VRDN-001, A Potent and Selective Insulin-Like Growth Factor-1 Receptor (IGF-1R) Antagonist Antibody for Thyroid Eye Disease (TED): Interim Phase 1 Safety and Pharmacodynamic Results in Healthy Volunteers

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Poster #568

KEY TAKEAWAYS

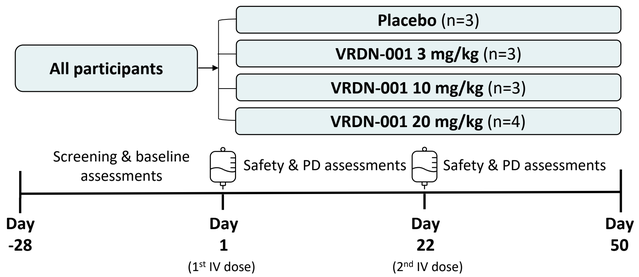
We report an interim analysis of our phase 1/2 clinical trial evaluating **VRDN-001** dosed at 3, 10, and 20 mg/kg in a population of healthy volunteers:

- IGF-1 serum levels increased 5–7-fold from baseline, indicating maximal target engagement at all doses.
- All doses were generally safe and well tolerated, with no cases of hearing impairment or treatment-related hyperglycemia.
- These results suggest a favorable safety profile in a new mAb with high affinity and high potency for IGF-1R blockade.

INTRODUCTION

- **VRDN-001**, a potent and selective antagonist antibody to IGF-1R, is under development for the treatment of TED.
- TED is a debilitating autoimmune disorder associated with orbital inflammation, proptosis, diplopia, and soft tissue changes.[1]
- Clinical and preclinical evidence indicates a central role for IGF-1R antagonism in reducing inflammation and proptosis that occur in TED.[2-4]
- We assessed the PD and safety of **VRDN-001** administered intravenously to healthy volunteers at 3, 10, and 20 mg/kg.

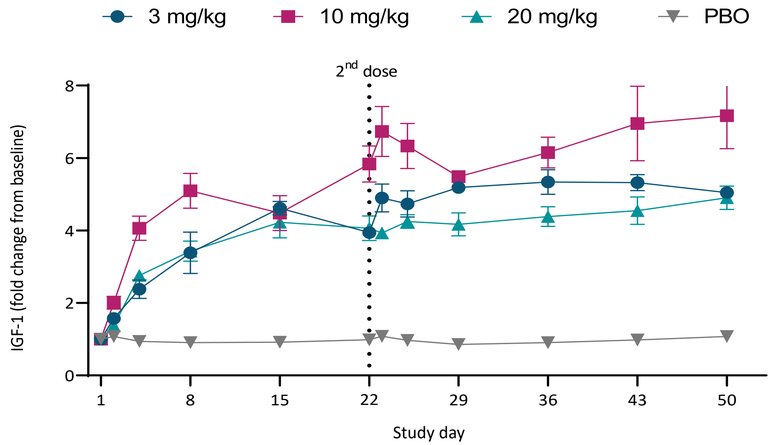
STUDY DESIGN AND PARTICIPANTS



- 13 participants were randomized to treatment and 12 completed the trial; 1 in the 20 mg/kg group withdrew for personal reasons after the first infusion and was followed through Day 35.
- The 13 participants were healthy volunteers, with a mean age of 49 years (range: 25 to 73); 8 were male and 5 were female.

PHARMACODYNAMIC RESPONSE

VRDN-001 increased IGF-1 serum levels in healthy volunteers *(serum IGF-1 is a biomarker for IGF-1R antagonism)*



Data are mean and SEM. Missing baseline samples were normalized to population baseline average. Data from the withdrawn participant (20 mg/kg) are included for the 1st dose.

- Mean IGF-1 levels increased from 74–211 ng/mL at baseline to 472–924 ng/mL after 2 infusions for all **VRDN-001** doses, representing a 5–7-fold increase.
- Increases occurred within a day of the first infusion and were sustained through 50 days.

THERAPEUTIC IMPLICATIONS

- Increased levels of IGF-1 induced by **VRDN-001** in this cohort are consistent with the 6-fold IGF-1 increases induced by VRDN-001 in oncology patients[5] and indicate maximal target engagement, even at the lowest dose.
- The robust in vivo PD response observed with **VRDN-001** is consistent with in vitro data demonstrating that **VRDN-001** more completely inhibits ligand binding to IGF-1R and more completely antagonizes IGF-1R signaling than is seen with teprotumumab (see Poster #132).

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- In a small cohort of TED patients, rapid and clinically meaningful improvement was seen in resolution of proptosis, inflammation, and diplopia at 6 weeks, following only 2 infusions of 10 mg/kg **VRDN-001** (see Poster #535).

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SAFETY RESULTS

Previously reported AEs from IGF-1R blockade	Placebo (n=3)	VRDN-001 3 mg/kg (n=3)	VRDN-001 10 mg/kg (n=3)	VRDN-001 20 mg/kg (n=4)
Muscle spasms	1	0	0	0
Headache	0	2[a]	0	0
Nausea	0	1	0	0
Hyperglycemia	0	0	1[a]	0
Fatigue	0	0	0	0
Hypotension	0	0	1	0
Hypertension	0	1[a]	0	1[a]
Alopecia	0	0	0	0
Diarrhea	0	0	0	0
Hearing impairment	0	0	0	0
Dry skin	0	0	0	0
Dysgeusia	0	0	0	0
Infusion reactions	0	0	0	0

[a] Deemed unrelated to treatment by the masked investigator.

- 11 of the 13 participants had a total of 19 treatment emergent AEs (16 mild and 3 moderate).
- The only AEs deemed treatment related by the masked investigator were muscle spasms (placebo group) and transient hypotension (10 mg/kg group).
- No serious AEs, treatment related hyperglycemia, hearing impairment, or infusion reactions were observed.

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References: **1.** Bahn RS. *NEJM*; 362(8):726–738 (2015); **2.** Pritchard J et al. *J Immunol*; 170:6348–6354 (2003); **3.** Krieger CC et al. *J Clin Endocrinol Metabolism;* 100:1071–1077 (2015). **4.** Smith TJ et al. *NEJM*; 376:1748–1761 (2017); **5.** Soria et al. *Eur J Cancer*; 49:1799–1807 (2013).

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Abbreviations used in poster: mAB, monoclonal antibody; PD, pharmacodynamic; SEM, standard error of mean; AE, adverse event.

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