hertel proptosis change (all VRDN-001 patients)

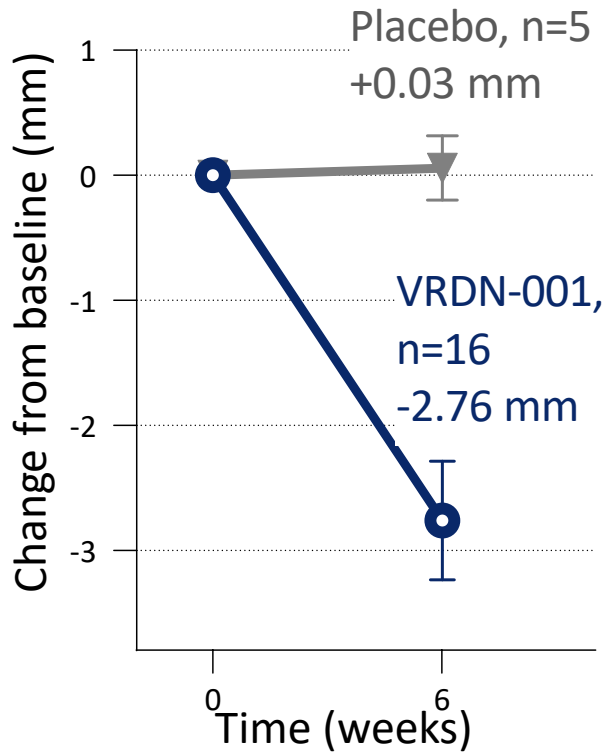


Individual MRI/CT proptosis change (all patients with scans**)



*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**)

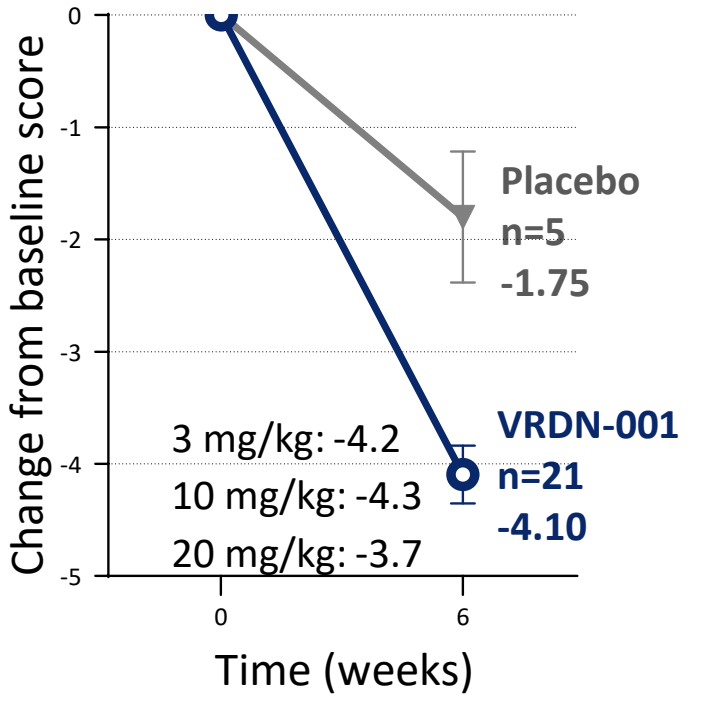


**Masked, centrally reviewed MRI/CT data were available for 5 of 5 placebo patients and 16 of 21 VRDN-001 patients. All MRI/CT images were reviewed centrally by 2 independent, masked readers.

Improvement in CAS

Preliminary data after 2 infusions (6 weeks)

Mean change in CAS (from baseline to Week 6)

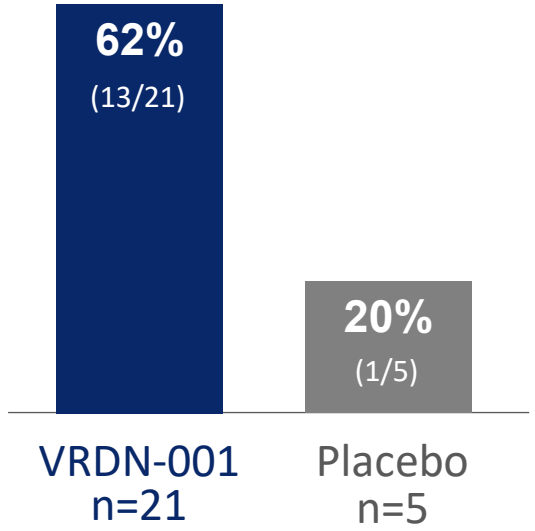


CAS of 0 or 1 at Week 6

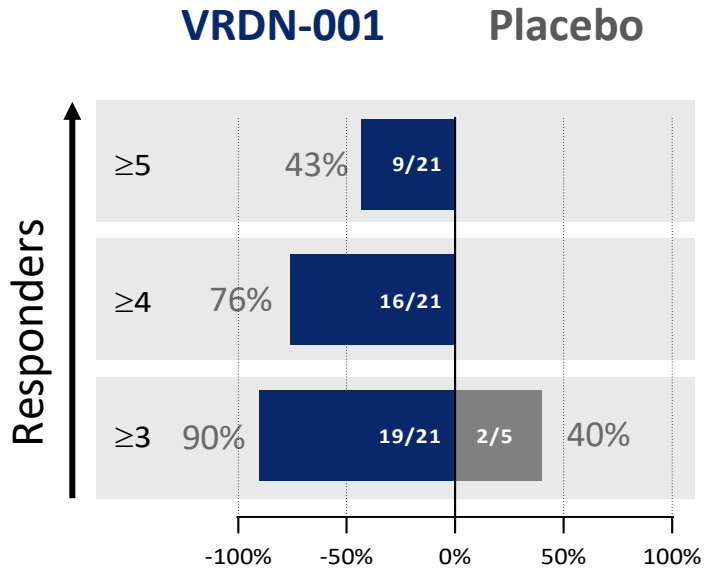
3 mg/kg: 67%

10 mg/kg: 83%

20 mg/kg: 33%

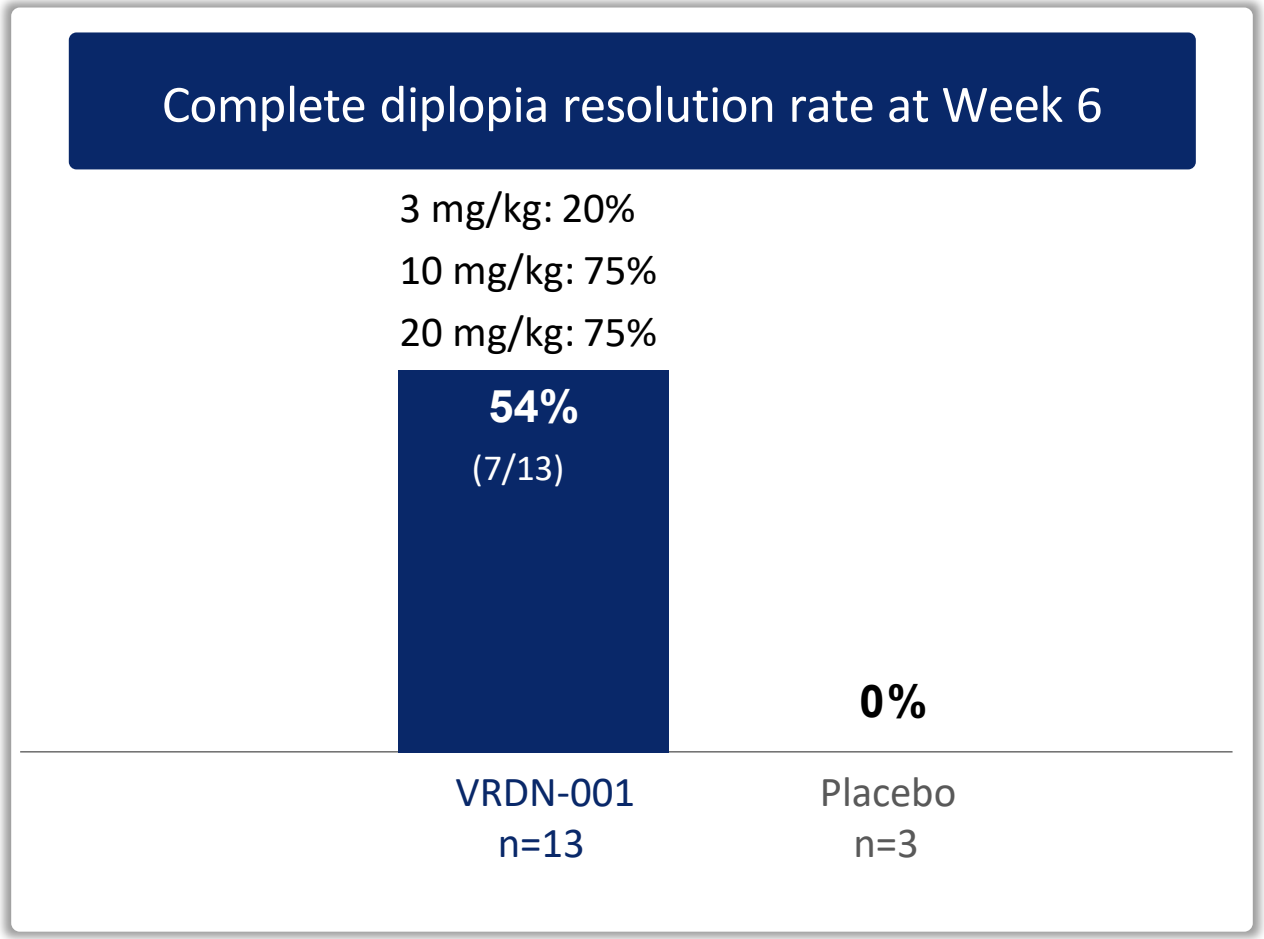


Reduction in CAS (from baseline to Week 6)



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

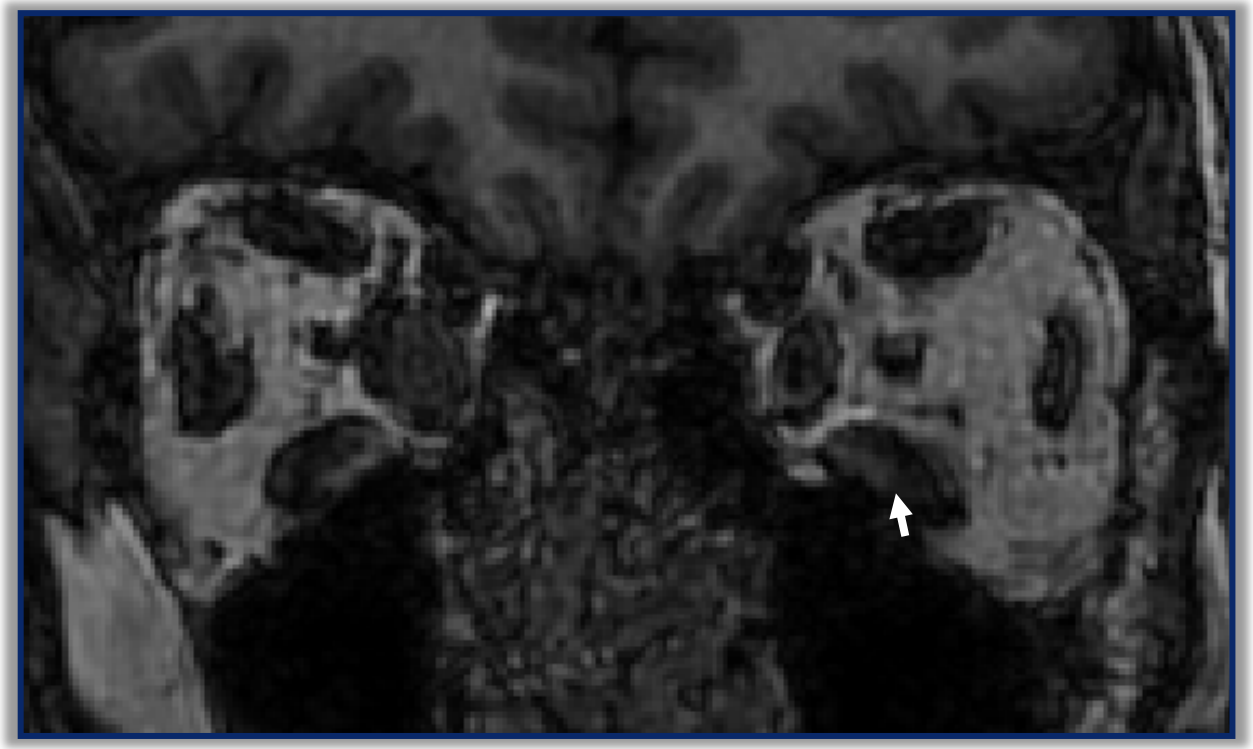
Adverse Reactions	VRDN-001 3 mg/kg (n=9), n	VRDN-001 10 mg/kg (n=6), n	VRDN-001 20 mg/kg (n=6), n	Placebo (n=6), n
Muscle spasms	2	2	2**	-
Nausea	2	-	-	-
Alopecia	-	-	-	1
Diarrhea	1	2**	1*	-
Fatigue	-	1	-	3
Hyperglycemia	1	-	1*	-
Hearing impairment	1	1	-	-
Dysgeusia	-	-	1	-
Headache	2	1	1	2**
Dry skin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

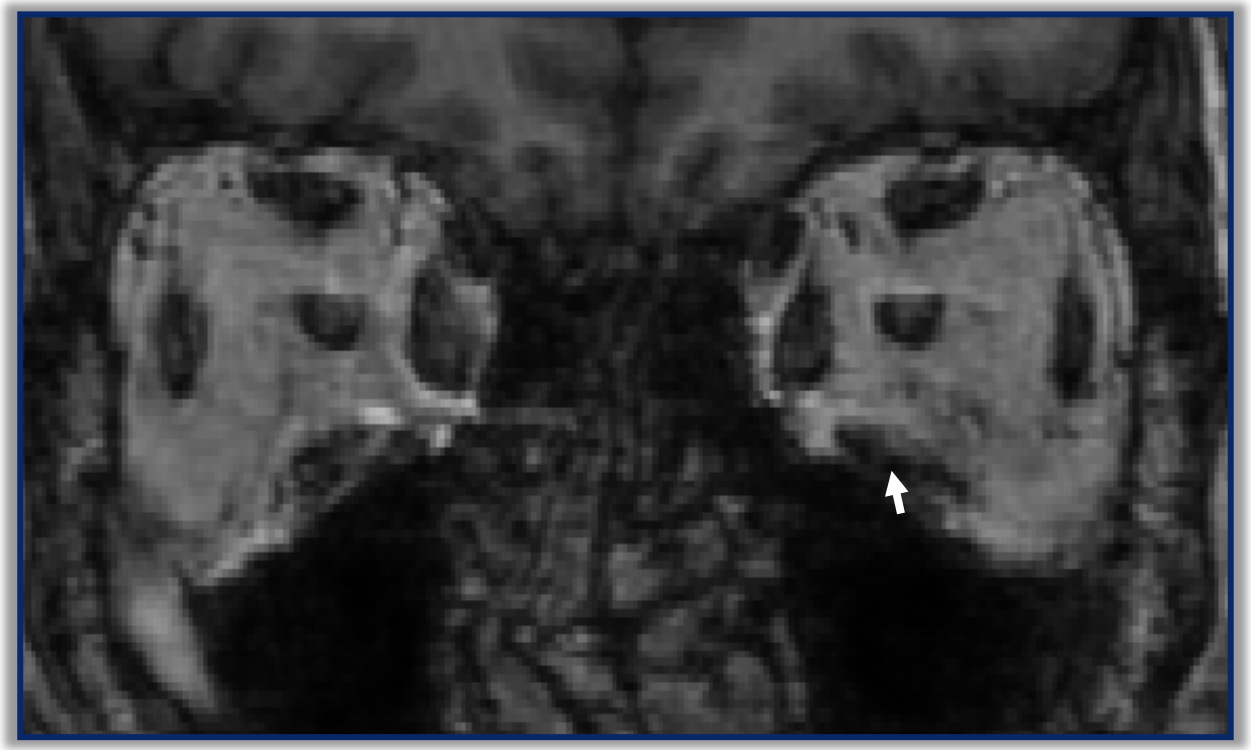
Data are as of data cutoff of December 19, 2022. Other AE that occurred in more than 1 patient and deemed related to study drug by masked investigators was acne (n=2). Instances were mild and did not require intervention. Muscle spasms were mild and did not require intervention; hearing impairment (n=2) resolved without intervention in both cases. 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

Baseline (Week 0)



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



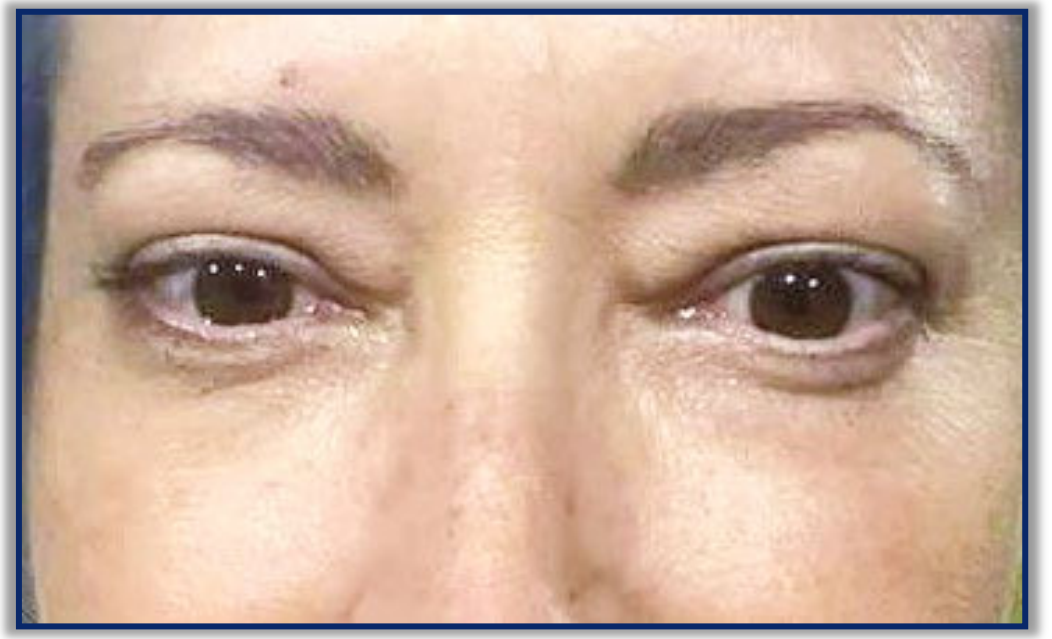
White arrows highlight reduction in size of the inferior rectus muscle.

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.

Update:

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 (3 and 10 mg/kg) 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.

Update:

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

Preliminary data

- **VRDN-001** was generally 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 phase 2 POC results show 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

Thank you!
Questions?

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Raymond S. Douglas
Cedars-Sinai Medical Center, Los Angeles, CA

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