VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor in Development for Thyroid Eye Disease (TED), Binds to a Distinct Epitope from Teprotumumab

Vahe Bedian, Jordan Tsai, Rachel Newell, Yang Zhao
Viridian Therapeutics Inc., Waltham, MA
Disclosures

• This study was sponsored by Viridian Therapeutics Inc. VRDN-001 is an investigational therapy not approved in any country. All authors met the ICMJE authorship criteria and had full access to relevant data.

• The authors would like to thank the study investigators and research teams who make this research possible.

• Vahe Bedian, Jordan Tsai, Rachel Newell, and Yang Zhao are employees of Viridian Therapeutics Inc.

• Contact information: info@viridiantherapeutics.com
TED: Stimulation of TSHR/IGF-1R signaling complex results in inflammation and tissue expansion in the fixed bony orbit.

- Orbital adipogenesis
- Deposition of hyaluronan/GAGs
- Differentiation of fibrocytes into myofibroblasts
- Release of inflammatory cytokines and chemokines
- Expanded orbital muscles
- Conjointival chemosis
- Exophthalmos
- Optic nerve compression
- Increased adipose tissue volume
- Additional signs include eyelid retraction, orbital congestion, and restrictive strabismus
Study rationale

- VRDN-001 and teprotumumab are both high-affinity, IGF-1R antagonist antibodies
- Teprotumumab is FDA-approved for the treatment of TED; VRDN-001 is in clinical development for the treatment of TED.
- VRDN-001 and teprotumumab have overlapping epitopes by surface plasmon resonance (SPR).
- We further assessed similarities/differences in:
  1. Binding epitopes by mutational scan analysis
  2. Ability to block ligand binding
  3. Ability to antagonize IGF-1R signaling
Epitope analysis

- To assess differences in binding, 3 N-terminal truncations (L1, L1+CR, L1+CR+L2) and 40 point mutants of human IGF-1R were generated:
  - All residues at or near the IGF-1 binding site and all human/rodent differences were included in mutated sites
- VRDN-001 and teprotumumab binding to these IGF-1R variants was tested by biolayer interferometry (Octet)
Teprotumumab and VRDN-001 are sensitive to the same IGF-1R domain deletions

For both antibodies, deletion of L1 domain (pink) reduced binding, while deletion of both L1 domain and CR domain (red), or of L1, CR, and L2 domains, eliminated binding.
Teprotumumab and VRDN-001 have distinct receptor interactions

- Mutation in 2 adjacent residues involved in teprotumumab binding:
  - I285A reduced binding (lower association and faster dissociation)
  - L286A abrogated binding
- None of the 40 point mutations impacted VRDN-001 binding
- VRDN-001 was sensitive to the same domain deletions as teprotumumab but was not sensitive to the same point mutations, consistent with overlapping but distinct receptor interactions
Analysis of antagonist properties

Three assays were used to assess antagonist properties:

1. Inhibition of ligand binding to IGF-1R on FreeStyle™ 293-F Cells
2. Inhibition of IGF-1 mediated IGF-1R phosphorylation in human ocular choroidal fibroblasts (HOCFs)
3. Inhibition of IGF-1 mediated AKT phosphorylation in HOCFs
Inhibition of ligand binding

30 nM biotinylated IGF-1 binding to FreeStyle™ 293-F Cells

- VRDN-001 gives near complete inhibition of IGF-1 binding at ≥50 nM.
- Teprotumumab inhibition does not exceed ~50% up to 300 nM.
VRDN-001 provides more complete inhibition of IGF-1–induced IGF-1R and AKT phosphorylation in the dose range tested.
Conclusions

• VRDN-001 and teprotumumab have overlapping but distinct epitopes.
• Differences in binding correlate with differences in antagonist characteristics.
  – VRDN-001 inhibits ligand binding and IGF-1 mediated signaling more completely than teprotumumab in the dose ranges tested
• VRDN-001’s pharmacological differences may potentially explain:
  – 5- to 7-fold increases in IGF-1 serum levels observed at 6 weeks in healthy volunteers and patients with active TED (Poster# FRI-546)
  – clinical effects observed in the phase 2 proof-of-concept study of VRDN-001 in active TED (Poster# FRI-545)
• The efficacy and safety of VRDN-001 for the treatment of patients with active TED will be further assessed in the ongoing THRIVE phase 3 clinical trial (NCT05176639).