Antagonist Properties of VRDN-003, a Next-Generation, Half-life Extended Antibody to IGF-1 Receptor for Thyroid Eye Disease (TED)

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#PO363

Disclosures

- These studies were sponsored by Viridian Therapeutics, Inc. All data are proprietary.
- VRDN-001 and **VRDN-003** are investigational therapies not approved in any country. All authors met the ICMJE authorship criteria and had full access to relevant data.
- Rachel Newell, Yang Zhao, Tyler Swanson, Thomas Ciulla, and Vahe Bedian are employees of Viridian Therapeutics, Inc.
- The authors would like to thank the study investigators and research teams who make this research possible.

Background

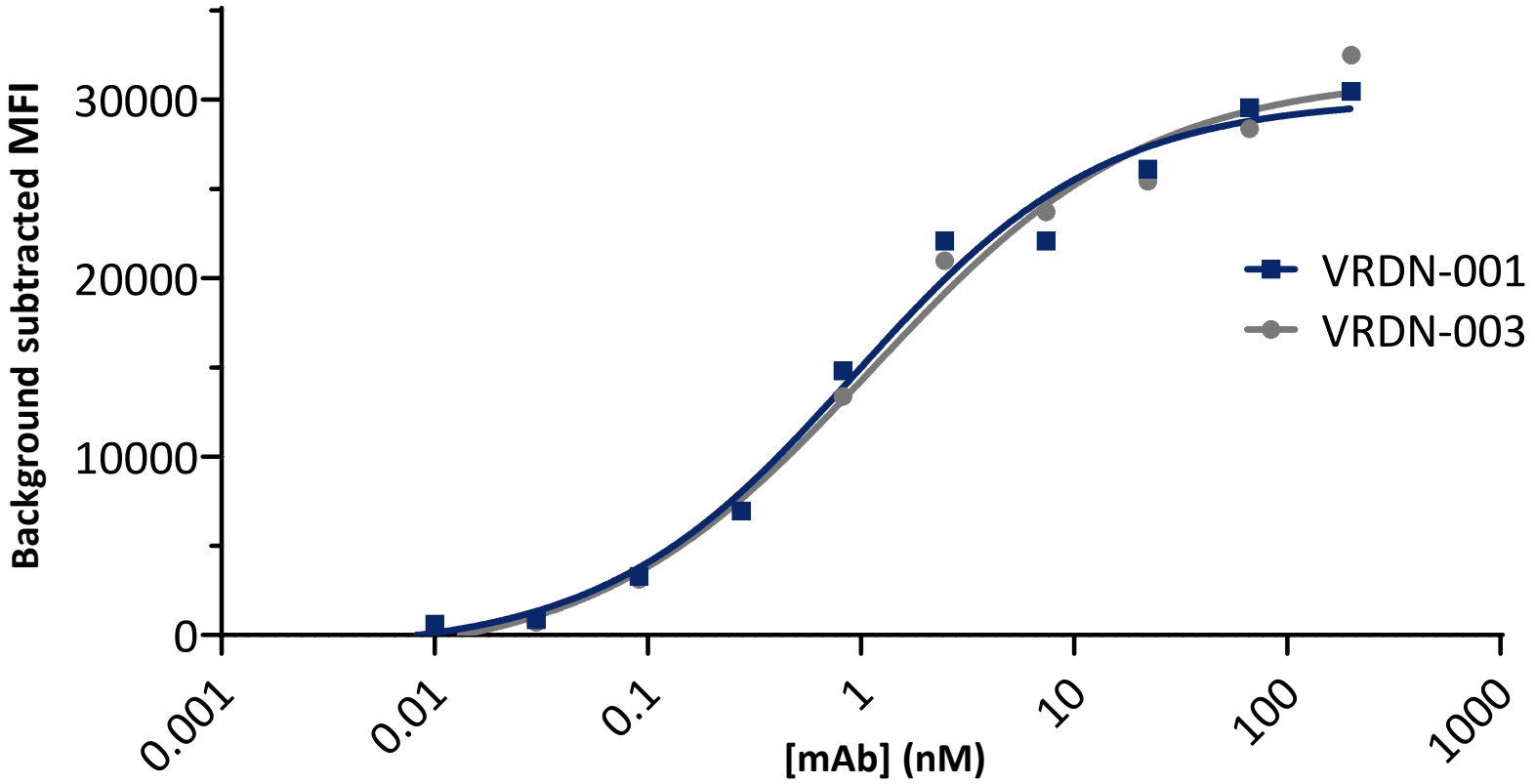
- Clinical and preclinical evidence suggests a central role for IGF-1 receptor antagonism in reducing the inflammation and proptosis that occur in TED[1-4]
- VRDN-001, a full antagonist antibody to IGF-1R with subnanomolar affinity, is in development for the treatment of TED
  - VRDN-001 showed clinical activity in a small cohort of patients with active or chronic TED in phase 2 proof-of-concept studies (AAO presentation #PA012)
- **VRDN-003** is a next-generation, half-life extended version of VRDN-001 designed to optimize subcutaneous administration
- Given **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

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); **4.** Douglas RS et al. *NEJM*; 382:4 (2020).

Methods

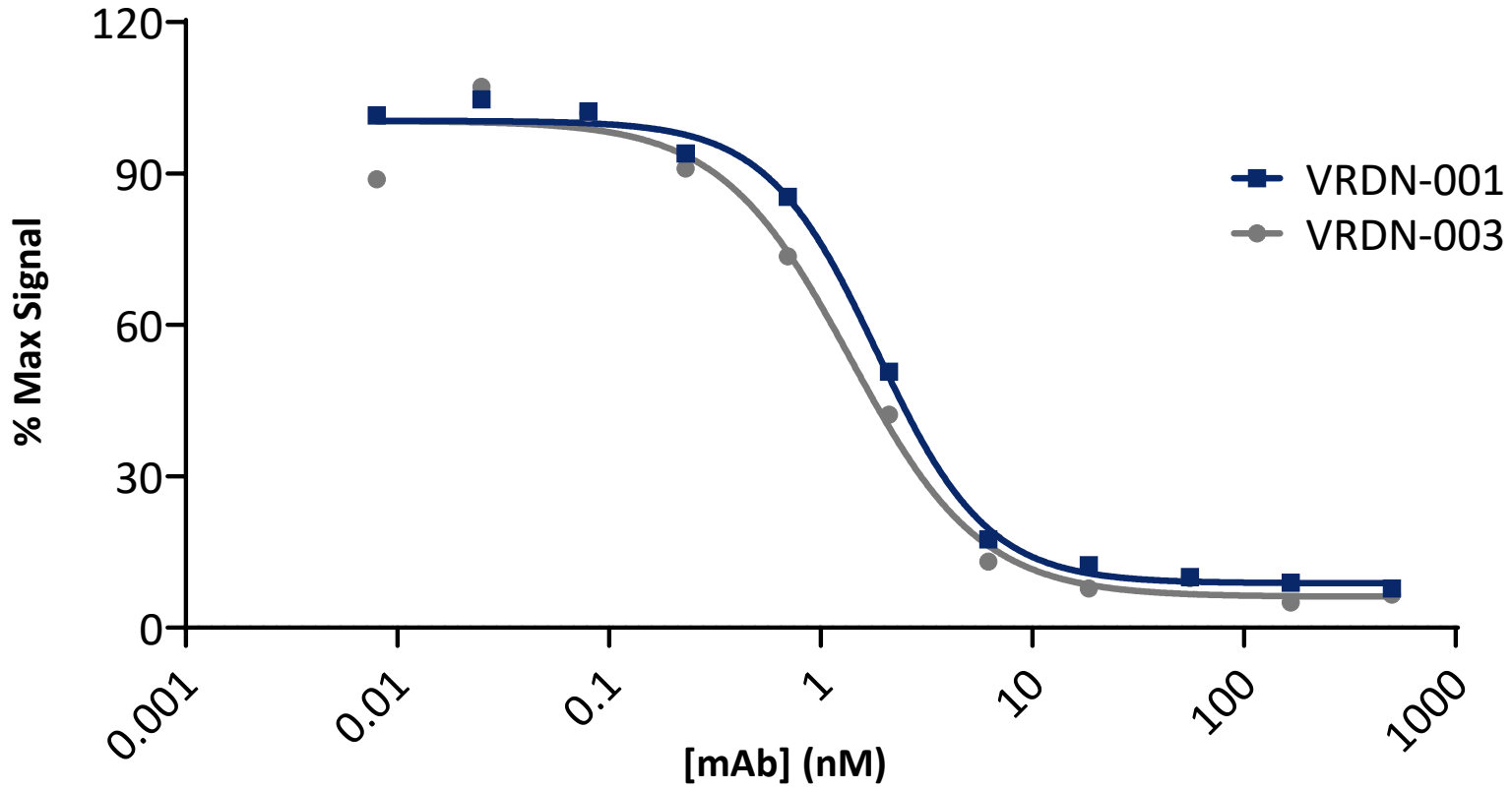
- **Antibody binding to IGF-1R:** Antibody binding to endogenously expressed cell surface IGF-1R was characterized in human ocular choroid fibroblasts (HOCFs)
- **Inhibition of ligand binding:** Dose responses of inhibition of biotinylated IGF-1 binding to IGF-1R-expressing FreeStyle™ 293-F cells were 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-1R



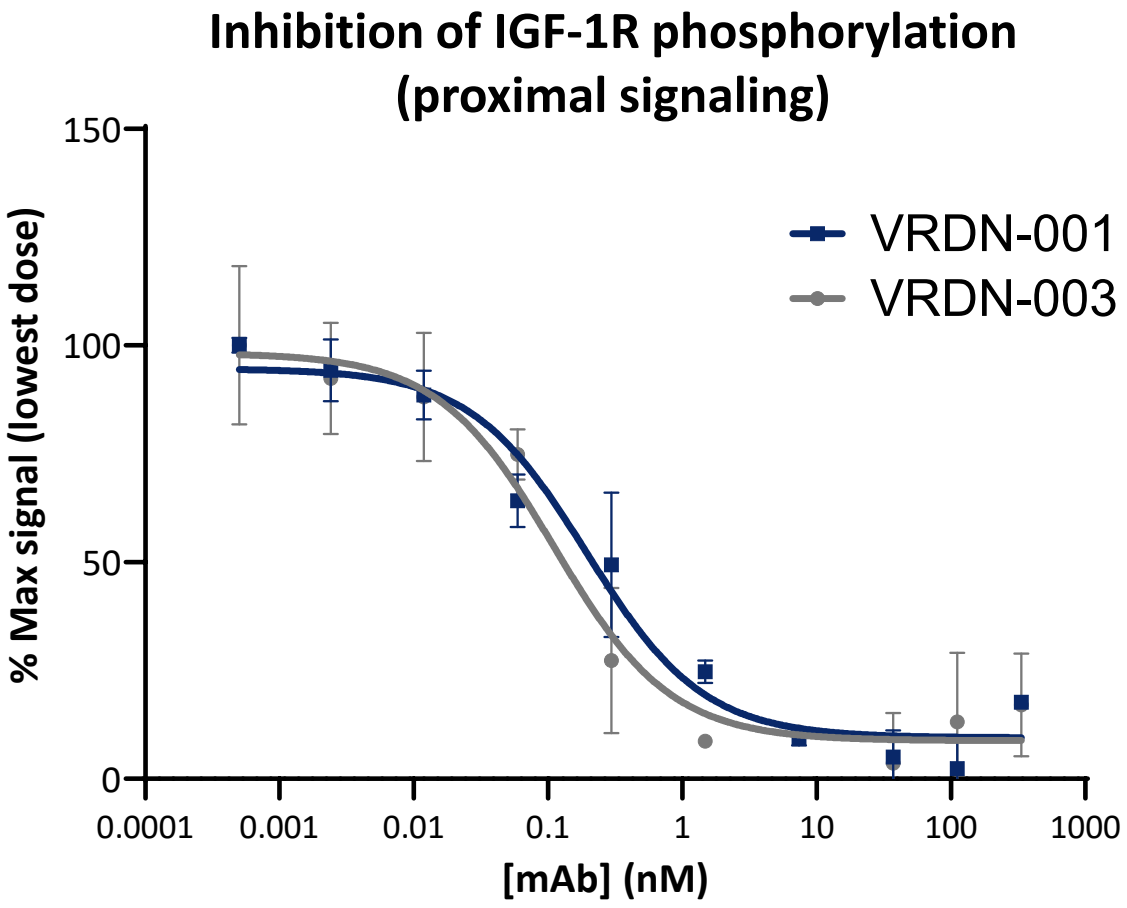
- **VRDN-003** bound to IGF-1R-expressing HOCF cells with high affinity, similar to VRDN-001

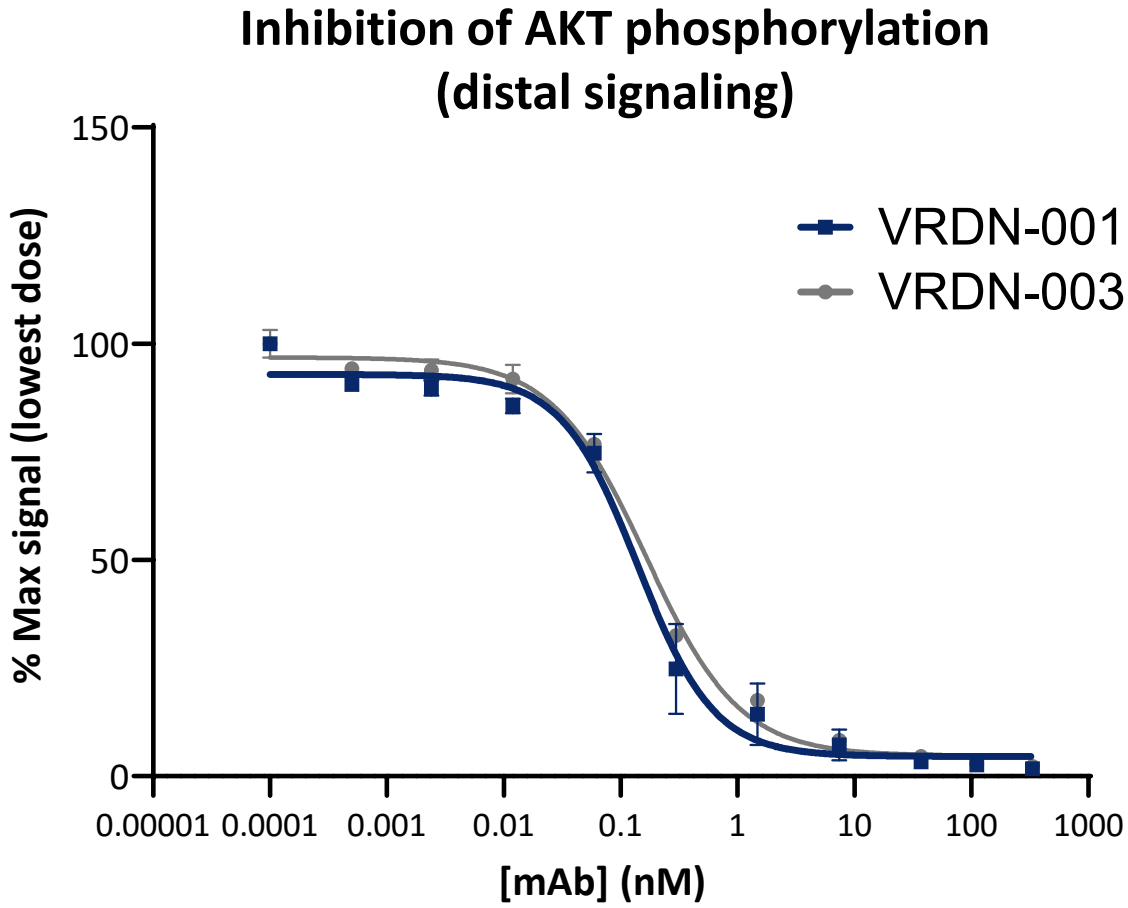
Antibody inhibition of ligand binding to IGF-1R



- **VRDN-003** provided near complete inhibition of IGF-1 binding (>95%), almost identical to VRDN-001

Antibody antagonism of IGF-1R signaling





- Similar inhibition of distal and proximal signaling events between VRDN-001 and **VRDN-003** indicated half-life extension modifications in **VRDN-003** did not impact pharmacology of the variable domains

Conclusions and Therapeutic Implications

- **VRDN-003** and VRDN-001 both provided near complete inhibition of ligand binding to IGF-1R and phosphorylation of IGF-1R and AKT
- Given that **VRDN-003** and VRDN-001 show indistinguishable antagonist properties, **VRDN-003** has the potential to show similar clinical effects as observed in the phase 2 studies of VRDN-001 in active and chronic TED (AAO presentation #PA012)
- Furthermore, the extended half-life of **VRDN-003** was observed to be twice that of VRDN-001 in a preclinical study in cynomolgus monkeys (AAO poster #PO394), demonstrating its potential for subcutaneous self-administration

Thank you!
Questions?

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