VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor for Thyroid Eye Disease (TED): Phase 1/2 Clinical Study in Patients

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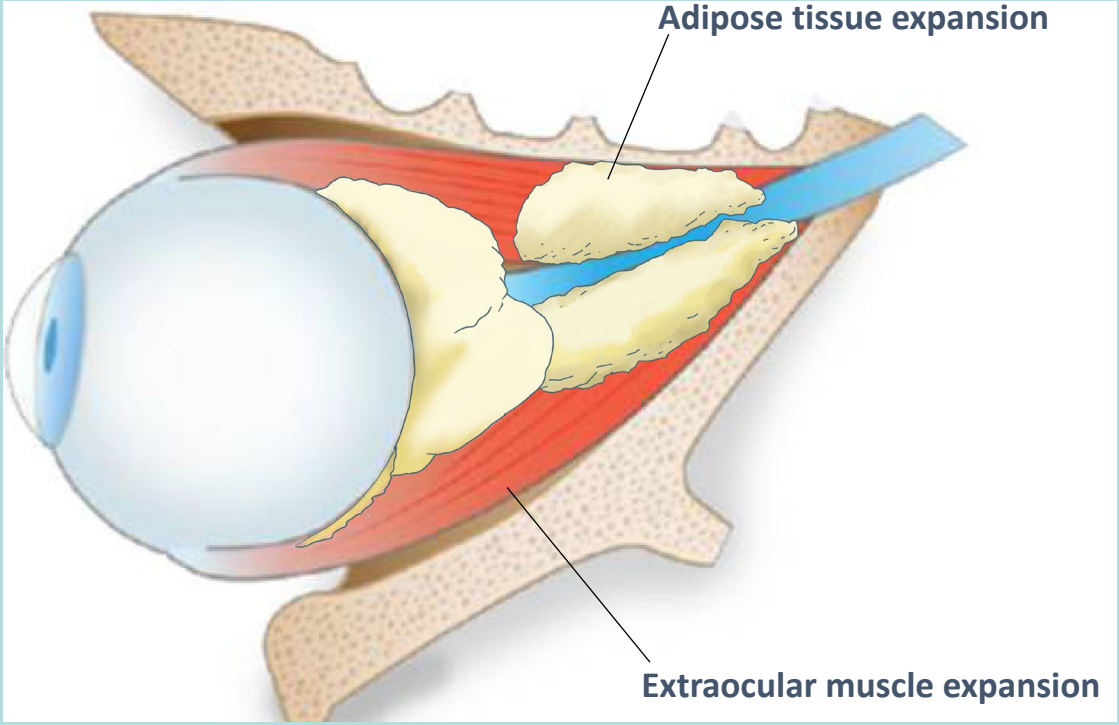
TED: Inflammation, Tissue Expansion, and Remodeling in the Orbit

TED results in inflammation and tissue expansion in the fixed bony orbit. These changes result in short-term and long-term consequences including proptosis and dysmotility.



Medical Treatment of Moderate-to-Severe TED

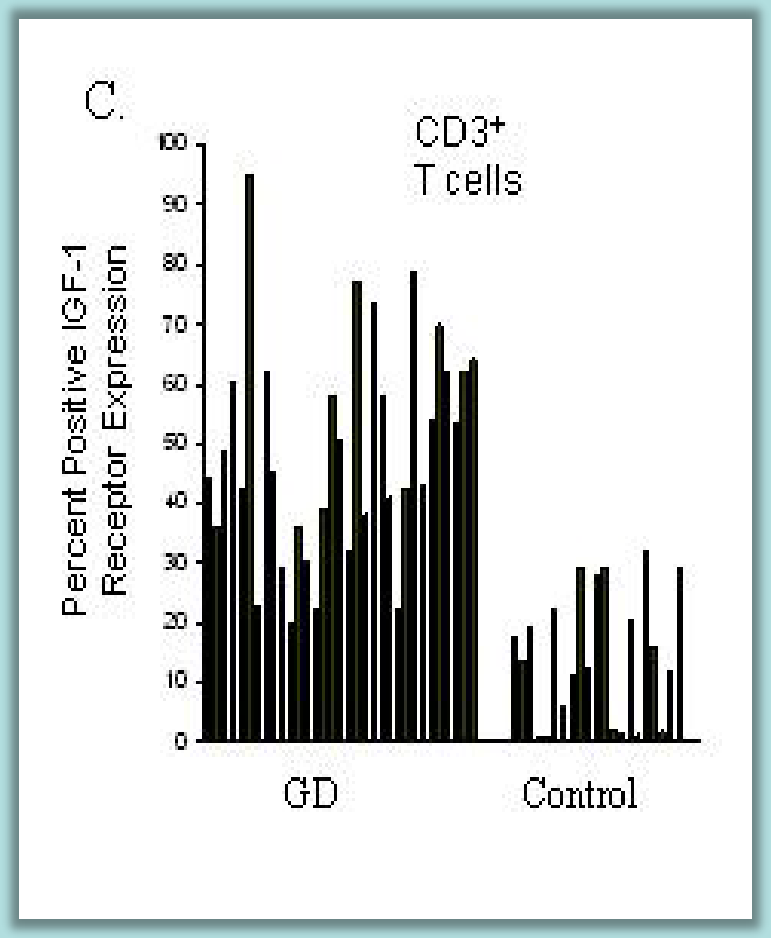
- **Intravenous corticosteroids:** Utilized in TED with inflammatory signs including conjunctival injection, chemosis, eyelid erythema and edema. Does not address proptosis or significant impact on dysmotility.
- **Radiotherapy:** Utilized in conjunction with corticosteroids in some patients with inflammatory signs. Does not reduce proptosis or have significant impact on dysmotility.
- **Teprotumumab:** Preferred treatment, if available, when significant proptosis, dysmotility with or without inflammatory signs.
- **Rituximab and tocilizumab:** May be considered for glucocorticoid-resistant patients but not FDA approved and not widely used.

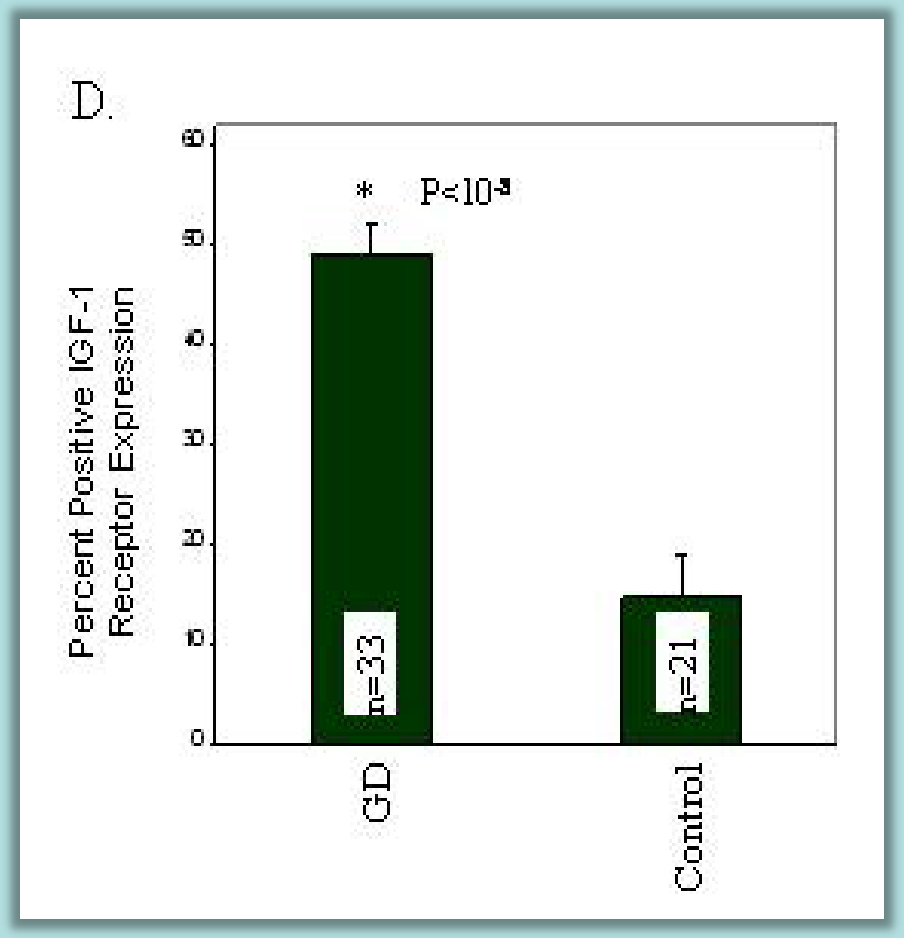
Burch HB, Perros P, Bednarczuk T, Cooper DS, Dolman PJ, Leung AM, Mombaerts I, Salvi M, Stan MN. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid. 2022 Dec;32(12):1439-1470.

Insulin-like Growth Factor-1 Receptor

- Overexpressed on Graves' Disease (GD) fibroblasts
- Signaling of fibroblasts and immune cells mimics pathologic findings
- Antibodies to these receptors in GD patients

IGF-1R Overexpression is a Hallmark of GD





Douglas RS, et al. *J Immunology,* 2007. 178(5):3281-3287.

Antigen Specific (IGF-1R) Therapies for Active and Chronic TED

	Delivery	Phase	Status
Teprotumumab mAb	IV infusion	Approved in US	Approved in US since 2020
VRDN-001 mAb	IV infusion	Phase 3	Positive phase 1/2 data, phase 3 expected in 2024
Linsitinib Small molecule	PO	Phase 2b	Phase 2b data expected in 2023
VRDN-002 mAb	SC	Phase 2	Phase 2 data expected in 2023
Lonigutamab mAb	SC	Phase 1b	Phase 1b data expected in 2023
Teprotumumab mAb	SC	Phase 1	Phase 1 underway
VRDN-003 mAb	SC	Preclinical	Phase 1 data expected in 2023

VRDN-001 Proof-of-Concept Study Tested 3 Different Doses in Active TED

Randomized, Double-Blind Trial vs Placebo

Active TED

- Clinical activity score (CAS) of ≥4
- Onset of symptoms within past 12 months

Cohort 1

VRDN-001 10 mg/kg Q3W x 2 (n=6)

Placebo (n=2)

Cohort 2

VRDN-001 20 mg/kg Q3W x 2 (n=6)

Placebo (n=2)

Cohort 3

VRDN-001 3 mg/kg Q3W x 2 (n=9)

Placebo (n=1)*

*2 patients were randomized to the placebo arm, with 1 patient in the 3 mg/kg cohort's placebo arm discontinuing the study before week 6.
Data contained within presentation are interim data as not all patients have completed the study.

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Baseline Patient Characteristics

	VRDN-001 (3, 10, and 20 mg/kg)	VRDN-001 3 mg/kg	VRDN-001 10 mg/kg	VRDN-001 20 mg/kg	Placebo	Teprotumumab Ph2	Teprotumumab Ph3
n	**21**	9	6	6	5	42	41
Proptosis, mean (SEM)	**23.7 (0.7)**	23.1 (1.2)	24.8 (1.2)	23.6 (1.3)	22.8 (2)	23.4	22.6
CAS, mean (SEM)	**5.4 (0.2)**	5.4 (0.4)	5.2 (0.3)	5.5 (0.4)	5.0 (0.5)	5.1	5.1
Diplopia, n (%)	**13 (62%)**	5 (56%)	4 (67%)	4 (67%)	3 (60%)	38 (90%)	28 (67%)
Diplopia, mean (SEM)	**1.3 (0.3)**	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	1.6 (0.7)	1.8	Not reported
Months since onset of TED signs/symptoms, mean (SEM)	**7.4 (0.8)**	7.7 (1.1)	7.3 (1.7)	6.9 (1.7)	7.0 (2.0)	4.7	6.2
Age, years (SEM)	**47 (3.3)**	51.2 (4.8)	38.7 (5.2)	48.8 (7.0)	44.2 (4.3)	51.6	51.6
Female, n (%)	**19 (90%)**	8 (89%)	4 (67%)	6 (100%)	3 (60%)	28 (65%)	29 (71%)

SEM = Standard error of the mean

Teprotumumab Phase 2 data: Smith TJ, et al, NEJM 376:18, May 2017. Teprotumumab Phase 3 data: Douglas RS, et al, NEJM 382:4, Jan 2020. FDA clinical review of teprotumumab (BLA 761143)

All data regarding teprotumumab in this presentation are from separate teprotumumab studies. Conclusions are not based on head-to-head results.

VRDN-001 Efficacy Measures

Signs — Improvement in proptosis

Symptoms — Improvement in clinical activity score (CAS) and diplopia score

	Overall response: Signs + symptoms (Improvement in proptosis & clinical activity score)	Proptosis: Responder rate (% with ≥2mm reduction from baseline to week 6)	Proptosis: Mean change by exophthalmometry (change from baseline to week 6)	CAS: Score of 0 or 1 (% achieving CAS of 0 or 1 at week 6)	CAS: Mean change (change from baseline to week 6)	Diplopia: Complete resolution* (% improved to a score of 0 at week 6)
VRDN-001 (3, 10 or 20 mg/kg; week 6) n=21	**67%**	**71%**	**-2.3 mm**	**62%**	**-4.1**	**54%**
3 mg/kg n=9 / 10 mg/kg n=6 / 20 mg/kg n=6	56% / **83%** / 67%	67% / **83%** / 67%	-2.7 mm / **-2.4 mm** / -1.7 mm	67% / **83%** / 33%	-4.2 / **-4.3** / -3.7	20% / **75%** / 75%
Teprotumumab (at 10 mg/kg → 20 mg/kg; week 6)	**44%**	**56%**	**-1.9 mm**	**22%**	**-2.1**	**36%**

Clinical Activity Score (CAS) = a composite 0-7 scale scoring signs and symptoms of TED
*Diplopia was present at baseline in 13 out of 21 drug-treated patients; 4 in 10 mg/kg cohort, 4 in 20 mg/kg cohort and 5 in the 3 mg/kg cohort
All data regarding teprotumumab in this presentation are from separate teprotumumab studies. Conclusions are not based on head-to-head results.

Teprotumumab Phase 3 data:
Douglas RS, et al, NEJM 382:4, Jan 2020, Douglas RS, et al, Ophthalmology 129:4, Apr 2022

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Exophthalmometry and MRI Together Provide Robust Assessment of Proptosis

Hertel Exophthalmometer

- Most commonly used
- Successfully used as primary endpoint in prior clinical trials in TED
- THRIVE Phase 3 trial primary endpoint

Magnetic Resonance Imaging

- More precise
- 3D reconstruction algorithm used
- Centrally read by 2 masked reviewers
- Exploratory measure to potentially differentiate overall data findings

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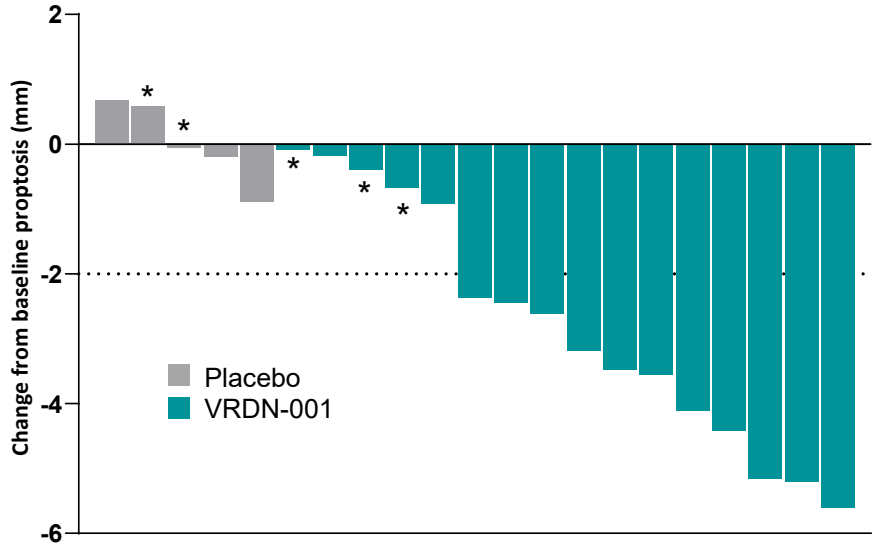
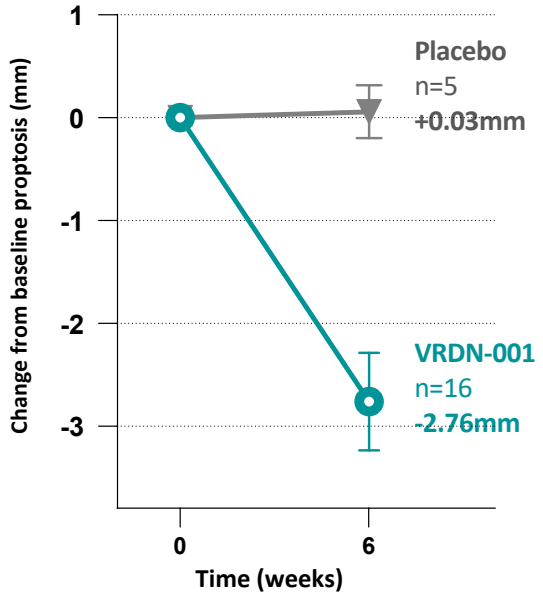
VRDN-001 Proptosis Improvement by Exophthalmometer and MRI

Proptosis change by MRI
(from baseline to week 6)

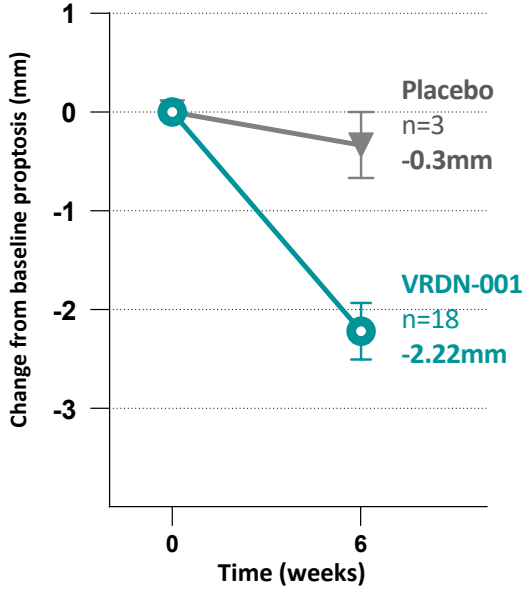


Blinded, centrally reviewed MRI data were available for 5/5 placebo patients and 16/21 VRDN-001 patients. All MRI images were reviewed centrally by 2 independent, blinded readers.
*2 placebo patients and 3 VRDN-001 patients were proptosis responders by exophthalmometer, but response was not confirmed by MRI.

Mean proptosis change
(by MRI)



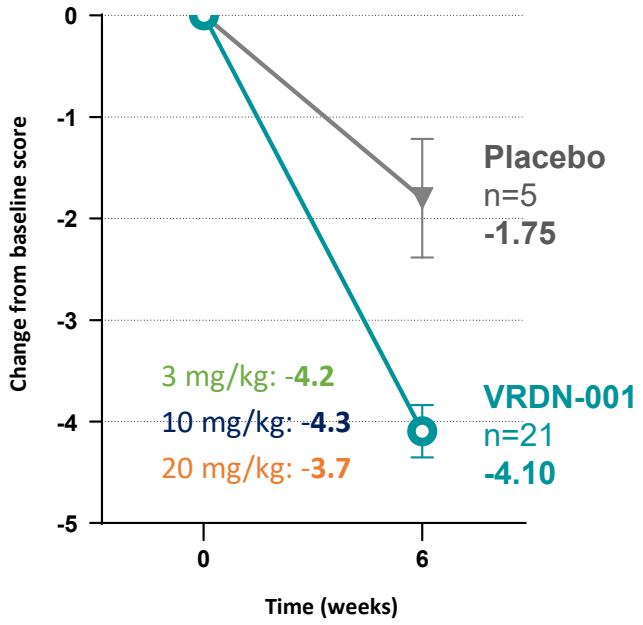
Adj. mean proptosis change
(by exophthalmometer)



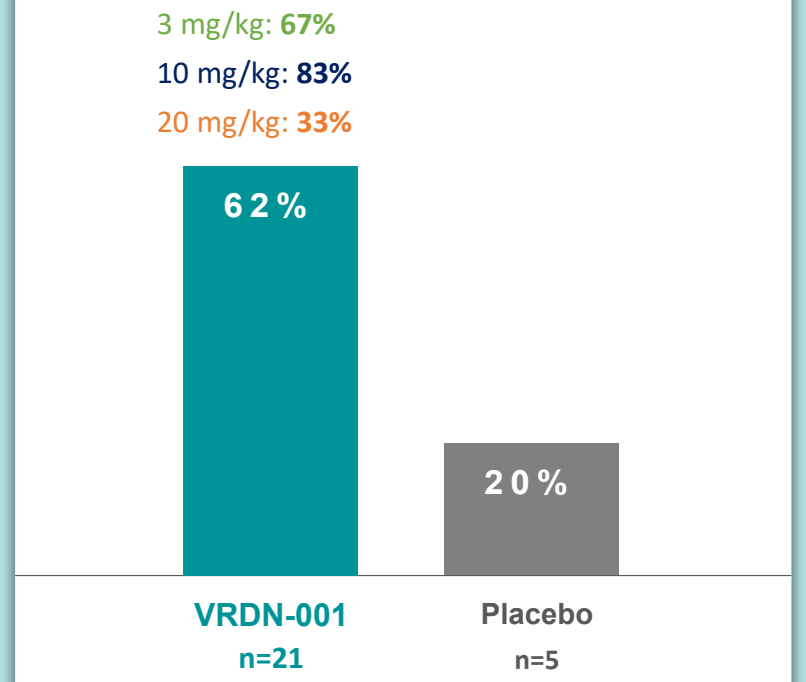
Patients where MRI did not confirm exophthalmometer response were excluded from this analysis.

Improvement in Signs and Symptoms as Measured by CAS

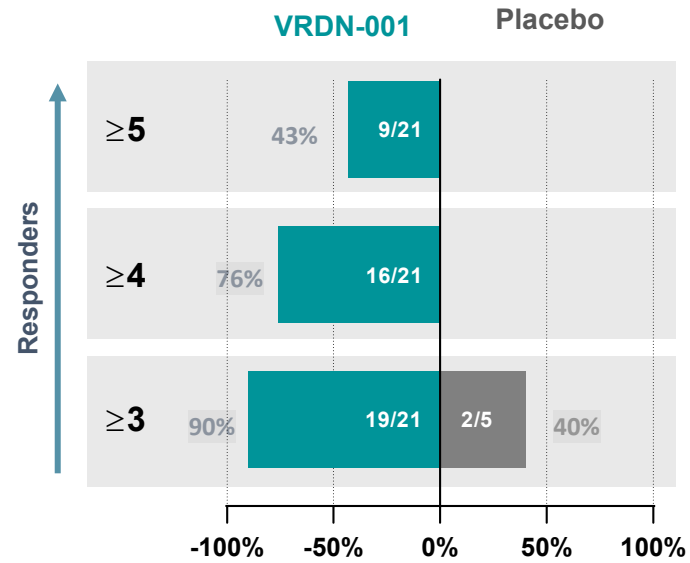
Mean change in CAS
(from baseline to week 6)



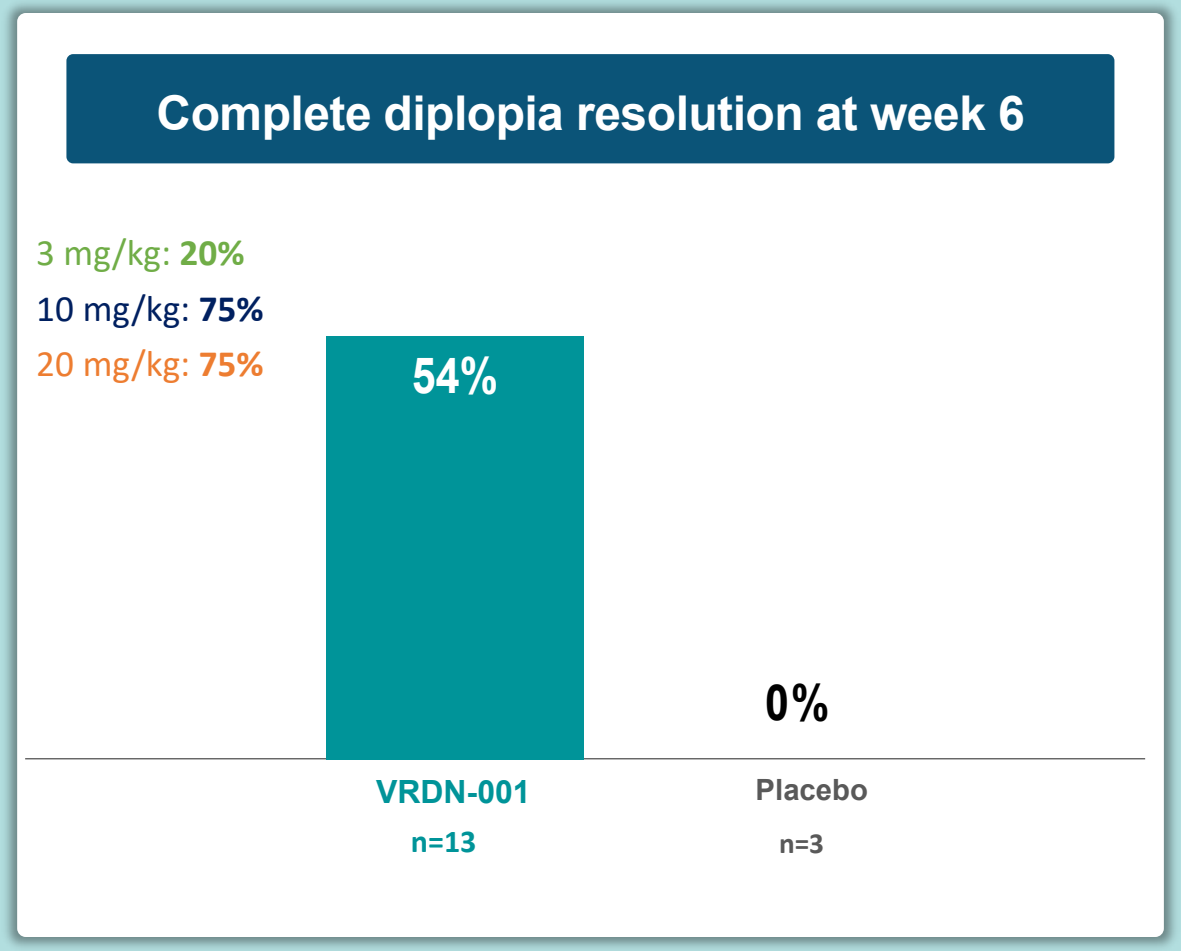
CAS of 0 or 1 at week 6



Reduction in CAS
(from baseline to week 6)



54% of VRDN-001 Patients Had Complete Diplopia Resolution at Week 6



Diplopia resolution rate defined as % of patients with diplopia at baseline that improved to a score of 0

For patients with diplopia at baseline, complete diplopia resolution defined as Gorman subjective diplopia score of zero

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Favorable Safety Profile

No serious adverse events (SAEs), no infusion reactions, and no discontinuations in patients treated with VRDN-001

	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	Teprotumumab label: Teprotumumab (n=84), n (%)	Teprotumumab label: Placebo (n=86), n (%)
Muscle spasms	2	2	2**	-	21 (25%)	6 (7%)
Nausea	2	-	-	-	14 (17%)	8 (9%)
Alopecia	-	-	-	1	11 (13%)	7 (8%)
Diarrhea	1	2**	1*	-	10 (12%)	7 (8%)
Fatigue	-	1	-	3	10 (12%)	6 (7%)
Hyperglycemia	1	-	1*	-	8 (10%)	1 (1%)
Hearing impairment	1	1	-	-	8 (10%)	0 (0%)
Dysgeusia	-	-	1	-	7 (8%)	0 (0%)
Headache	2	1	1	2**	7 (8%)	6 (7%)
Dry skin	1	-	1	-	7 (8%)	0 (0%)
Infusion reactions	-	-	-	-	4%	N/A

*Deemed unrelated to study drug by the masked investigators
** One patient deemed related and one patient deemed unrelated to study drug by the masked investigators

Data are as of data cut-off of December 19, 2022. Other AE that occurred in more than one 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.

All data regarding teprotumumab in this presentation are from separate teprotumumab studies. Conclusions are not based on head-to-head results.

Patient Case Report after 2 Infusions of 3 mg/kg VRND-001

Baseline patient characteristics

- Proptosis: **29 mm**
- CAS: **7**

Photo taken by patient 2 days before first dose of VRDN-001

Following VRDN-001 treatment, at week 6

- Change in proptosis by Hertel: **-5 mm**
- Change in proptosis by MRI: **-5.2 mm**
- Change in CAS: **-6 points**

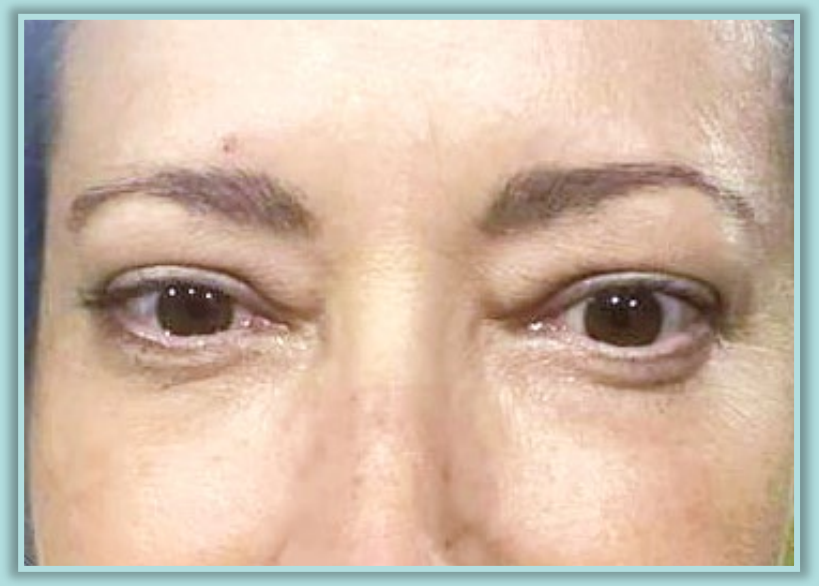

Photo taken by patient 2 days following second dose of VRDN-001

Case report patient information and 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.

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Conclusion

- Based on the results of this phase 2 proof-of-concept study of 3 different doses of VRDN-001, VRDN-001 shows promise for the treatment of TED.
- The efficacy and safety of VRDN-001 for the treatment of TED will be further assessed in the ongoing THRIVE Phase 3 clinical trial (NCT05176639)