# Subcutaneous VRDN-003 vs Veligrotug (VRDN-001), Full Antagonist Monoclonal Antibodies to IGF-1R for Thyroid Eye Disease (TED): Phase 1 Safety/PK/PD Studies in Healthy Volunteers

Jody Abrams[1], Thomas Ciulla[2], Brent Dickinson[2], Jyothi Vijayaraghavan[2], Cathy Michalsky[2], Vahe Bedian[2]

[1]Sarasota Retina Institute, Sarasota, FL; [2]Viridian Therapeutics, Inc., Waltham, MA.

PO104

# Disclosures

- Veligrotug (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.
- The authors thank Kelly Foster and Abiola Matthew, employees of Viridian at the time this work was completed, for their significant contributions to this work.
- The authors would like to thank the study investigators, research teams, and study participants who made this research possible.
- Presenting author: Jody Abrams is a clinical research investigator, advisory board member, and consultant for Viridian Therapeutics, Inc.; and is a clinical research investigator, advisory board member, consultant, and speaker for Horizon Therapeutics.
- Contact information: info@viridiantherapeutics.com

# Introduction

- **VRDN-003** is a next-generation monoclonal antibody that has the same binding domain as veligrotug (VRDN-001) with half-life extension to optimize SC dosing
- Prior phase 2 proof-of-concept results showed 2 IV infusions of veligrotug were generally well tolerated with clinical activity in active and chronic TED
- Recent topline data from THRIVE, a phase 3 study of veligrotug in active TED, showed:
  - 5 IV infusions of 10 mg/kg veligrotug administered Q3W led to significant and clinically meaningful improvements in TED symptoms at 15 weeks and were generally well tolerated
  - The primary and all secondary endpoints were statistically significant ($p < 0.0001$)
  - Veligrotug was generally well-tolerated, with no treatment-related SAEs and low (5.5%) placebo-adjusted rate of hearing impairment AEs
- Positive THRIVE data provide support for **VRDN-003** clinical development

# Introduction (cont.)

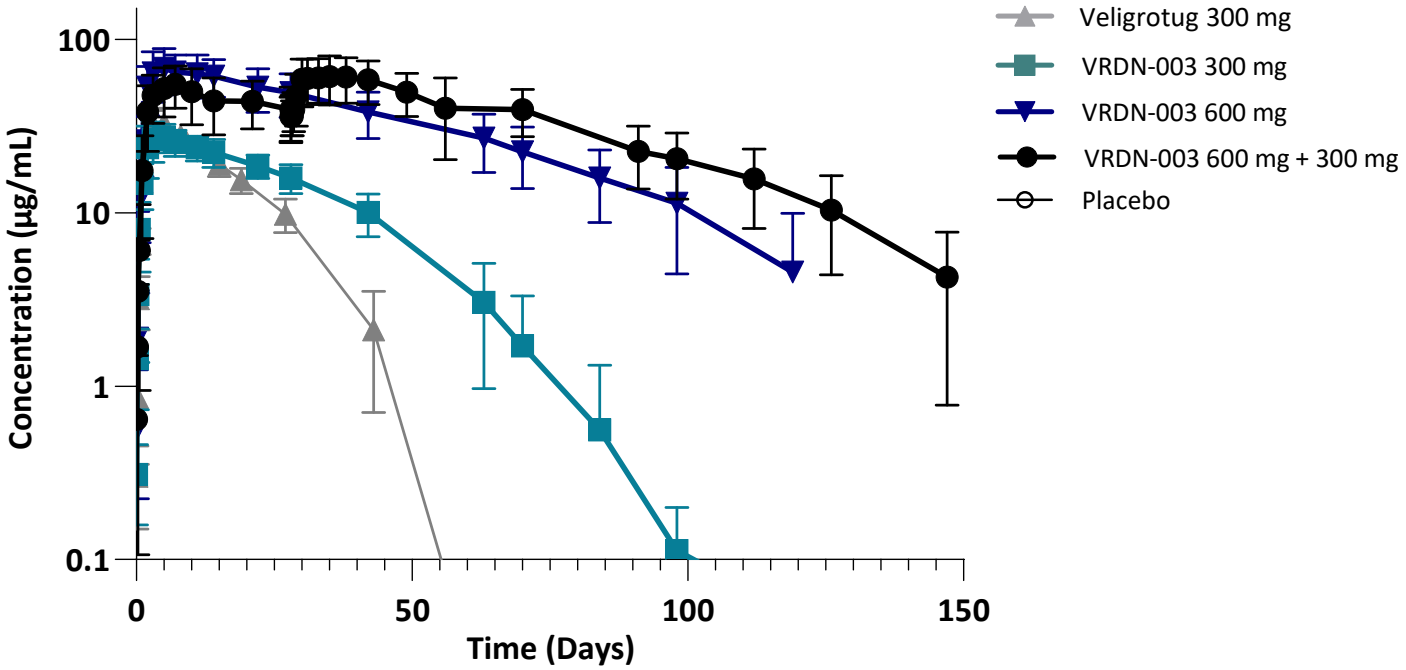
- The preliminary safety and pharmacokinetics/pharmacodynamics (PK/PD) of **VRDN-003** were compared with those of veligrotug based on data collected in separate phase 1 studies in healthy volunteers (HVs)
- Preliminary data were utilized to model **VRDN-003** SC dosing regimens that would achieve $C_{min}$ and AUC values similar to those achieved with veligrotug IV dosing

# Methods

- In separate studies, 24 HVs received either **VRDN-003** or veligrotug
  - **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)
  - Veligrotug 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 veligrotug cohort)
- PK parameters were assessed by noncompartmental analysis
- PD was assessed by measuring IGF-1 serum levels
- 2-compartment Population PK model was employed to simulate **VRDN-003** SC exposures following repeat dosing at different intervals (Q2W, Q4W, Q8W)

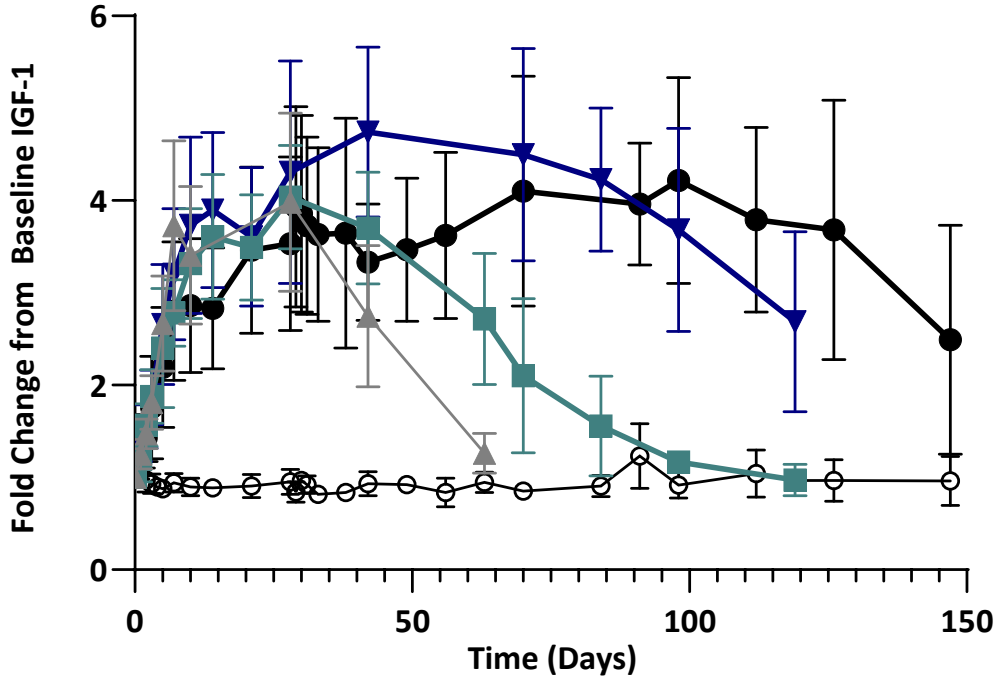
# PK/PD of subcutaneous **VRDN-003** vs veligrotug

## Pharmacokinetics



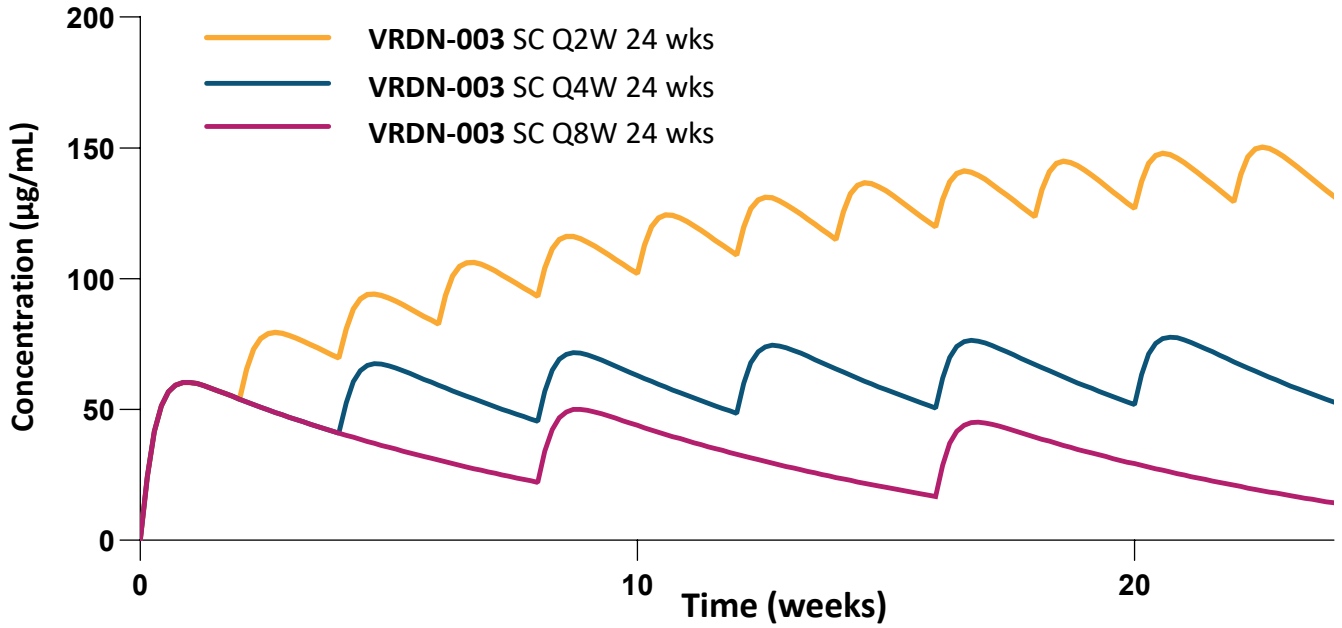

- Veligrotug and **VRDN-003** have similar bioavailability (≥60%; IV data not shown)
- **VRDN-003** half-life (40-50 days) is 4-5 times longer than veligrotug half-life (10-12 days)

## Pharmacodynamics




- IGF-1 serum levels were similar for both antibodies (>4-fold above baseline) but sustained longer for **VRDN-003** (>40 days)

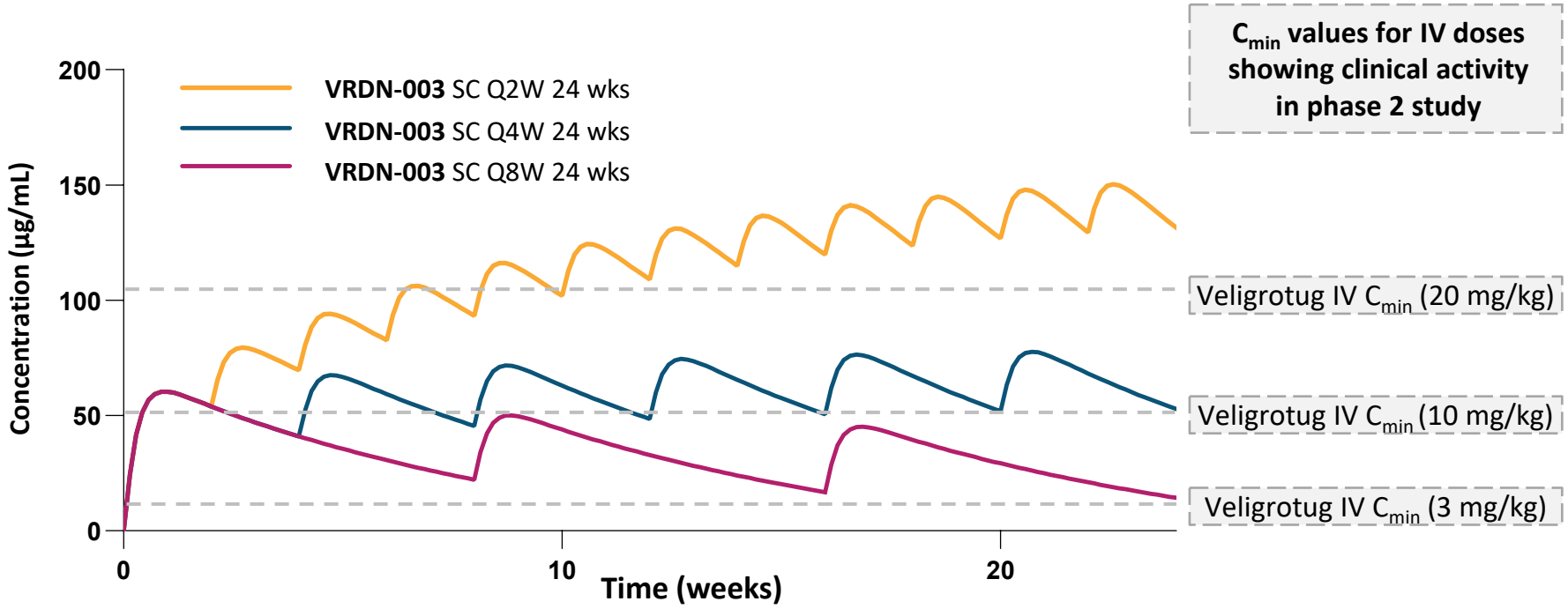
# Simulated **VRDN-003** PK exposures with repeat subcutaneous dosing




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

- Three different **VRDN-003** SC dosing regimens were simulated

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

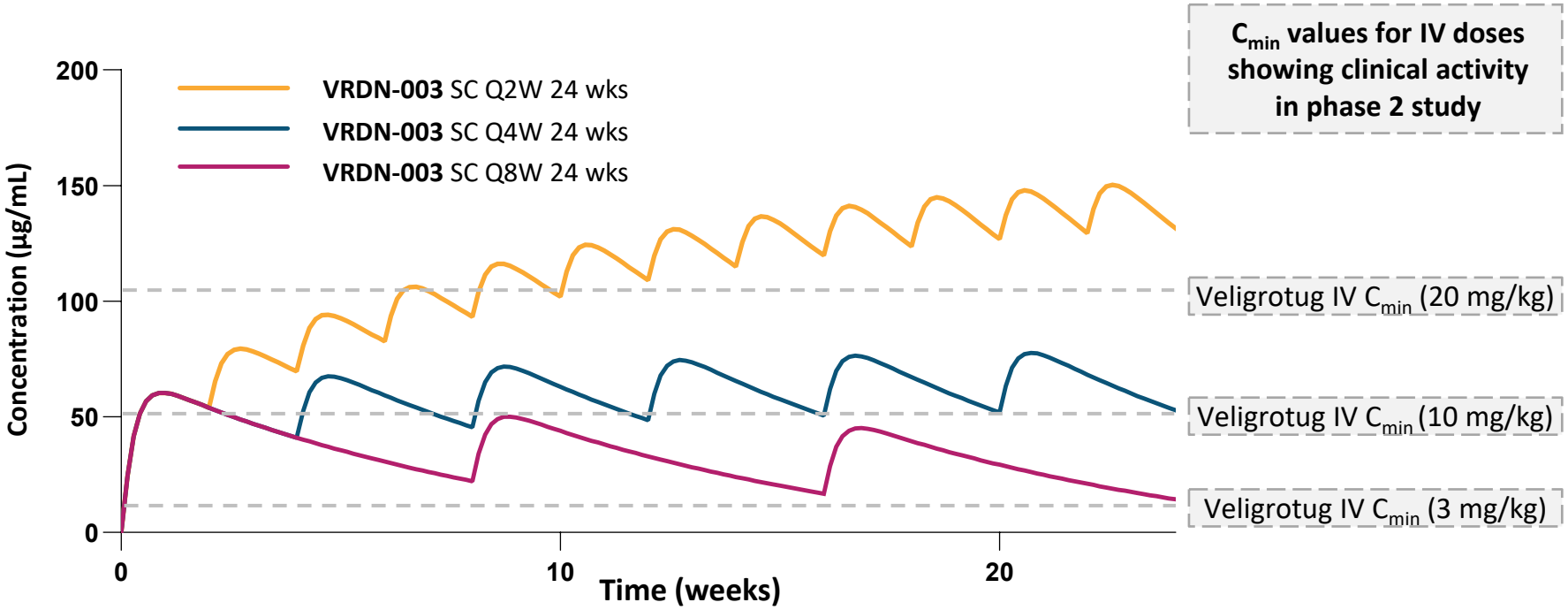



Veligrotug IV $C_{mins}$ are from December 2023 PK model using data from phase 1 and phase 2 studies

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
- They yielded predicted exposures within the range observed for veligrotug IV in its phase 2 study

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




Veligrotug 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
- They yielded predicted exposures within the range observed for veligrotug IV in its phase 2 study
- The **VRDN-003** SC phase 3 studies, REVEAL-1 (active TED) and REVEAL-2 (chronic TED), are assessing 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 with following | **VRDN-003** SC 1 dose (n=12) | **VRDN-003** SC 2 doses (n=4) | Veligrotug SC 1 dose (n=8) |
|---|---|---|---|
| **Any 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

- Phase 1 PK/PD/safety:
  - **VRDN-003** half-life when administered SC was appx 40-50 days, 4-5 times longer than that of veligrotug
  - PK modeling shows SC dosing of **VRDN-003** Q2W, Q4W, or Q8W could achieve similar exposure levels to IV dosing of veligrotug Q3W
  - **VRDN-003** SC demonstrated sustained increases in IGF-1 serum levels
  - At 2 dose levels, single and repeat injections of **VRDN-003** SC were well tolerated
- **VRDN-003** SC has the potential to reduce treatment burden via convenient, infrequent administration
- Two ongoing pivotal clinical studies are assessing the safety and efficacy of **VRDN-003** SC administration and each includes 2 dosing regimens, Q4W or Q8W:
  - **REVEAL-1 (Active TED)**
  - **REVEAL-2 (Chronic TED)**

# Thank you!
# Questions?

**Subcutaneous VRDN-003 vs Veligrotug (VRDN-001), Full Antagonist Monoclonal Antibodies to IGF-1R for Thyroid Eye Disease (TED): Phase 1 Safety/PK/PD Studies in Healthy Volunteers**

Jody Abrams
Sarasota Retina Institute, Sarasota, FL.

PO104