Preclinical Pharmacokinetics and Clinical Exposure Prediction for VRDN-003, a Next-Generation Half-life Extended Antibody to the IGF-1 Receptor for Thyroid Eye Disease (TED)

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#OP-09-02

Disclosures

- These studies were sponsored by Viridian Therapeutics, Inc. All data are proprietary.
- VRDN-001 and **VRDN-003** are investigational therapies not approved in any country. All authors met the ICMJE authorship criteria and had full access to relevant data.
- Kelly Foster, Brent Dickinson, and Vahe Bedian are employees of Viridian Therapeutics, Inc.
- The authors would like to thank the study investigators and research teams who make this research possible.

Background

- Clinical and preclinical evidence suggest a central role for IGF-1 receptor antagonism in reducing the inflammation and proptosis that occur in TED[1-4]
- VRDN-001, a full antagonist antibody to IGF-1R with subnanomolar affinity, is in development for the treatment of TED
  - 2 infusions of VRDN-001 showed clinical activity in a small cohort of patients with active or chronic TED in phase 2 proof-of-concept studies (ETA #OP-09-01)
- **VRDN-003** is a next-generation version of VRDN-001, with the same antigen binding domain[5] and an extended half-life, designed as a subcutaneous (SC) treatment option in TED

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.** Douglas RS et al. *NEJM*; 382:4 (2020); **5.** Newell R et al. ARVO poster 4044-B0361. *Invest. Ophthalmol. Vis. Sci*. 2023;64(8):4044.

Objectives

- Investigate the pharmacokinetic (PK) parameters of **VRDN-003** compared with those of VRDN-001 in nonhuman primates (NHPs)
- Investigate **VRDN-003** SC dosing regimen simulations using PK modeling in humans

PK of VRDN-003 vs VRDN-001 in nonhuman primates (NHPs)

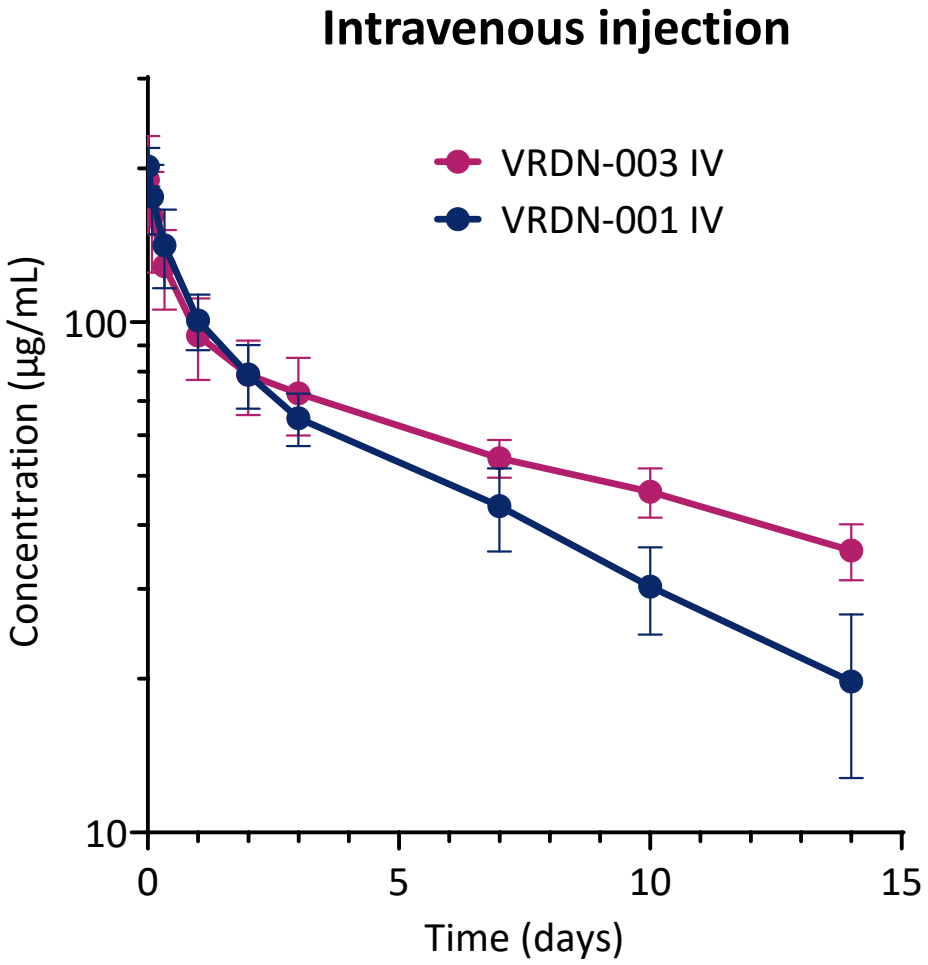
Methods for NHP study

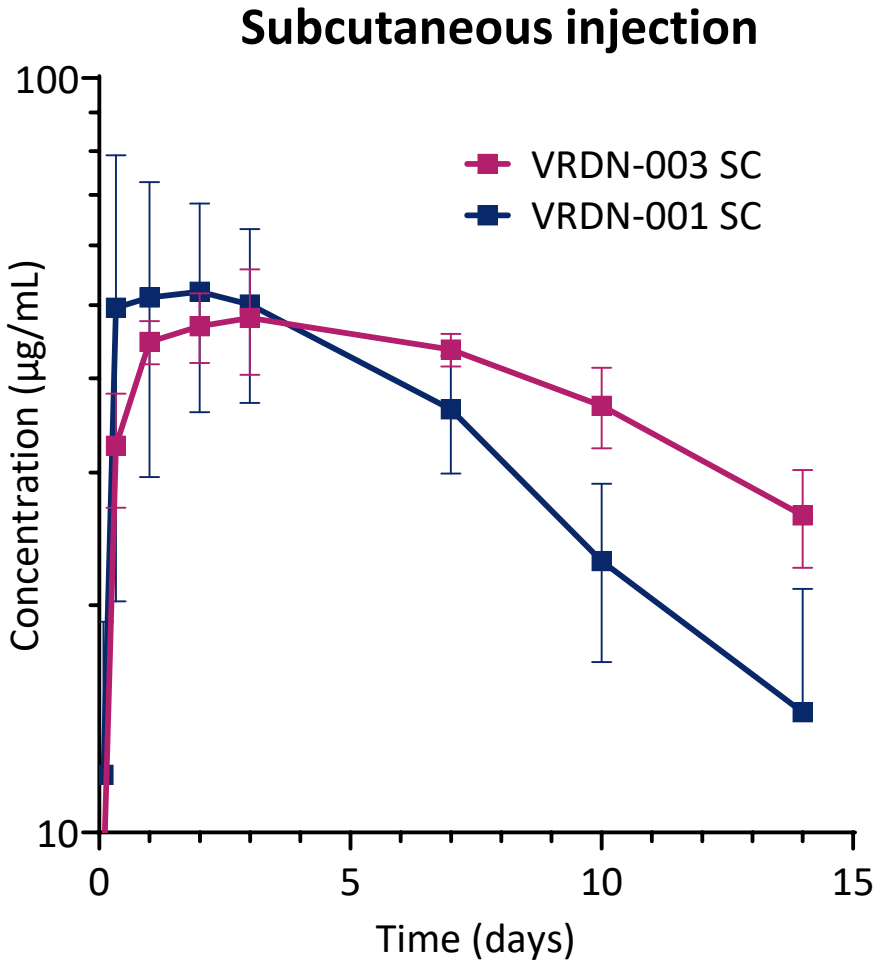
- VRDN-001 or **VRDN-003** was administered to a total of 16 cynomolgus monkeys as a single dose by either IV injection or SC injection at 7.5 mg/kg
- PK samples were collected at 9 time points through 14 days
- Data were analyzed using WinNonlin noncompartmental analysis

	ROA	n
VRDN-001	IV	4
	SC	4
VRDN-003	IV	4
	SC	4

ROA, route of administration; IV, intravenous; SC, subcutaneous

Concentration over time: VRDN-003 vs VRDN-001 in NHPs





Exposure was greater for **VRDN-003** than for VRDN-001 for both IV and SC administration

PK parameters in NHPs

	ROA	V_z[a] (mL/kg)	CL[a] (mL/day/kg)	$t_{1/2}$ (days)	AUC_{inf} (day*µg/mL)	%F
VRDN-001	IV	78 ± 6	8.5 ± 2.1	6.6 ± 1.3	915 ± 191	70
	SC	112 ± 23	13.1 ± 5.6	6.3 ± 1.4	636 ± 222	
VRDN-003	IV	86 ± 17	5.2 ± 0.8	11.9 ± 3.4	1480 ± 223	71
	SC	132 ± 2	7.2 ± 1.2	12.8 ± 2.0	1050 ± 182	

ROA, route of administration; V_z, apparent volume of distribution of the terminal phase; CL, total clearance rate; $t_{1/2}$, half-life; AUC_{inf}, area under curve extrapolated to infinity; %F, bioavailability. [a]V_z and CL are V_z/F and CL/F for SC groups. All values (except %F) are provided as mean ± standard deviation.

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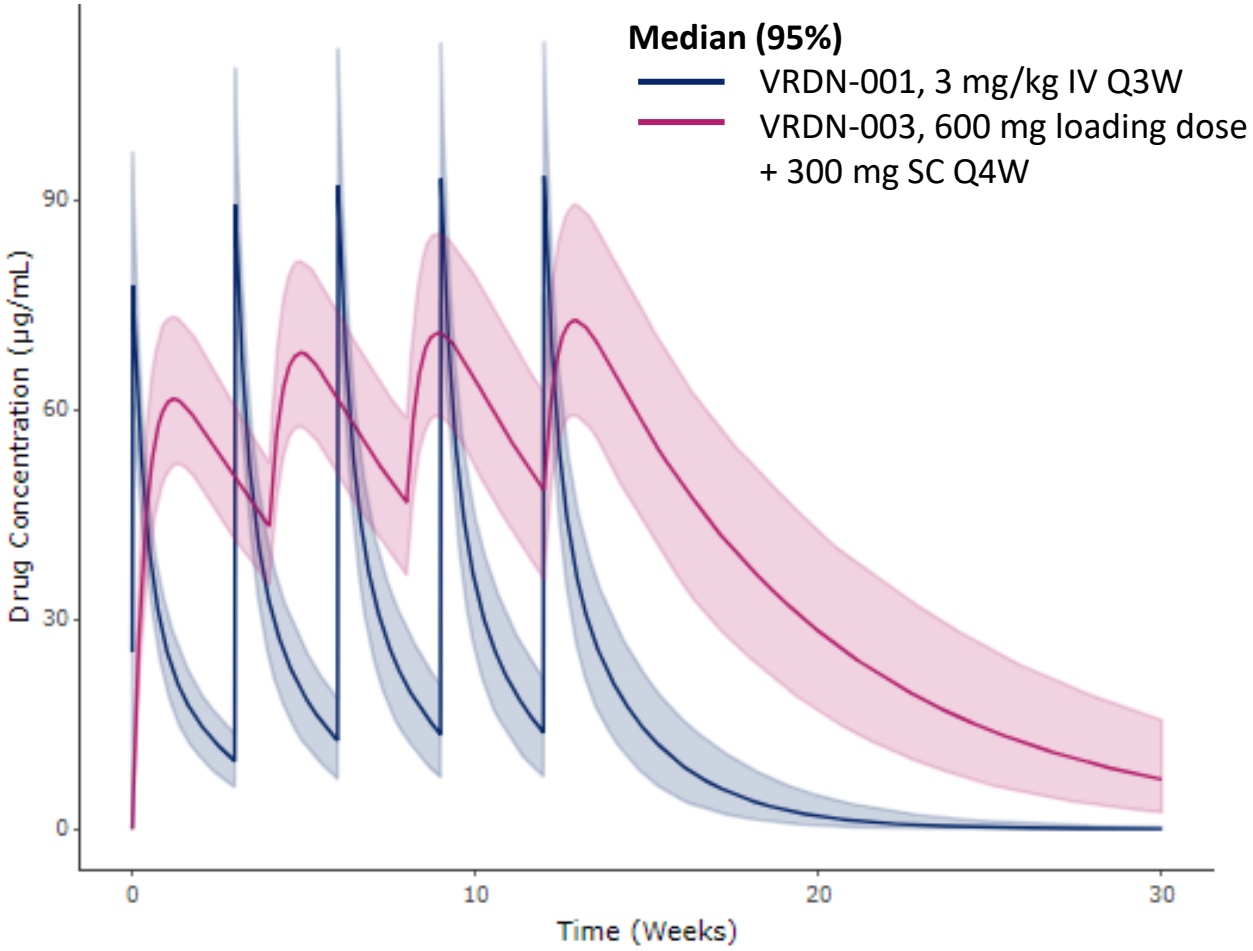
- Compared with VRDN-001, **VRDN-003** half-life was approximately 2 times as long, AUC_{inf} approximately 65% greater, and clearance approximately 40% less
- Bioavailability (%F; ratio AUC-SC/AUC-IV) was similar for the 2 antibodies

VRDN-003 SC dosing regimen simulations using PK modeling in humans

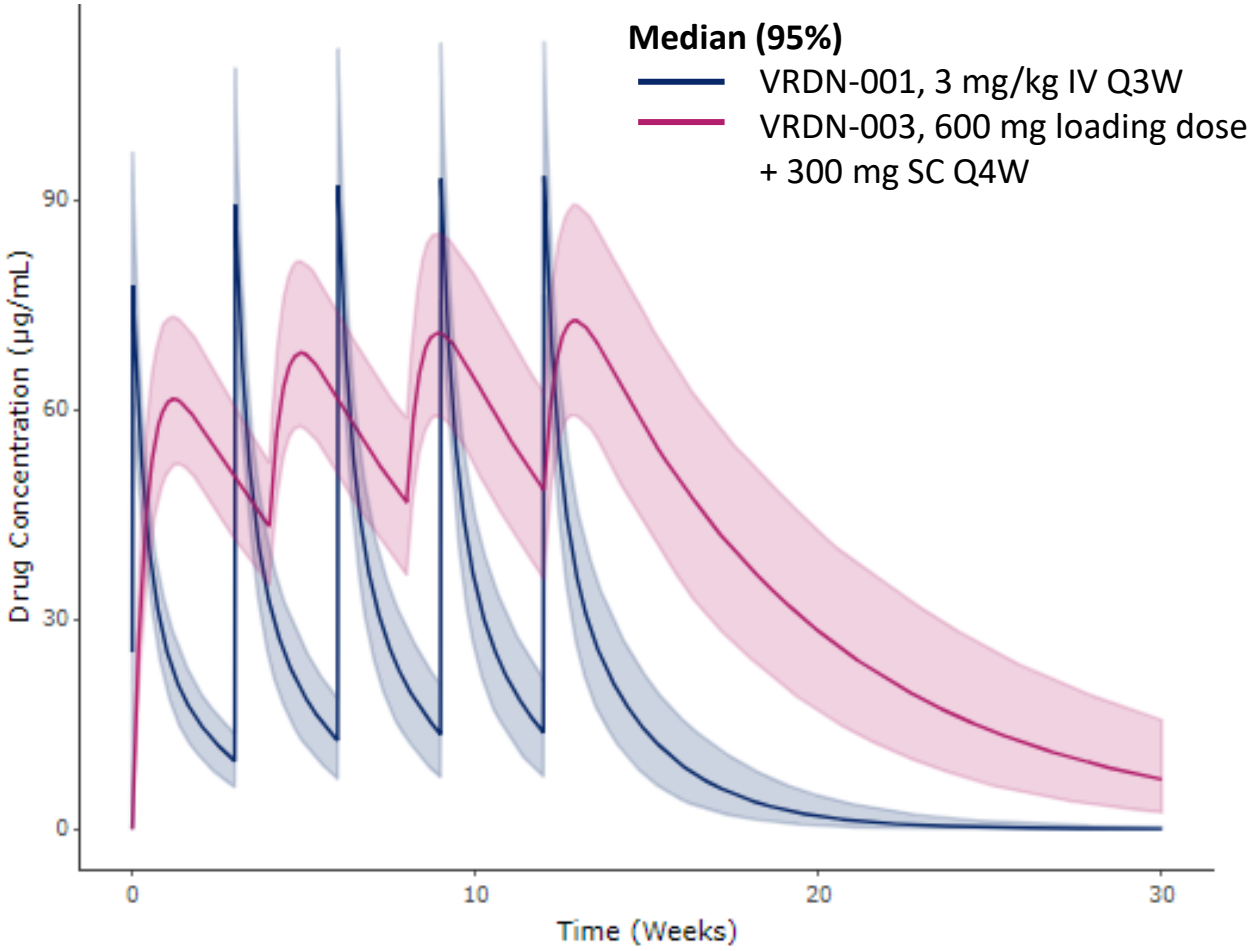
Methods for PK modeling in humans

- Population PK models were developed based on data obtained from VRDN-001 dosed in healthy volunteers
- VRDN-001 is described by a 2-compartment model with linear elimination from the central compartment
- **VRDN-003** is described by a model that uses identical parameters to the VRDN-001 model with the exception that clearance from the central compartment is reduced by 70%

VRDN-003 SC dosing simulations in humans



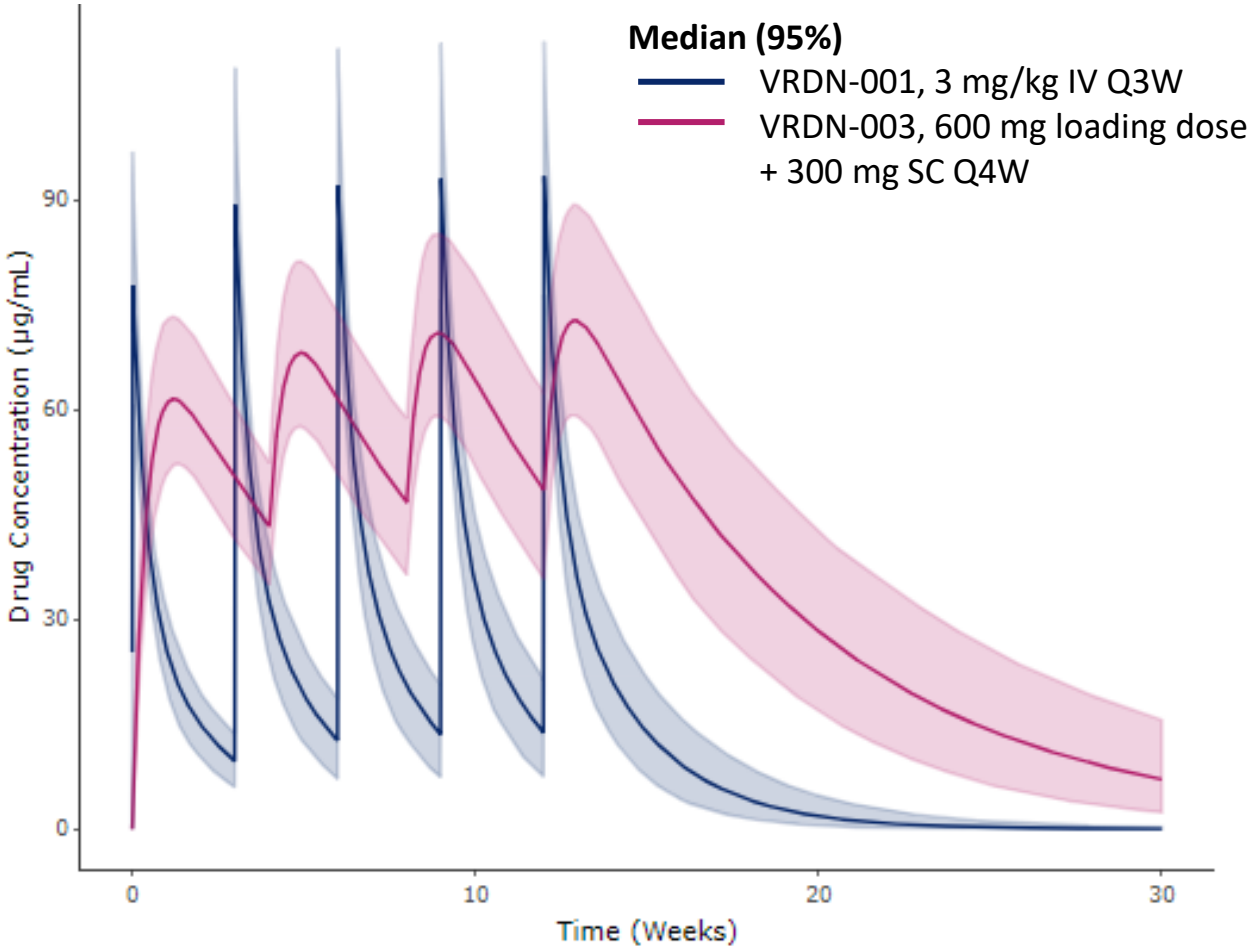
VRDN-003 SC dosing simulations in humans



Dosing regimen		C_{min} (µg/mL)
VRDN-001 IV	3 mg/kg Q3W	14
VRDN-003 SC (with 600 mg loading dose)	300 mg Q4W	49

Q2W, Q3W, Q4W; once every 2, 3, or 4 weeks

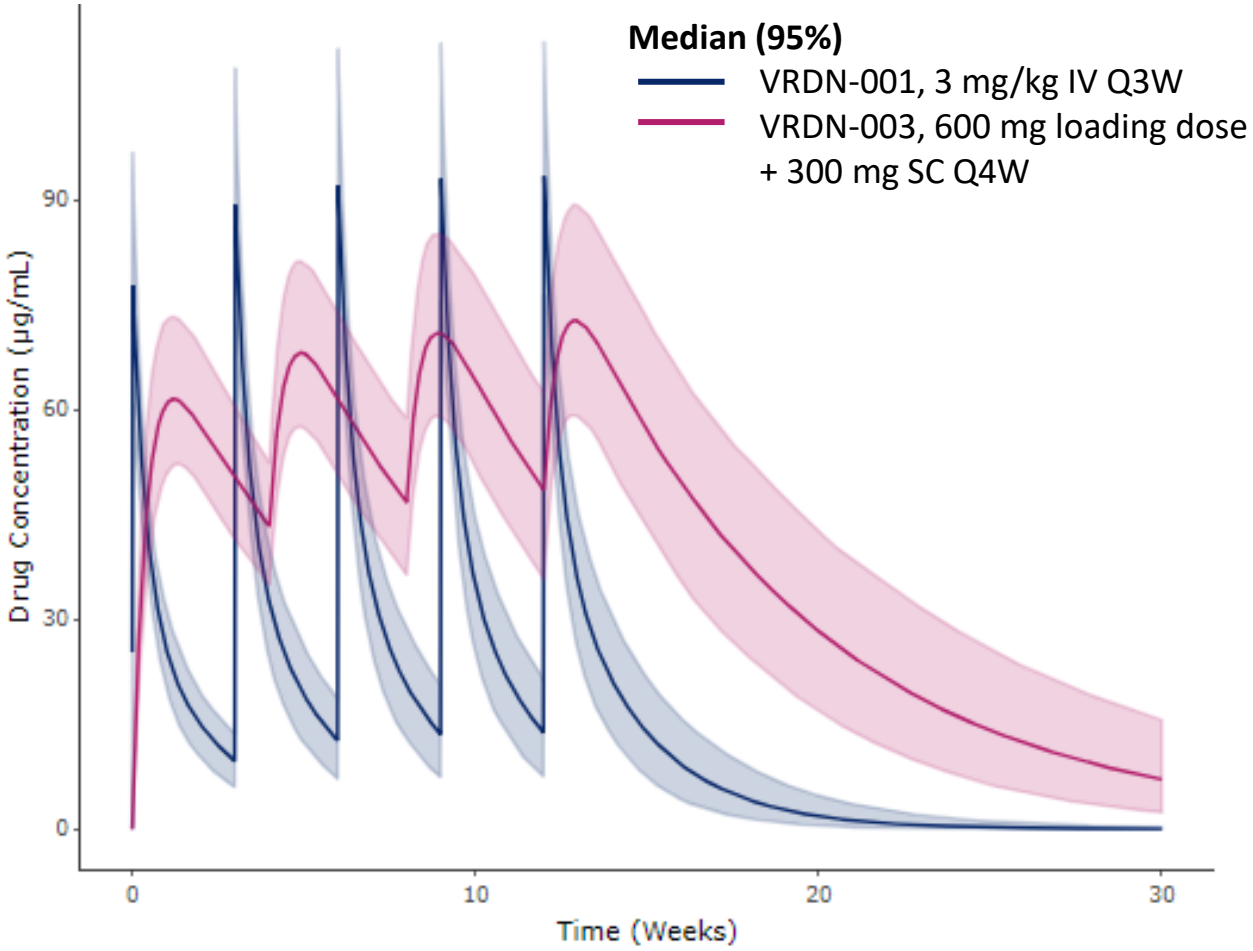
VRDN-003 SC dosing simulations in humans



Dosing regimen		C_{min} (µg/mL)
VRDN-001 IV	3 mg/kg Q3W	14
	10 mg/kg Q3W	46
VRDN-003 SC (with 600 mg loading dose)	300 mg Q4W	49

Q2W, Q3W, Q4W; once every 2, 3, or 4 weeks

VRDN-003 SC dosing simulations in humans



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	10 mg/kg Q3W	46
VRDN-003 SC (with 600 mg loading dose)	300 mg Q4W	49
	300 mg Q2W	104

Q2W, Q3W, Q4W; once every 2, 3, or 4 weeks

Conclusions

- **VRDN-003,** a next-generation half-life extended version of VRDN-001
  - Demonstrated greater exposure and twice the half-life of VRDN-001 for both IV and SC administration in NHPs
  - Demonstrated exposures with SC administration that matched or exceeded IV administration of VRDN-001 in human PK modeling
- Given **VRDN-003** has an extended half-life compared to VRDN-001, it has the potential for SC administration with similar clinical activity observed in the phase 2 studies of IV administration of VRDN-001 in active and chronic TED (ETA #OP-09-01)

Thank you!
Questions?

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