Next Generation TED Therapy in Clinical Development

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

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

KEY TAKEAWAYS

Results from in vitro assays demonstrate the unique binding epitope and functional characteristics of VRDN-001:

- Similar binding site to teprotumumab, but does not exhibit sensitivity to certain mutations in IGF-1R binding region, while teprotumumab does
- More completely inhibits IGF-1 binding and IGF-1R signaling (phosphorylation of IGF-1R and AKT) than teprotumumab

These findings may explain the favorable results of VRDN-001 in the phase 1/2 TED proof-of-concept trial (NANOS Platform Session I) and support the ongoing THRIVE phase 3 trial (NCT05176639, Poster #296).

INTRODUCTION

- Clinical and preclinical studies have confirmed IGF-1R antagonism reduces the inflammation and proptosis that occur in TED. 1,3
- VRDN-001, a full antagonist antibody to IGF-1R, is under development for the treatment of TED.
- As different anti-IGF-1R antibodies may have distinct characteristics, we compared the binding epitope and in vitro antagonist properties of the IGF-1R antibody VRDN-001 with teprotumumab.

STUDY DESIGN

- Mutational scan: A panel of 40 IGF-1R ECD point mutants at potential IGF-1R binding residues or human/rodent differences* and 3 N-terminal truncations (L1, L1+CR, L1+CR+L2) were generated. Binding was assessed by BLI (Octet).
- 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 human ocular choroidal fibroblasts (HOCFs).

*Structural studies with VRDN-001 and teprotumumab bound human IGF-1R but not rodent IGF-1R; human-specific residues were considered more likely to be part of the binding epitope.

ANTIBODY INHIBITION OF LIGAND BINDING TO IGF-1R

Inhibition of IGF-1 binding

<table>
<thead>
<tr>
<th>Antibody</th>
<th>%Max Signal (lowest dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRDN-001</td>
<td>50%</td>
</tr>
<tr>
<td>Teprotumab</td>
<td>70%</td>
</tr>
</tbody>
</table>

ANTIBODY ANTAGONISM OF IGF-1R SIGNALING

- VRDN-001 provides more complete inhibition of IGF-1–induced AKT phosphorylation than teprotumumab.
- By 10 nM, VRDN-001 nearly fully inhibits IGF-1–induced proximal signaling, while teprotumumab plateaus at only partial inhibition.

THERAPEUTIC IMPLICATIONS

- In healthy volunteers and TED patients, VRDN-001 elicited rapid and sustained increases in IGF-1 serum levels (target engagement biomarker) that were similar across groups, indicating maximal target engagement at even the lowest dose (Poster #298).
- In a phase 2 proof of concept trial in TED patients, rapid and clinically meaningful reductions in proptosis, inflammation, and diplopia were observed at 6 weeks, following only 2 infusions of VRDN-001 at all doses tested (NANOS Platform Session II).