Phase 1 Results in Healthy Volunteers Show Potential for Subcutaneous Administration of VRDN-003, a Half-life Extended Full Antagonist Antibody to IGF-1R, for Thyroid Eye Disease (TED)

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Disclosures

- VRDN-001/**VRDN-003** are being investigated in clinical studies and are not currently approved for commercial use in any country.
- These studies were sponsored by Viridian Therapeutics, Inc. and were conducted by IQVIA, a contract research organization, at a single site (QPS Miami in Miami, Florida).
- All authors met the ICMJE authorship criteria and had full access to relevant data.
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- The authors would like to thank the study investigators, research teams, and study participants who made this research possible.
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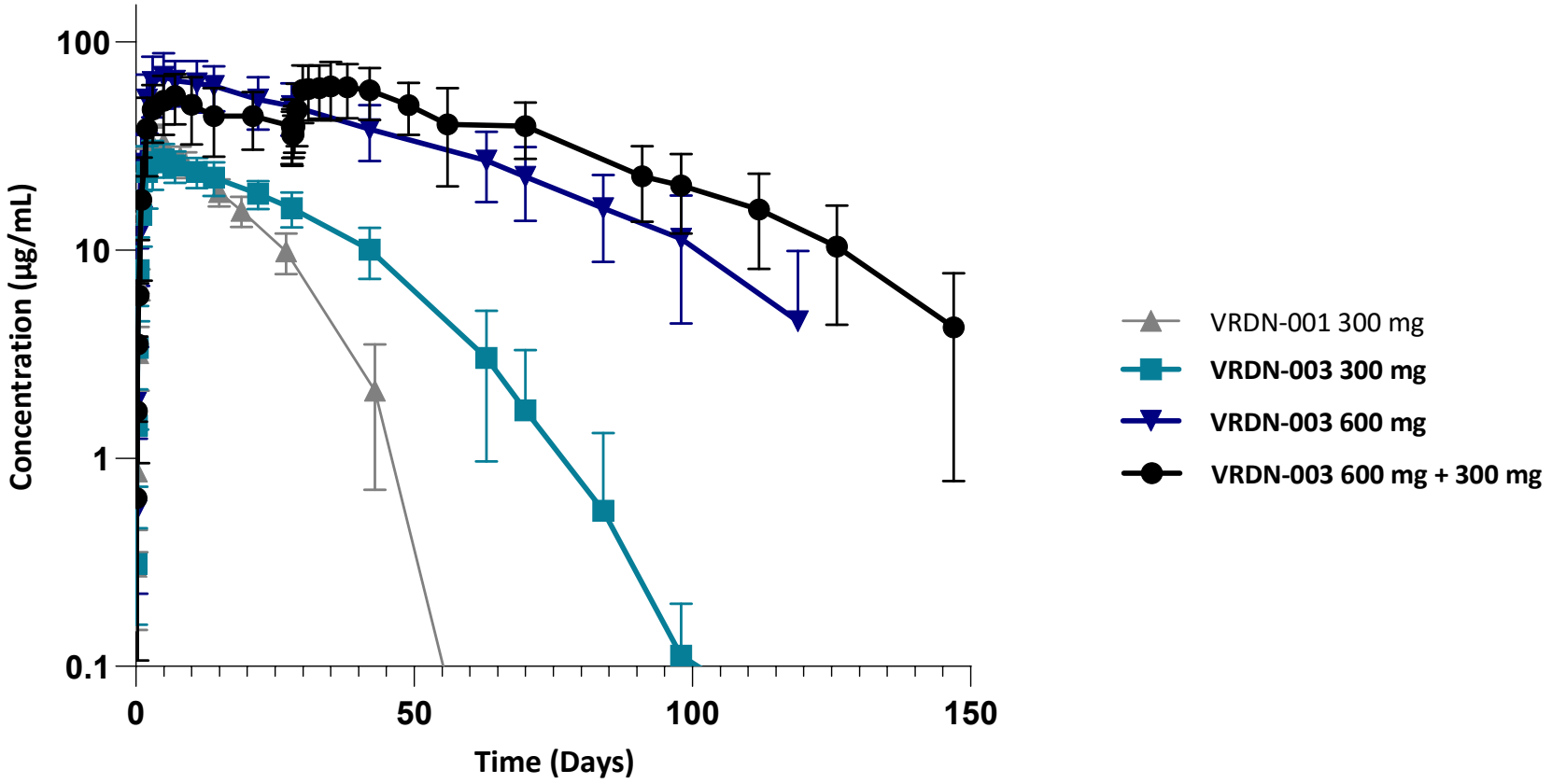
Introduction

- **VRDN-003** is a next-generation antibody that has the same binding domain as VRDN-001 with half-life extension modifications to optimize SC administration
- Phase 3 data in patients with active TED (THRIVE) showed significant improvements in TED symptoms after 5 IV infusions of VRDN-001 (10 mg/kg) administered Q3W and was generally well tolerated
- The preliminary safety and pharmacokinetics (PK) of **VRDN-003** were compared to those of VRDN-001 based on data collected in separate phase 1 studies in healthy volunteers (HVs)
- Preliminary data were utilized to model **VRDN-003** SC dosing regimens that would achieve C_{min} and AUC values similar to those achieved with VRDN-001 IV dosing

Methods

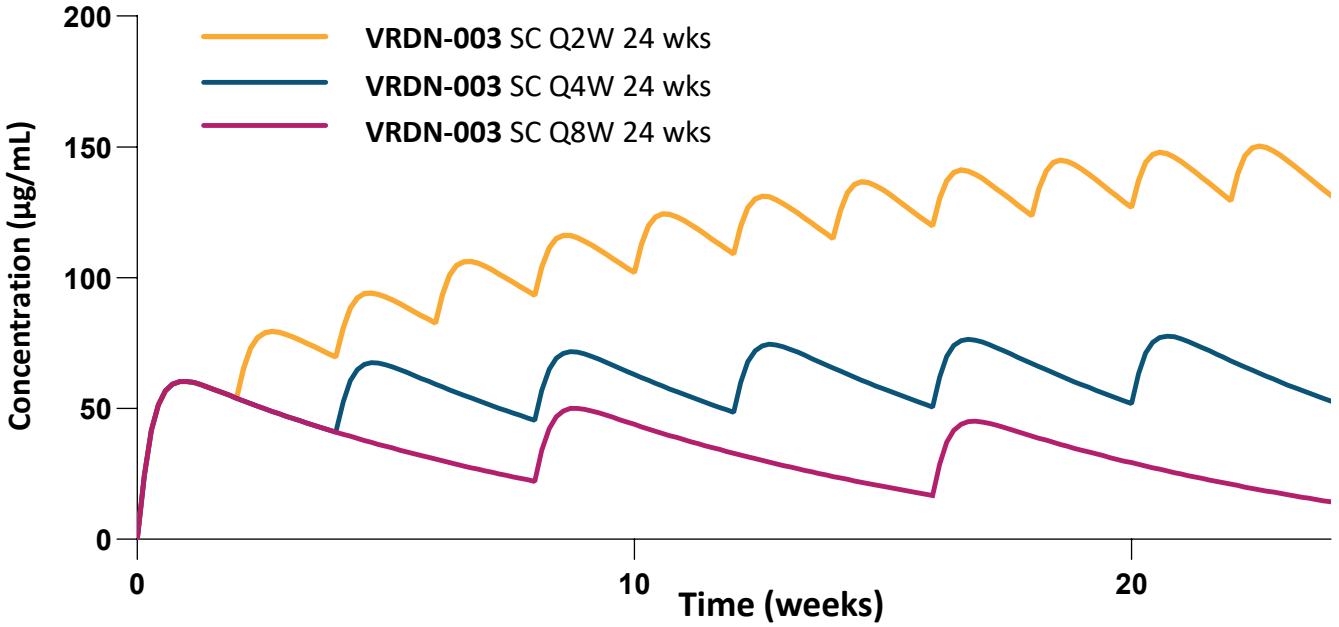
- In separate studies, 24 HVs received either **VRDN-003** or VRDN-001
  - **VRDN-003** SC:
    - 1 dose: 300 mg (n=6) or 600 mg (n=6)
    - 2 doses: 600 mg followed by 300 mg 28 days later (n=4)
  - VRDN-001 SC: 1 dose of 300 mg (n=8)
- Preliminary treatment-emergent adverse events (AEs) were assessed throughout the study follow-up period (120 days for **VRDN-003** 1-dose cohort, 148 days for **VRDN-003** 2-dose cohort, and 64 days for VRDN-001 cohort)
- PK parameters were assessed by noncompartmental analysis
- 2-compartment Population PK model was employed to simulate **VRDN-003** SC exposures following repeat dosing at different intervals (Q2W, Q4W, Q8W)

PK of subcutaneous VRDN-001 vs **VRDN-003**



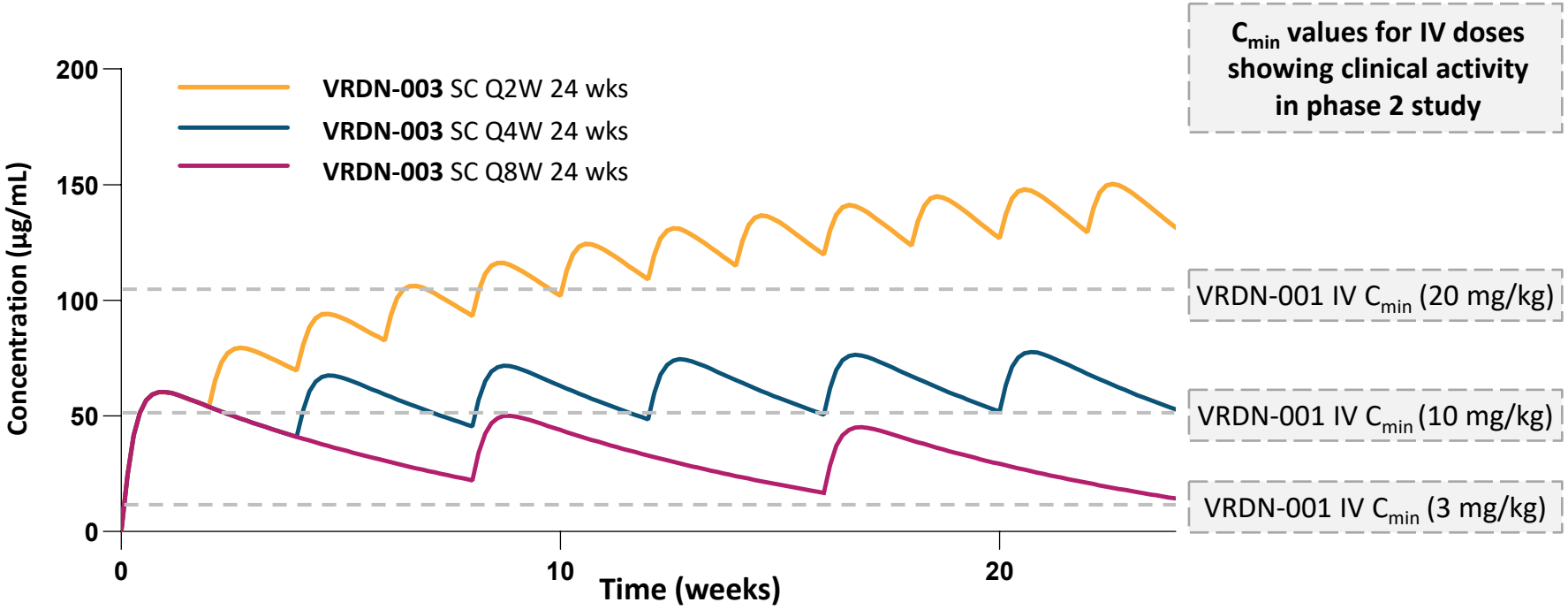
- VRDN-001 and **VRDN-003** have similar bioavailability (≥60%; IV data not shown)
- **VRDN-003** half-life (40-50 days) is 4-5 times longer than VRDN-001 half-life (10-12 days)

Simulated **VRDN-003** PK exposures with repeat subcutaneous dosing



PK model included a **VRDN-003** SC loading dose of 600 mg with subsequent SC injections of 300 mg for all 3 simulated dosing regimens

Simulated **VRDN-003** PK exposures with repeat subcutaneous dosing



VRDN-001 IV C_{mins} are from December 2023 PK model using data from phase 1 and phase 2 studies

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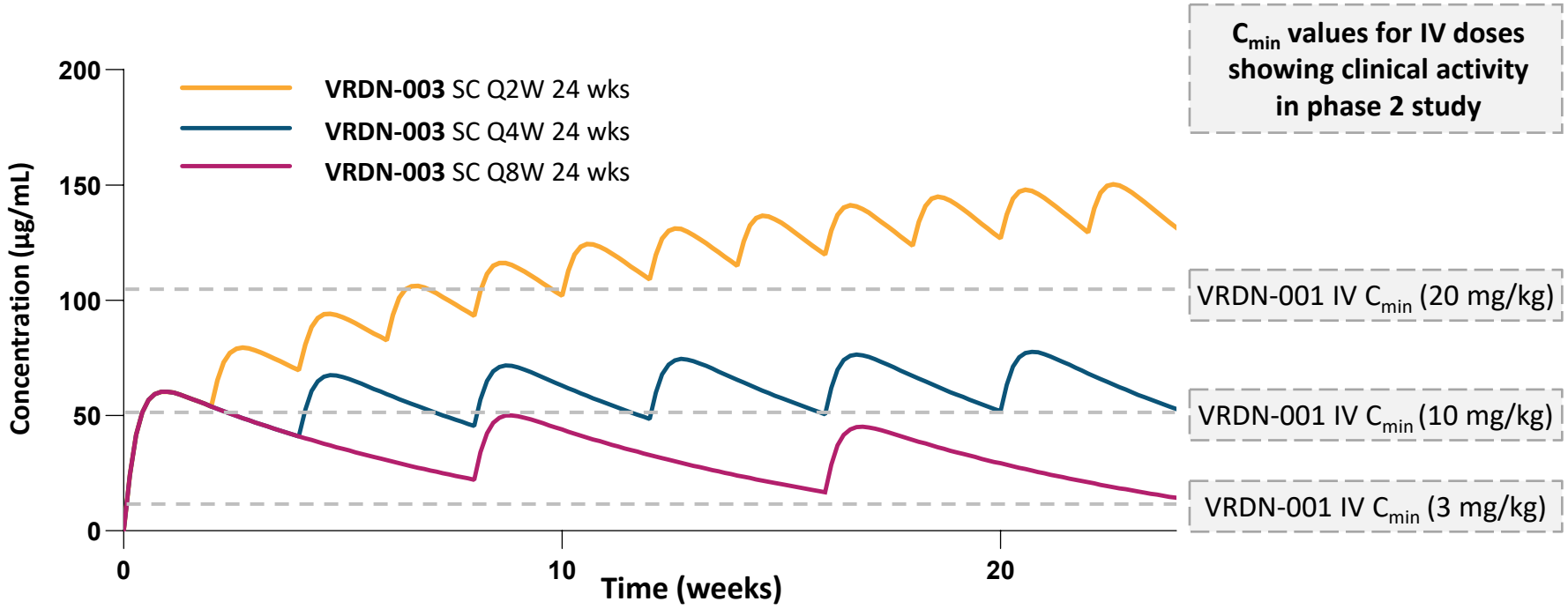

VRDN-001 IV C_{mins} are from December 2023 PK model using data from phase 1 and phase 2 studies

PK model included a **VRDN-003** SC loading dose of 600 mg with subsequent SC injections of 300 mg for all 3 simulated dosing regimens

- Three different **VRDN-003** SC dosing regimens were simulated, yielding predicted exposures within the range observed for VRDN-001 IV during its phase 2 dose-ranging proof-of-concept study
- The **VRDN-003** SC phase 3 studies, REVEAL-1 (active TED) and REVEAL-2 (chronic TED), are expected to assess both **Q4W** and **Q8W** regimens compared with placebo

Safety results

- There were no treatment-related discontinuations
- All treatment-related AEs resolved during follow-up

Patients, n	**VRDN-003** SC 1 dose (n=12)	**VRDN-003** SC 2 doses (n=4)	**VRDN-001** SC 1 dose (n=8)
All AEs	3	2	3
Treatment-related AEs	3	1	3
Injection site reactions*	1	--	1
Hyperglycemia	--	1	1
Thrombocytopenia	--	--	1
Insomnia	1	--	--
Hepatic enzyme increased	1	--	--
Serious AEs	--	--	--
Hearing impairment AEs*	--	--	--
Grade 3/4 AEs	--	--	--

* Injection site reactions and hearing impairment each include multiple MedDRA terms.
Preliminary data as of April 2024.

Conclusions

- **VRDN-003** half-life when administered SC was estimated to be 40-50 days, 4-5 times longer than that of VRDN-001
- PK modeling shows SC dosing of **VRDN-003** Q2W, Q4W, or Q8W could achieve similar exposure levels to IV dosing of VRDN-001 Q3W
- At 2 dose levels, single and repeat injections of **VRDN-003** SC were well tolerated
- Two pivotal clinical studies are planned to assess the safety and efficacy of **VRDN-003** SC injections at 2 dose regimens, Q4W or Q8W for 20 weeks:
  - **REVEAL-1 (Active TED)**
  - **REVEAL-2 (Chronic TED)**

UPDATE:

Topline results from **VRDN-001** (10 mg/kg) phase 3 study in active TED released Sept 10th

- **Achieved primary endpoint proptosis responder rate** with statistical significance ($p < 0.0001$): 70% for VRDN-001 vs 5% for placebo
- **Achieved all secondary endpoints** with statistical significance ($p < 0.0001$), including measures of proptosis, diplopia, and CAS
- **Generally well-tolerated**, with no treatment-related SAEs and **low (5.5%) placebo-adjusted rate of hearing impairment AEs**

AE = adverse event, IGF-1R = insulin-like growth factor-1 receptor, SAE = serious adverse event, TED = thyroid eye disease.

Thank you!
Questions?

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