VRDN-002, A Second-Generation Insulin-Like Growth Factor-1 Receptor (IGF-1R) Antibody for TED: Preclinical PK Profile and Clinical Promise

BRENT DICKINSON, CHRISTIAN CLAUSEN*, LINDA PESTANO*, VAHE BEDIAN*

INTRODUCTION

TED is an autoimmune condition most commonly associated with Graves’ disease and hypothyroidism but can also be found in patients who are euthyroid or hypothyroid. Orthotopy in TED is driven by Thyroid Stimulating Hormone (TSH) agonistic autoantibodies and crosstalk between TSHR and IGF-1R. Pathological remodeling of the orbit and peri-orbital tissues results invariant presentations which may include dry eyes, increased lacrimation, local irritation, eyelid retraction and essentially proptosis, diplopia, and optic nerve compression, with ensuing vision loss.

The underlying pathology of TED is the activation of an inflammatory cascade within the orbit, primarily due to recruitment of fibrocytes and immune cells. Overexpression of IGF-1R has been demonstrated within the orbit of TED patients, and it has been surmised that IGF-1R inhibitory antibodies may disrupt the IGF-1R and TSHR cross-talk and dampen the inflammatory cascade. Indeed, IGF-1R antagonism has been demonstrated to robustly relieve much of the inflammatory symptomology that affects TED patients.

VRDN-002 is a monoclonal antibody that inhibits IGF-1-mediated signaling via IGF-1R with substantially improved efficacy and a clinically validated Fc modifications to extend half-life. We hypothesize that VRDN-002 may offer a more favorable PK profile with the potential for a less burdensome treatment paradigm for patients than conventional IgG therapeutic antibodies.

METHODS

VRDN-002 was administered to cynomolgus monkeys by 30-min intravenous (IV) infusions at 2, 10, and 50 mg/kg, and by subcutaneous (SC) injection at 2 mg/kg. VRDN-002 was administered to cynomolgus monkeys by 30 min intravenous (IV) infusions at 2, 10, and 50 mg/kg, and by subcutaneous (SC) injection at 2 mg/kg. PK model to project potential human dosing regimens.

OBJECTIVE

VRDN-002 is a novel anti-IGF-1R antibody incorporating half-life extension modifications in its Fc region intended for potential treatment of Thyroid Eye Disease (TED). We sought to compare the pharmacokinetic (PK) parameters of VRDN-002 in cynomolgus monkeys to the marketed IGF-1R antibody, teprotumumab, and construct a PK model to project potential human dosing regimens.

NON-HUMAN PRIMATE PK

**VRDN-002 SERUM CONCENTRATIONS ADMINISTERED IV OR SC**

<table>
<thead>
<tr>
<th>Days</th>
<th>ROA</th>
<th>Dose (mg/kg)</th>
<th>Serum Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>IV</td>
<td>2</td>
<td>10.2 ± 3.29</td>
</tr>
<tr>
<td>0</td>
<td>SC</td>
<td>2</td>
<td>11.2 ± 3.34</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>2</td>
<td>243 ± 40.9</td>
</tr>
<tr>
<td>5</td>
<td>IV</td>
<td>2</td>
<td>89 ± 26.0</td>
</tr>
<tr>
<td>10</td>
<td>IV</td>
<td>2</td>
<td>14.4 ± 4.01</td>
</tr>
<tr>
<td>10</td>
<td>SC</td>
<td>2</td>
<td>98.6 ± 21.9</td>
</tr>
<tr>
<td>28</td>
<td>IV</td>
<td>2</td>
<td>2300 ± 312</td>
</tr>
<tr>
<td>28</td>
<td>SC</td>
<td>2</td>
<td>232 ± 3.27</td>
</tr>
<tr>
<td>56</td>
<td>IV</td>
<td>2</td>
<td>1230 ± 190</td>
</tr>
<tr>
<td>56</td>
<td>SC</td>
<td>2</td>
<td>1408 ± 158</td>
</tr>
</tbody>
</table>

**VRDN-002 HALF-LIFE EXTENSION MODIFICATIONS PROLONG EXPOSURE**

At equivalent doses, SC dosed VRDN-002 has greater exposure than intravenously infused teprotumumab and achieves ~2x half-life of teprotumumab in NHPs. Estimated 52% bioavailability (F) of VRDN-002 from SC dosing using peripheral distribution volume were included central distribution volume, transcompartmental clearance, and peripheral distribution volume were combined with estimated NHP parameters for TMDD and SC absorption to provide a drug translation framework.

**NHP TO HUMAN PK TRANSLATION**

A SEMI-MECHANIcAL POPULATION PK MODEL FOR VRDN-002

**PK SIMULATION RESULTS**

The prolonged half-life of VRDN-002 suggests the potential to administer as a low-volume, convenient SC injection, or as an IV infusion requiring fewer and/or less frequent administrations vs. conventional therapeutic IgG antibodies. Efforts are underway to generate a high concentration formulation suitable for potential low volume SC injection. Initial clinical trials are planned to start in 2022 to explore safety, tolerability, PK, PO, SC bioavailability, and to gain a better understanding of the exposures that may be required for efficacy in TED.

**ACKNOWLEDGEMENTS**

*VRIDIAN THERAPEUTICS, *COGNIGEN

References: