VRDN-003, a Novel Half-life Extended IGF-1 Receptor Antibody for Thyroid Eye Disease (TED): Preclinical Pharmacokinetics

Brent Dickinson, Kelly Foster, Barrett Katz, Vahe Bedian

Viridian Therapeutics, Inc., Waltham, MA

#PO394

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.
- Brent Dickinson, Kelly Foster, Barrett Katz, 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 (AAO presentation #xxxx)
- **VRDN-003** is a next-generation version of VRDN-001, with the same binding domain and an extended half-life, designed as a subcutaneous (SC) treatment option in TED
- A comparison of **VRDN-003** vs VRDN-001 pharmacokinetic parameters from a non-human primate (NHP) study are presented

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).

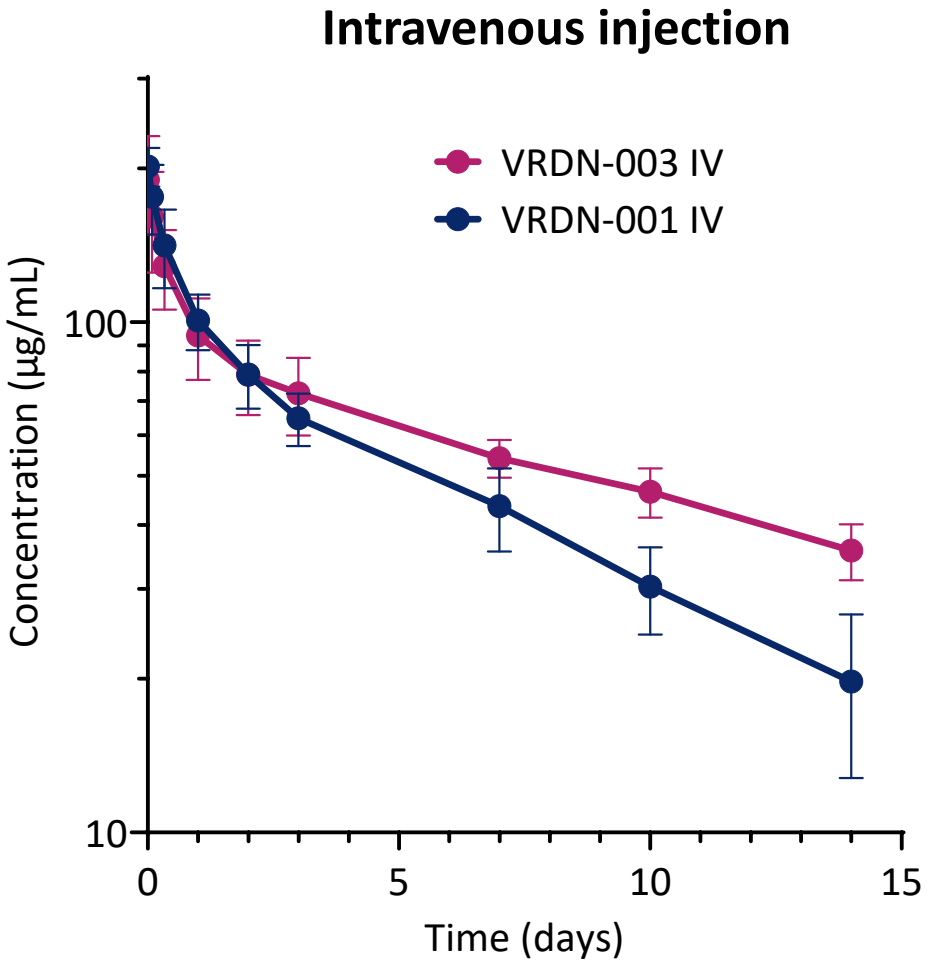
Methods for NHP study

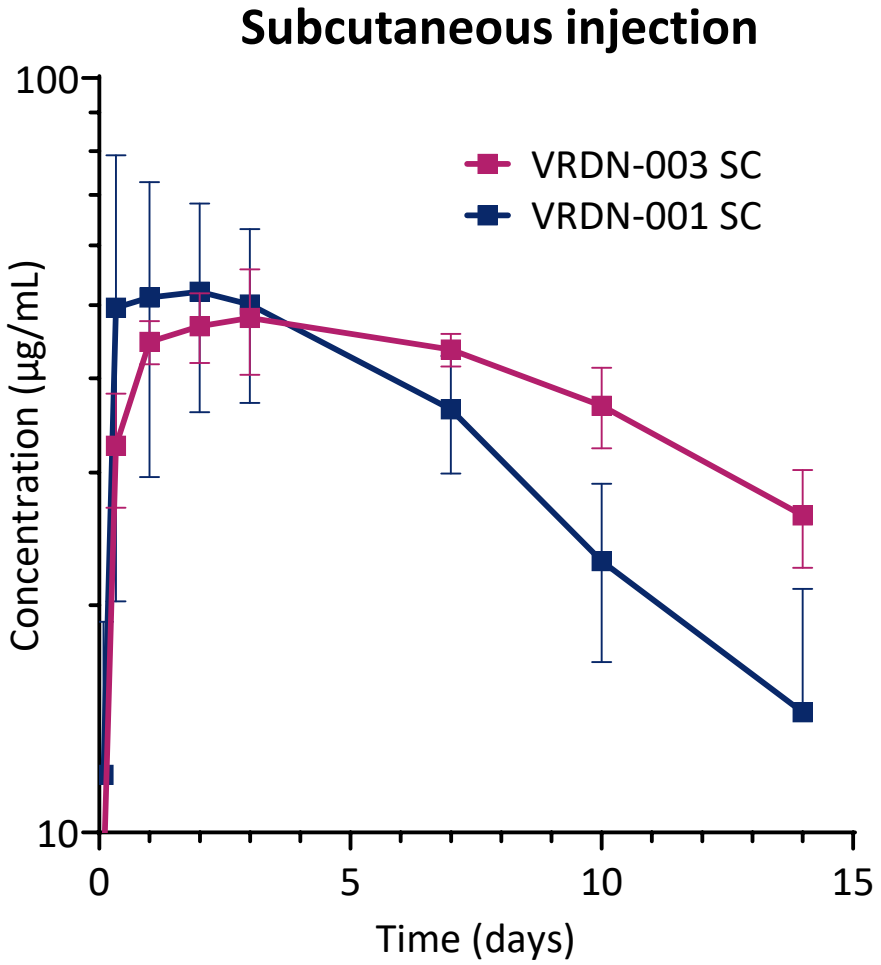
- VRDN-001 or **VRDN-003** was administered to a total of 16 cynomolgus monkeys as a single dose by either IV injection or SC injection at 7.5 mg/kg
- PK samples were collected at 9 time points through 14 days
- Data were analyzed using WinNonlin noncompartmental analysis

	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.

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.

- 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

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
- 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 (AAO presentation #PA012) potentially lessening the treatment burden for patients with TED

Thank you!
Questions?

VRDN-003, a Novel Half-life Extended IGF-1 Receptor Antibody for Thyroid Eye Disease (TED): Preclinical PK and Human PK Modeling

Brent Dickinson
Viridian Therapeutics, Inc., Waltham, MA

#PO394