Preclinical Pharmacokinetics and Bioavailability of VRDN-002, a Next-Generation Half-Life Extended Antagonist Antibody to the IGF-1 Receptor for Thyroid Eye Disease (TED)

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KEY TAKEAWAYS

- **VRDN-002**, a next-generation anti-IGF-1 receptor antibody, has an extended half-life relative to unmodified IgG1 antibodies.
- In nonhuman primates, a single dose of **VRDN-002** at 10-100 mg/kg had a mean half-life up to 14 days, with an estimated bioavailability ranging from 60% to 69%.
- Results suggest the potential for **VRDN-002** to be a subcutaneous self-administered therapy for TED patients.

INTRODUCTION

- Clinical and preclinical studies have confirmed IGF-1R inhibition reduces the inflammation and proptosis that occur in TED.[1-3]
- **VRDN-002** is a next-generation, partial antagonist antibody to IGF-1R with modification to the Fc region to extend half-life in development for TED.
- We conducted preclinical studies in cynomolgus monkeys to evaluate the pharmacokinetics (PK) and bioavailability (F) of **VRDN-002.**

METHODS

- A total of 15 naive cynomolgus female monkeys were administered a single dose of **VRDN-002** via either subcutaneous (SC) injection or 30-minute intravenous (IV) infusion.

VRDN-002	IV	SC
10 mg/kg	3	3
30 mg/kg	-	3
100 mg/kg	3	3

- Serum samples were collected on Day 0 before dosing and up to 8 hours post-dose, and on Day 1 through Day 56 post-dose.
- **VRDN-002** concentrations were measured using a human IgG-specific sandwich ELISA method and analyzed using a noncompartmental approach.

PK PARAMETERS

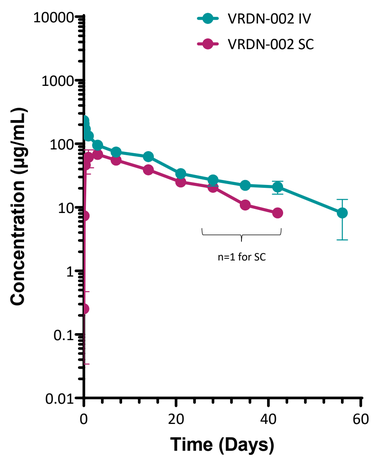
VRDN-002	ROA	C_{max} (µg/mL)	V_{ss} or V_z/F (mL/kg)[a]	CL or CL/F (mL/day/kg)[a]	$t_{1/2}$ (days)	AUC_{inf} (day*µg/mL)	F
10 mg/kg	IV	232 (3)	86 (11)	4.4 (0.6)	14 (4)	2300 (312)	-
	SC[b]	69 (11)	124	7.2	12	1390	60%
30 mg/kg	IV	-	-	-	-	-	-
	SC	193 (38)	111 (24)	6.9 (0.5)	11 (3)	4330 (290)	-
100 mg/kg	IV	2460 (155)	93 (12)	4.9 (0.9)	14 (2)	20800 (3400)	-
	SC	707 (156)	142 (40)	7.5 (2.8)	14 (4)	14400 (4420)	69%

Data are mean and SD. F is ratio of AUC-SC/AUC-IV. [a]V_{ss} and CL for IV and V_z/F and CL/F for SC. [b] Only 2 subjects for all parameters except C_{max}; thus SD is n/a.

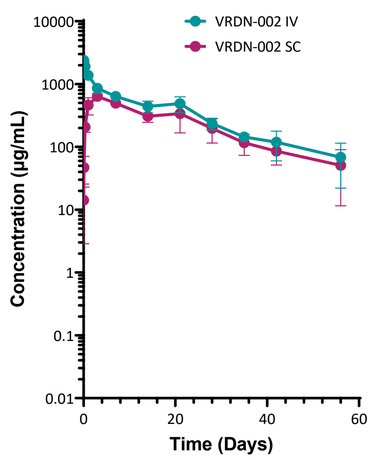
- Mean **VRDN-002** half-life ($t_{½}$) estimates ranged from 11.2 to 14.4 days across all study groups.
- VRDN-002 has ~2-fold greater half-life than typical unmodified IGF-1R antibodies.[4]

SUBCUTANEOUS BIOAVAILABILITY

VRDN-002 10 mg/kg



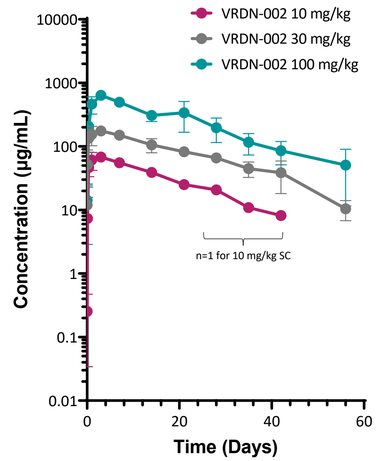
VRDN-002 100 mg/kg



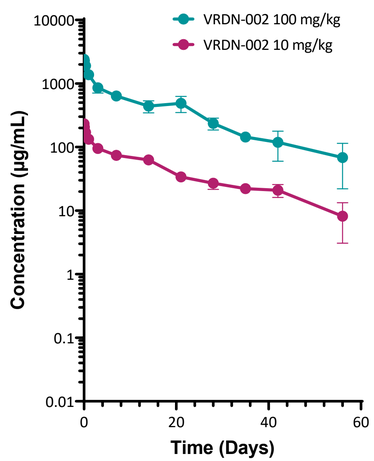
- Estimated **VRDN-002** SC bioavailability (ratio of mean area under the curve [AUC_{inf}] for SC vs IV):
  - 60% for 10 mg/kg (1390 day*µg/mL vs 2300 day*µg/mL)
  - 69% for 100 mg/kg (14400 day*µg/mL vs 20800 day*µg/mL)

DOSE PROPORTIONALITY

VRDN-002 SC



VRDN-002 IV



- Mean volume of distribution of the terminal phase (V_z/F) ranged from 111 to 142 mL/kg and CL/F ranged from 6.9 to 7.5 mL/day/kg for the SC arms.
- Mean volume of distribution at steady state (V_{ss}) ranged from 85.7 to 92.7 mL/kg and clearance (CL) ranged from 4.4 to 4.9 mL/day/kg for the IV arms.
- Dose-proportional increases in serum concentrations were observed for IV and SC doses from 10 to 100 mg/kg, suggesting linear PK in this dose range.

THERAPEUTIC IMPLICATIONS

- **VRDN-002** demonstrated an extended half-life compared with typical unmodified antibodies and favorable bioavailability.
- These preclinical SC data combined with our phase 1 IV data in healthy volunteers (Poster #4035) suggest **VRDN-002** could be delivered via a SC dosing regimen to patients.

Poster #4038

Disclosures: This study was sponsored by Viridian Therapeutics. **VRDN-002** is an investigational therapy not approved in any country. Formatting and editorial assistance was provided by Keira Kim. All authors met the ICMJE authorship criteria and had full access to relevant data. All authors are employees of Viridian Therapeutics. The authors would like to thank the study investigators, research teams, and study participants who make this research possible.

References: **1.** Pritchard J et al. *J Immunol*; 170:6348–6354 (2003); **2.** Krieger CC et al. *J Clin Endocrinol Metab;* 100:1071–1077 (2015); **3.** Smith TJ et al. *NEJM;* 376:1748–1761 (2017); **4.** FDA clinical review of Tepezza (BLA 761143).

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Abbreviations used in poster: ROA, route of administration; V_z, apparent volume of distribution of the terminal phase; V_{ss}, estimated volume of distribution at steady state; CL, total clearance rate; $t_{1/2}$, half-life; AUC_{inf}, area under curve extrapolated to infinity; F, bioavailability.

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