Preclinical Pharmacokinetics of VRDN-003, a Next-Generation Half-life Extended Antibody to the IGF-1 Receptor for Thyroid Eye Disease

KEY TAKEAWAYS

- **VRDN-003**, a next-generation, half-life extended version of VRDN-001, demonstrated a pharmacokinetic (PK) profile that could enable subcutaneous administration via a self-administered pen.
- Compared with VRDN-001, VRDN-003 half-life was approximately 2 times as long, AUC was approximately 65% greater, and clearance was approximately 40% less.
- Results of this study demonstrate the potential for VRDN-003 to be a subcutaneous self-administered therapy for people with thyroid eye disease (TED).

INTRODUCTION

- Clinical and preclinical studies have confirmed IGF-1R antagonism can reduce the inflammation and proptosis that occur in TED.³
- VRDN-001, a full antagonist antibody to IGF-1R with subnanomolar affinity, is under development for the treatment of TED; it has shown marked improvements in proptosis, diplopia, and clinical activity in a phase 2 proof-of-concept trial (ARVO oral #5432).
- VRDN-003 is a next-generation, half-life extended version of VRDN-001 designed to enable subcutaneous administration via a self-administered pen.
- We compared the PK parameters of VRDN-003 with those of VRDN-001 in nonhuman primates.

METHODS

- VRDN-001 or VRDN-003 was administered to a total of 16 cynomolgus monkeys as a single dose by either intravenous (IV) infusion or subcutaneous (SC) injection at 7.5 mg/kg.
- PK samples were collected at 9 time points through 14 days.
- Data were analyzed using WinNonlin noncompartmental analysis.

PK PARAMETERS

<table>
<thead>
<tr>
<th>ROA</th>
<th>Vₐ (mL/kg)</th>
<th>CL (mL/day/kg)</th>
<th>t₁/₂ (days)</th>
<th>AUC₀₋inf (µg/mL)</th>
<th>%F</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>78 ± 6</td>
<td>8.5 ± 2.1</td>
<td>6.6 ± 1.3</td>
<td>915 ± 191</td>
<td>70</td>
</tr>
<tr>
<td>SC</td>
<td>112 ± 25</td>
<td>13.1 ± 5.6</td>
<td>6.3 ± 1.4</td>
<td>636 ± 222</td>
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<tr>
<td>IV</td>
<td>86 ± 17</td>
<td>5.2 ± 0.8</td>
<td>11.9 ± 3.4</td>
<td>1480 ± 223</td>
<td>71</td>
</tr>
<tr>
<td>SC</td>
<td>132 ± 2</td>
<td>7.2 ± 1.2</td>
<td>12.8 ± 2.0</td>
<td>1050 ± 182</td>
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</tbody>
</table>

- vn and CL are Vn/F and CL/F for SC groups. All values (except %F) are provided as mean ± standard deviation.
- Compared with VRDN-001, VRDN-003 half-life was approximately 2 times as long, 65% greater, and clearance approximately 40% less.
- Bioavailability (ratio AUC₀₋inf/AUC₀₋IV) was similar for the 2 antibodies.

THERAPEUTIC IMPLICATIONS

- VRDN-003’s extended half-life and other PK parameters observed in this study suggest that VRDN-003 administered SC should yield similar serum concentrations to those achieved with VRDN-001 administered IV.
- Separate in vitro studies have demonstrated VRDN-003 pharmacology is similar to that of VRDN-001: both fully antagonize IGF-1 binding to IGF-1R as well as IGF-1R proximal and distal signaling (ARVO poster #532).

- Given VRDN-003 has the same pharmacology as VRDN-001 with twice the half-life, it may provide a SC treatment option with similar clinical effects to that of VRDN-001 in nonhuman primates.

PK SIMULATIONS

- PK modeling of SC administration with a 600 mg loading dose shows:
  - VRDN-003 dosed at 300 mg Q4W exceeds exposure of VRDN-001 dosed at 3 mg/kg IV
  - VRDN-003 dosed at 300 mg Q2W matches exposure of VRDN-001 dosed at 10 mg/kg IV
- Given the early efficacy signals observed for VRDN-001 doses at 3 mg/kg and 10 mg/kg IV in patients with TED (ARVO oral #5432), results seen here suggest VRDN-003 has potential for clinically meaningful efficacy with SC administration.

DISCLOSURES: This study was sponsored by Viridian Therapeutics. VRDN-001 and VRDN-003 are investigational therapies, not approved in any country. Formatting and editorial assistance was provided by Shula Pollard, employee of Viridian Therapeutics.

REFERENCES:
- Brent Dickinson | Kelly Foster | Vahe Bedian
- Viridian Therapeutics, Waltham, MA
- Poster #4043 - B0360

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