Design and Preclinical Characterization of VRDN-003, a Next Generation, Half-life Extended Antibody to IGF-1R in Development for Thyroid Eye Disease (TED)

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Poster #4044 - B0361

KEY TAKEAWAYS

- Results from in vitro assays demonstrate VRDN-001 and **VRDN-003** provide indistinguishable and near-complete inhibition of IGF-1 binding and IGF-1R signaling.
- Prior studies with VRDN-001 have shown robust increases in IGF-1 levels in healthy volunteers and patients with TED as well as rapid, marked improvements in TED symptoms in a small cohort of TED patients (ARVO oral #5432).
- Given that VRDN-001 and **VRDN-003** antagonist properties are the same, **VRDN-003** should achieve similar in vivo pharmacodynamics and efficacy.

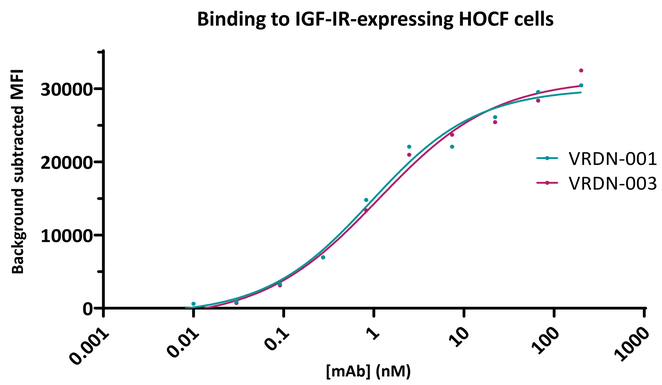
INTRODUCTION

- Clinical and preclinical studies have confirmed IGF-1R antagonism can reduce the inflammation and proptosis that occur in TED.[1-3]
- VRDN-001, a full antagonist antibody to IGF-1R with subnanomolar affinity, is under development for the treatment of TED.
- **VRDN-003** is a next-generation, half-life extended version of VRDN-001 designed to optimize subcutaneous administration via a self-administered pen.
- Given that **VRDN-003** is identical to VRDN-001 except for the half-life extension modification, we assessed whether they have the same in vitro antagonist characteristics.

METHODS

- **Antibody binding to IGF-1R:** Antibody binding to endogenously expressed cell surface IGF-1R was characterized in human ocular choroid fibroblasts (HOCFs).
- **Inhibition of ligand binding:** Dose responses of inhibition of biotinylated IGF-1 binding to IGF-1R-expressing FreeStyle™ 293-F cells were assessed by flow cytometry.
- **Antagonist properties:** Dose responses of inhibition of IGF-1R and AKT phosphorylation (endpoints of IGF-1-mediated signaling) were assessed in HOCFs.
- Representative experiments are shown for each endpoint.

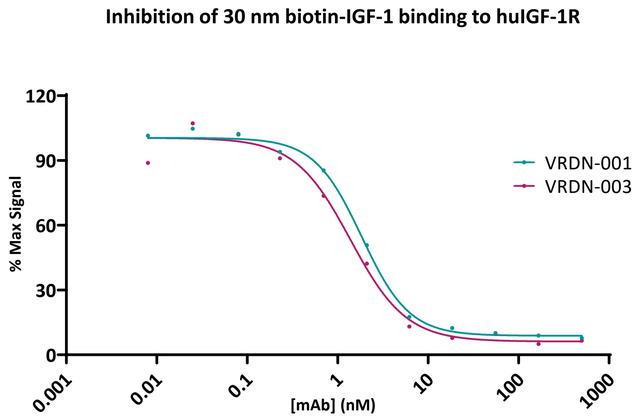
ANTIBODY BINDING TO IGF-IR



Methods: HOCF cells in logarithmic growth phase were blocked with an anti-human FcγR, incubated with unlabeled anti-IGF-1R antibody titration at 4°C. Bound antibody was detected with a Fab anti-human IgG, Fcγ AF488 secondary antibody.

- **VRDN-003** bound HOCF cells with high affinity similar to VRDN-001.
- Average EC50 across 3 independent experiments was 2.41 nM (range: 1.31-3.62 nM).

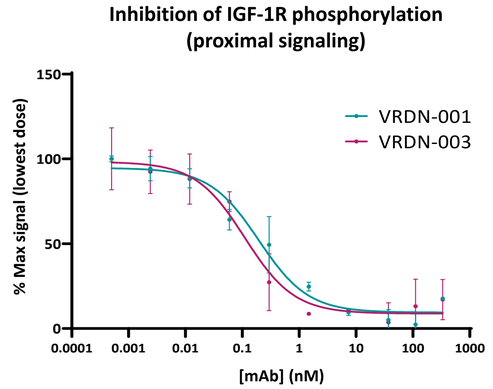
ANTIBODY INHIBITION OF LIGAND BINDING TO IGF-1R



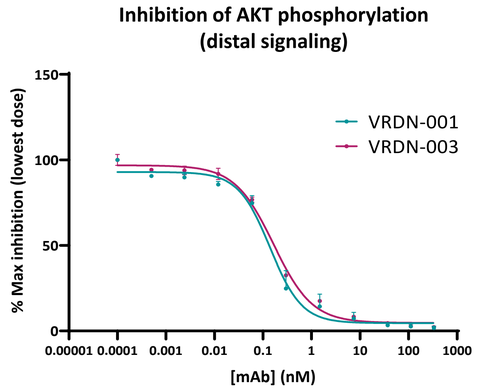
Methods: FreeStyle™ 293-F cells preincubated with antibody on ice. Incubation with 30 nM biotin-IGF-1; detection with streptavidin-APC.

- At concentrations ≥50 nM, **VRDN-003** provided near-complete inhibition of IGF-1 binding (>95%), almost identical to VRDN-001.

ANTIBODY ANTAGONISM OF IGF-1R SIGNALING



Methods: Serum-starved HOCF cells preincubated with antibody titration, then stimulated with 26 nM IGF-1 for 10 min. Phospho-IGF-1R was measured in cell lysates using an ELISA from R&D Systems.



Methods: Serum-starved HOCF cells preincubated with antibody titration, then stimulated with 23.5 nM IGF-1 for 40 minutes. Phospho-AKT was measured in cell lysates using an ECL immunoassay from Mesoscale Discovery.

- **VRDN-003** provided near-complete inhibition of IGF-1-induced phosphorylation of IGF-1R and phosphorylation of AKT, with results almost identical to VRDN-001.
- IC50 range was 0.1–0.2 nM.
- These results indicate that the half-life extension modifications did not impact pharmacology of the variable domains.

THERAPEUTIC IMPLICATIONS

- The similar antagonism characteristics for **VRDN-003** vs VRDN-001 shown here suggest **VRDN-003** should show similar clinical effect to that observed in the VRDN-001 phase 2 proof-of-concept study in patients with active TED (ARVO oral #5432).

Oral #5432

- **VRDN-003** pharmacodynamic parameters observed in cynomolgus monkeys demonstrated **VRDN-003** half-life was twice as long as VRDN-001 half-life (ARVO poster #4043), reinforcing its potential for subcutaneous self-administration.

Poster #4043

Disclosures: This study was sponsored by Viridian Therapeutics. VRDN-001 and VRDN-003 are investigational treatments not approved for any use in any country. Formatting and editorial assistance were provided by Nathalie Smith and funded by Viridian Therapeutics. All authors met the ICMJE authorship criteria and had full access to relevant data. All authors are employees of Viridian Therapeutics. The authors would like to thank the study investigators, research teams, and the study participants who make this research possible.

References: 1. Pritchard J et al. *J* Immunol; 170:6348–6354 (2003); **2.** Krieger CC et al. *J Clin Endocrinol Metab;* 100:1071–1077 (2015); **3.** Smith TJ et al. *NEJM;* 376:1748–1761 (2017).

PDF of poster and additional information: Scan QR code.

Abbreviations used in poster: HOCF, human ocular choroid fibroblast; Ab, antibody; mAb, monoclonal antibody; MFI, mean fluorescence intensity; ECL, electrochemiluminescence; APC, allophycocyanin.

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Poster #4044