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

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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.

INTRODUCTION

TED is an autoimmune condition most commonly associated with Graves' disease and hyperthyroidism but can also be found in patients who are euthyroid or hypothyroid. Orbitopathy in TED is driven by Thyroid Stimulating Hormone Receptor (TSHR) agonistic autoantibodies and crosstalk between TSHR and IGF-1R[1]. Pathological remodeling of the orbit and periorbital tissues results in varied presentations which may include dry eyes, increased lacrimation, local irritation, eyelid retraction and eventually 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. Over-expression of IGF-1R has been demonstrated within the orbit of TED patients[2], and it has been surmised that IGF-1R inhibitory antibodies may disrupt the IGF-1R and TSHR cross-talk and dampen the inflammatory cascade[3]. Indeed, IGF-1R antagonism has been demonstrated to robustly relieve much of the inflammatory symptomology that affects TED patients.[4]

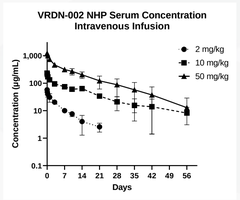
VRDN-002 is a monoclonal antibody that inhibits IGF-1 mediated signalling via IGF-1R with subnanomolar potency and incorporates clinically validated Fc modifications to extend half-life. We hypothesize that VRDN-002 may have a more favourable PK profile with the potential for a less burdensome treatment paradigm for patients than conventional IgG therapeutic antibodies.

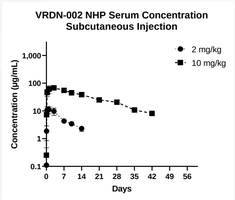
METHODS

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 and 10 mg/kg. Teprotumumab at 10 mg/kg was likewise administered by 30 min IV infusion. VRDN-002 and teprotumumab levels in serum were measured using a human IgG specific ELISA assay. Data were analyzed using the WinNonlin non-compartmental model. A semi-mechanistic model incorporating target mediated drug disposition was constructed using available human and cynomolgus data.

NON-HUMAN PRIMATE PK

VRDN-002 SERUM CONCENTRATIONS ADMINISTERED IV OR SC

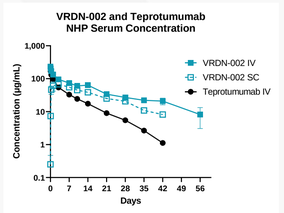




ROA	Dose (mg/kg)	C_{max} (µg/mL)	AUC_{inf} (µg*day/mL)	$t_{1/2}$ (Day)	Cl* (mL/day/kg)
IV	2	57.7 ± 7.19	243 ± 45.8	5.87 ± 1.19	8.43 ± 1.55
	10	232 ± 3.27	2300 ± 312	14.4 ± 4.07	4.40 ± 0.570
	50	1230 ± 190	8670 ± 2840	9.23 ± 1.93	6.15 ± 1.76
SC	2	11.2 ± 3.34	98.6 ± 21.9	6.21 ± 2.25	20.9 ± 4.32
	10	68.8 ± 11.0	1420 ± 62.4	12.6 ± 1.87	7.04 ± 0.307

Table shows PK parameters +/- SD. Evidence of target mediated drug disposition (TMDD) was observed at 2 mg/kg, but not at 10 and 50 mg/kg doses, in line with teprotumumab and other IGF-1R antibodies that have reported saturation of TMDD at higher doses[5,6,7].

VRDN-002 HALF-LIFE EXTENSION MODIFICATIONS PROLONG EXPOSURE

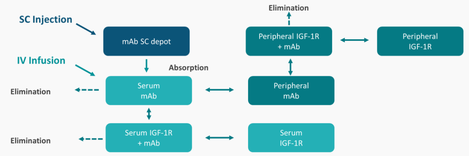


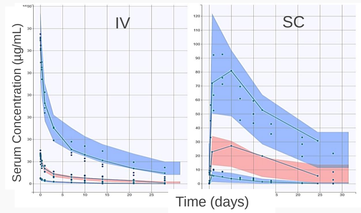
- At equivalent doses, SC dosed VRDN-002 has greater exposure than intravenously infused teprotumumab and achieves ~2x half-life of teprotumumab in NHPs
- Estimated 62% bioavailability (F) of VRDN-002 from SC dosing using preliminary discovery-stage formulation. Parameter estimates +/- SD shown below

Compound	Dose and ROA	AUC_{inf} (µg*day/mL)	Relative Exposure	$t_{1/2}$
VRDN-002	10 mg/kg, IV	2300 ± 312	2.9X	14.4 ± 4.07
VRDN-002	10 mg/kg, SC	1420 ± 62.4	1.8X	12.6 ± 1.87
Teprotumumab	10 mg/kg, IV	779 ± 79.4	1.0X	6.35 ± 0.322

NHP TO HUMAN PK TRANSLATION

A SEMI-MECHANISTIC POPULATION PK MODEL FOR VRDN-002





- Two-compartment TMDD drug disposition model for NHP PK. Binding to IGF-1R assumed to be substantially faster than absorption and elimination.
- Standard population method was used in Monolix 2020R1
- Diagnostic goodness-of-fit plots indicated that the model provided a good description of the data. Colored areas represent 90% confidence intervals around 5th, 50th and 95th percentiles from simulations; empirical percentiles shown by lines; individual PK data points shown as dots.

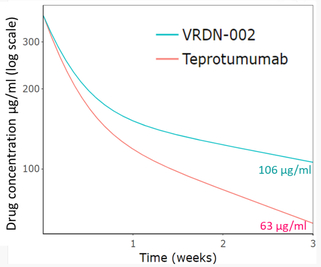
HUMAN PK MODELING SUGGESTS VRDN-002 HUMAN HALF LIFE ~2X TEPROTUMUMAB

Drug Translation Matrix

	Teprotumumab	VRDN-002
NHP	Data & PK model [Viridian]	Data & PK model [Viridian]
Human	Literature PK model parameters	Prediction from PK model

- To model human half-life for VRDN-002, model parameters from literature[8] including 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
- **From the PK model, VRDN-002 human half-life is projected to be ~2x teprotumumab, suggesting multiple potential dosing paradigms for treatment of TED.**

PK SIMULATION RESULTS



- Graph shows model predicted levels of VRDN-002 and teprotumumab administered at 20 mg/kg IV
- Predicted drug antibody levels at the end of three weeks are ~1.7X higher for VRDN-002 compared to teprotumumab

DISCUSSION

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 treatments 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, PD, SC bioavailability, and to gain a better understanding of the exposures that may be required for efficacy in TED.

ACKNOWLEDGEMENTS

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References:
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VIRIDIAN

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