

Phase 1/2 Trial of VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor, in Patients with Thyroid Eye Disease (TED)

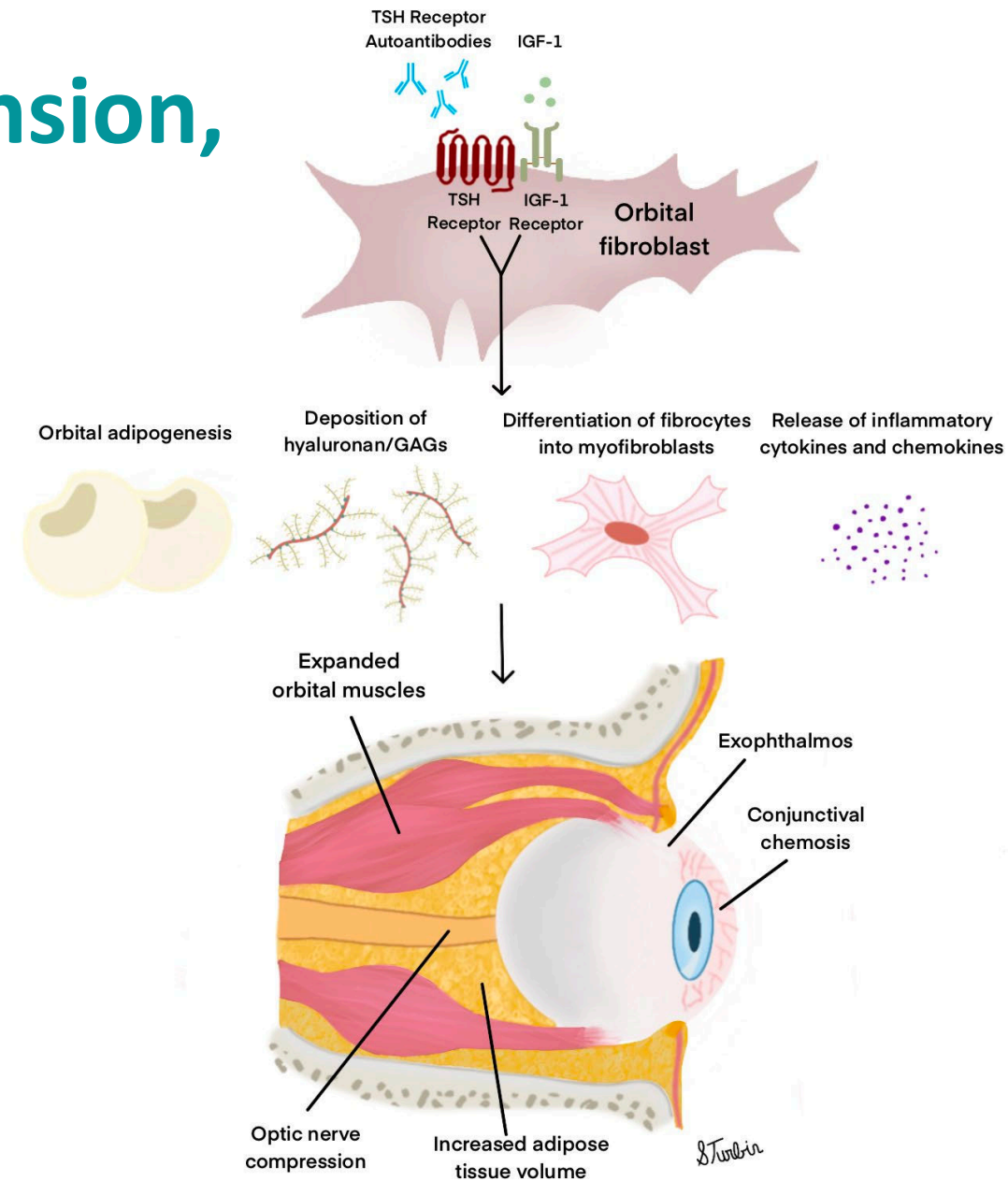
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TED: Inflammation, Tissue Expansion, and Remodeling in the Orbit

- 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.
- Insulin-like growth factor-1 receptor (IGF-1R) antagonism reduces TED-related inflammation and proptosis.
- **VRDN-001**, a full antagonist antibody to the IGF-1R, is under development for the treatment of TED.

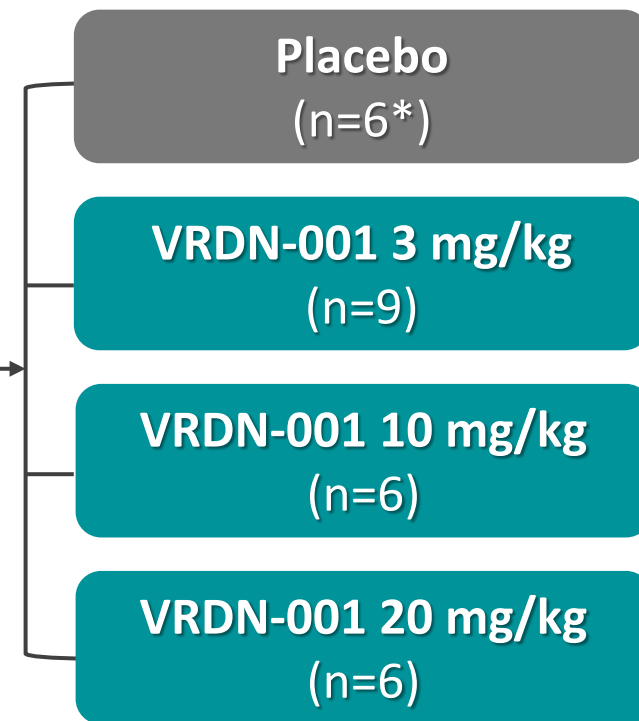


Additional signs include eyelid retraction, orbital congestion, and restrictive strabismus

VRDN-001 Proof-of-Concept Randomized, Double-Masked Trial Tested 3 Different Doses in Patients with Active TED

Patients with active TED:

- Clinical activity score (CAS) of ≥ 4
- Onset of signs/symptoms within prior 12 months



Patients receive 2 infusions
3 weeks apart

*2 patients were randomized to each 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.

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
n	21	9	6	6	5
Proptosis, mean (SEM)	23.7 (0.7)	23.1 (1.2)	24.8 (1.2)	23.6 (1.3)	22.8 (2)
CAS, mean (SEM)	5.4 (0.2)	5.4 (0.4)	5.2 (0.3)	5.5 (0.4)	5.0 (0.5)
Diplopia, n (%)	13 (62%)	5 (56%)	4 (67%)	4 (67%)	3 (60%)
Diplopia, mean (SEM)	1.3 (0.3)	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	1.6 (0.7)
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)
Age, years (SEM)	47 (3.3)	51.2 (4.8)	38.7 (5.2)	48.8 (7.0)	44.2 (4.3)
Female, n (%)	19 (90%)	8 (89%)	4 (67%)	6 (100%)	3 (60%)

SEM = Standard error of the mean

One placebo patient was withdrawn prior to the 6-week visit and thus is not included in the efficacy analysis but is included in the safety analysis.

VRDN-001 Efficacy Measures at 6 Weeks

	Signs Improvement in proptosis			Symptoms Improvement in clinical activity score (CAS) and diplopia score														
	Overall response: Signs + symptoms (% with ≥2-mm reduction in proptosis and ≥2-point reduction on CAS)			Proptosis: Responder rate (% with ≥2-mm 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 / 10 mg/kg / 20 mg/kg n=9 / n=6 / 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%

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 3 mg/kg cohort.

Independent Teprotumumab Phase 3 Study Results at 6 Weeks*

	Signs Improvement in proptosis			Symptoms Improvement in clinical activity score (CAS) and diplopia score		
	Overall response: Signs + symptoms (% with ≥ 2 -mm reduction in proptosis and ≥ 2 -point reduction on CAS)	Proptosis: Responder rate (% with ≥ 2 -mm 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)
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

*All data regarding teprotumumab in this presentation are from separate teprotumumab studies. Conclusions cannot be made without head-to-head study.

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

Exophthalmometry and MRI Together Provide Robust Assessment of Proptosis

Hertel Exophthalmometer

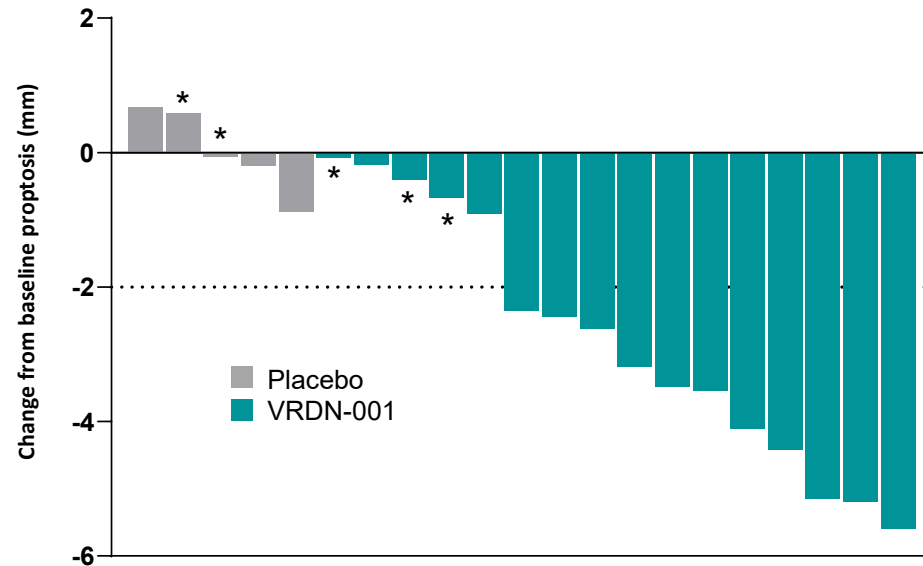
- Most commonly used and FDA-required for clinical studies
- Successfully used as primary endpoint in prior clinical trials in TED
- THRIVE phase 3 trial primary endpoint

Magnetic Resonance Imaging

- More precise
- 3D reconstruction algorithm used
- Read by 2 independent masked reviewers
- Exploratory measure to potentially confirm orbital measurements

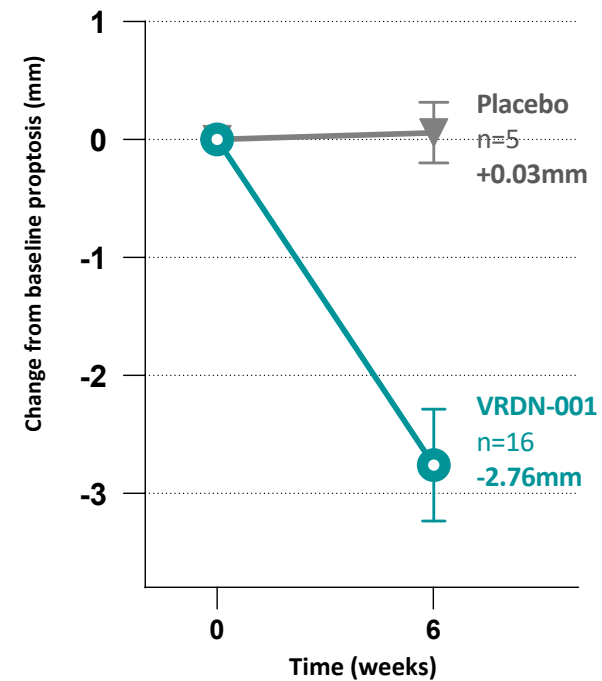
VRDN-001 Proptosis Improvement by Exophthalmometer and MRI

Proptosis change by MRI per patient
(preliminary results from baseline to Week 6)



Masked, 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, masked readers.
*2 placebo patients and 3 VRDN-001 patients were proptosis responders by exophthalmometer, but response was not confirmed by MRI.

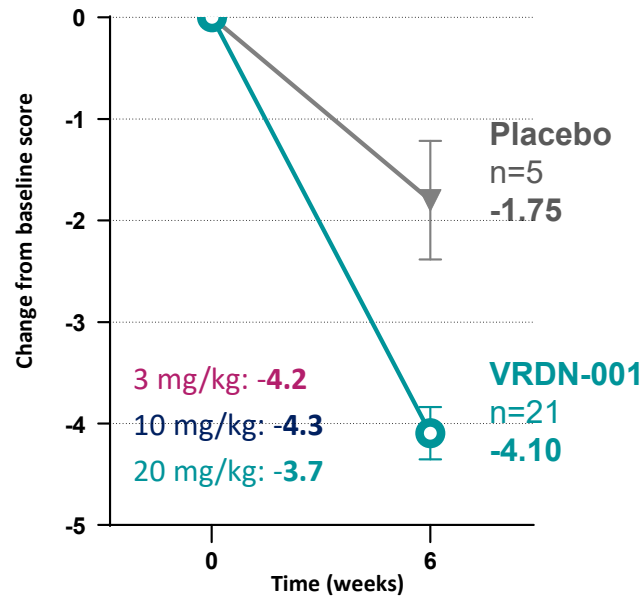
Mean proptosis change
(by MRI, preliminary topline data)



Improvement in Signs and Symptoms as Measured by CAS

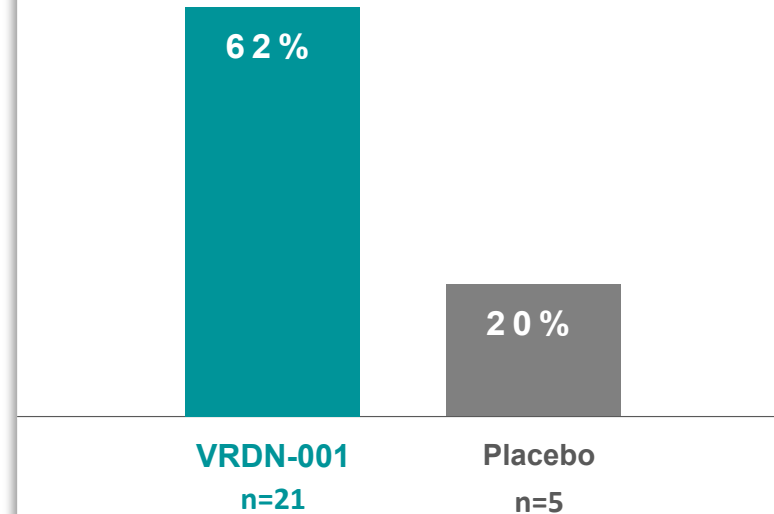
Mean change in CAS

(from baseline to Week 6)



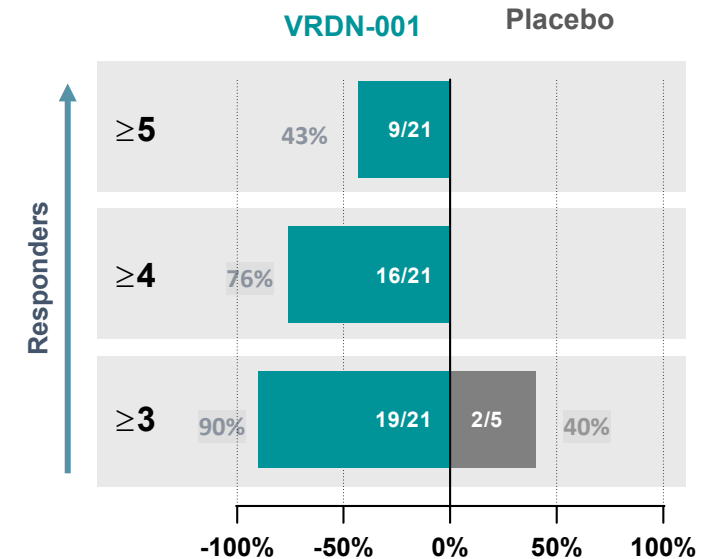
CAS of 0 or 1 at Week 6

3 mg/kg: 67%
10 mg/kg: 83%
20 mg/kg: 33%

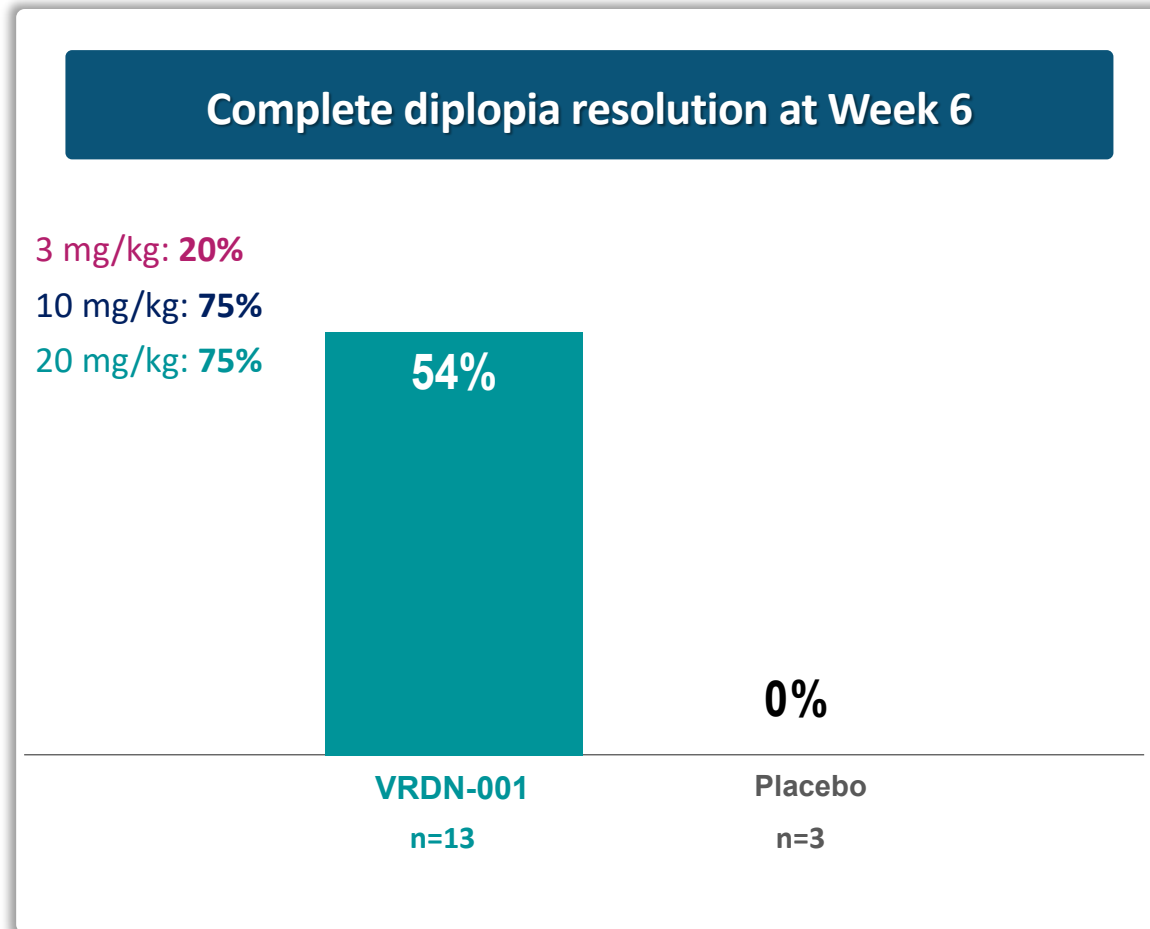


Reduction in CAS

(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 whose diplopia completely resolved

For patients with diplopia at baseline, complete diplopia resolution defined as Gorman subjective diplopia score of 0.

Durability of Response at 12 Weeks for VRDN-001 10 mg/kg Cohort

- 80% (4/5) of **VRDN-001** responders showed durability of effects at 12 weeks.
- Both “overall responders” and “proptosis responders” showed such durability.
- Mean proptosis reduction remained consistent (2.2 mm).
- Preliminary topline MRI analysis confirmed proptosis response in all 4 **VRDN-001** responders for whom scans were available.
- CAS decrease to 0 or 1 was maintained by 80% (4/5).
- Mean reduction in CAS remained consistent (4.2 points).
- Complete diplopia resolution was achieved or maintained for all 4 **VRDN-001** patients who presented with diplopia at baseline.

Safety Profile

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

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	-	-	-	-

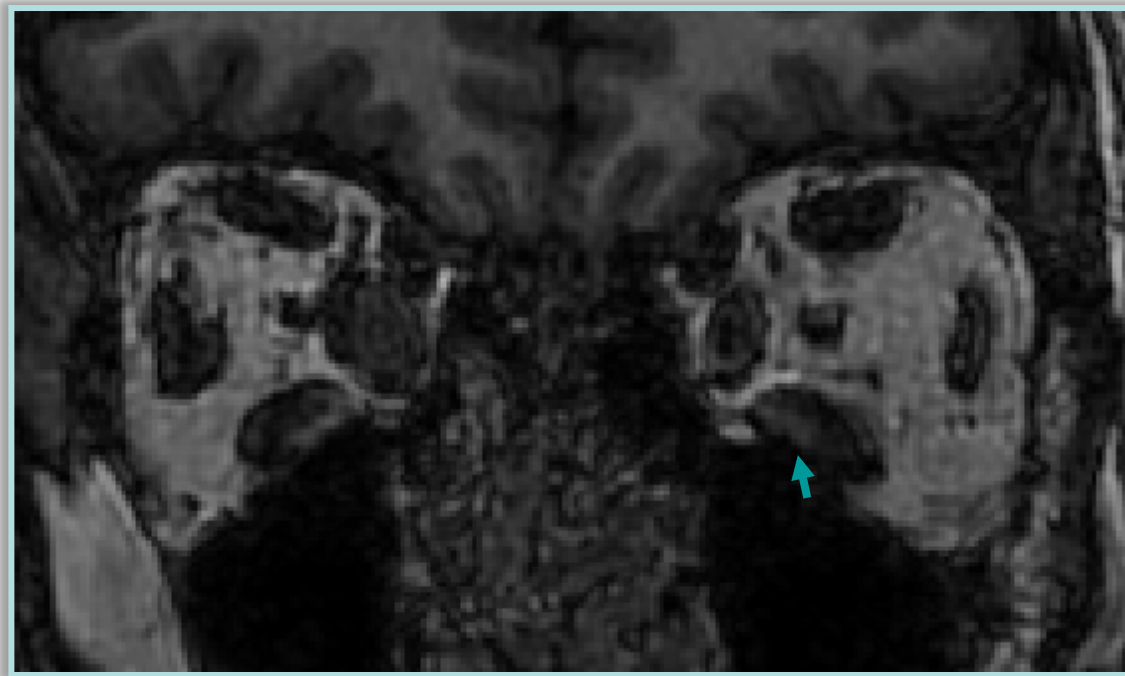
*Deemed unrelated to study drug by the masked investigators

** 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.

Representative Preliminary Observations: Pre/Post Treatment MRI Scans in VRDN-001 Responder

Baseline (Week 0)



After 2 VRDN-001 infusions (Week 6)



Coronal sections of orbital scans from one patient pre/post treatment.
Blue arrows highlight reduction in size of the inferior rectus muscle.

Patient Case Report After 2 Infusions of VRDN-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. Measures shown at baseline and Week 6 are for the study eye. Patient received 2 infusions in the study; in extended follow-up off treatment, TED symptoms have returned for this patient.

Conclusions

- Based on the preliminary results of this phase 2 proof-of-concept study of 3 different doses, **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).