American Society of Ophthalmic Plastic and Reconstructive Surgery

FINANCIAL DISCLOSURE

All authors have had the following financial relationships with ineligible companies in the past 24 months:

	Company	Relationship type	Ended/ not ended
Steven Leibowitz	Viridian Therapeutics, Inc.	Research investigator & Advisory Board member	Not ended
	Amgen	Speaker's bureau	Not ended
	Lassen	Research investigator	Not ended
Thomas Ciulla	Viridian Therapeutics, Inc.	Employee	Not ended
Antonio Manuel Garrido Hermosilla	Viridian Therapeutics, Inc.	Research investigator	Not ended
	Horizon/Amgen	Research investigator	Not ended
	Immunovant	Research investigator	Not ended
	AJL Ophthalmic	Research investigator	Not ended
	Roche	Research investigator	Not ended
	Lassen	Research investigator	Not ended
	Argenx	Research investigator	Not ended

Disclosures

- **VRDN-003** is being investigated in clinical studies and is not currently approved for commercial use in any country.
- All authors met the ICMJE authorship criteria and had full access to relevant data.
- The authors would like to thank the study investigators, research teams, and study participants who made this research possible.
- Contact information: info@viridiantherapeutics.com

VRDN-003, Next-Generation Full Antagonist Monoclonal Antibody to IGF-1R: Two Randomized Placebo-Controlled Clinical Studies in Patients With TED (REVEAL-1 and REVEAL-2)

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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
- **VRDN-003** half-life was estimated to be 4-5 times that of veligrotug in a phase 1 study with healthy volunteers, potentially enabling low-volume SC administration as infrequently as Q8W, while achieving exposures in the range of those observed with veligrotug IV dosing Q3W

	Veligrotug IV	VRDN-003 SC
Administration	Intravenous infusion	Subcutaneous injection
Mechanism	Full antagonist	Full antagonist
Treatment regimen in phase 3 clinical studies	5 infusions Q3W with 30-minute infusion time	Dosing Q4W or Q8W for 20 weeks

Introduction (cont)

- The safety and efficacy of **VRDN-003 SC** injections will be evaluated in the REVEAL-1 and REVEAL-2 phase 3 studies
- Given that veligrotug and **VRDN-003** share the same binding domain, the following veligrotug phase 3 results are encouraging for REVEAL-1 and REVEAL-2:

- Primary endpoint **proptosis responder rate** was statistically significant ($p < 0.0001$): 70% for veligrotug vs 5% for placebo
- **All secondary endpoints** were statistically significant ($p < 0.0001$), including measures of proptosis, diplopia, and CAS
- Veligrotug was **generally well tolerated**, with no treatment-related SAEs and low (5.5%) placebo-adjusted rate of hearing impairment AEs

REVEAL-1

ACTIVE TED

- Moderate-to-severe active TED with ≥3 mm proptosis
- CAS ≥4
- ≤15 months — Since onset of TED signs and symptoms
- Patients will be randomized to drug or placebo

REVEAL-2

CHRONIC TED

- Moderate-to-severe chronic TED with ≥3 mm proptosis
- Any CAS (0-7)
- >15 months — Since onset of TED signs and symptoms
- Patients will be randomized to drug or placebo

Primary efficacy endpoint in North America: proptosis responder rate (proptosis reduction ≥2 mm vs baseline) at 24 weeks

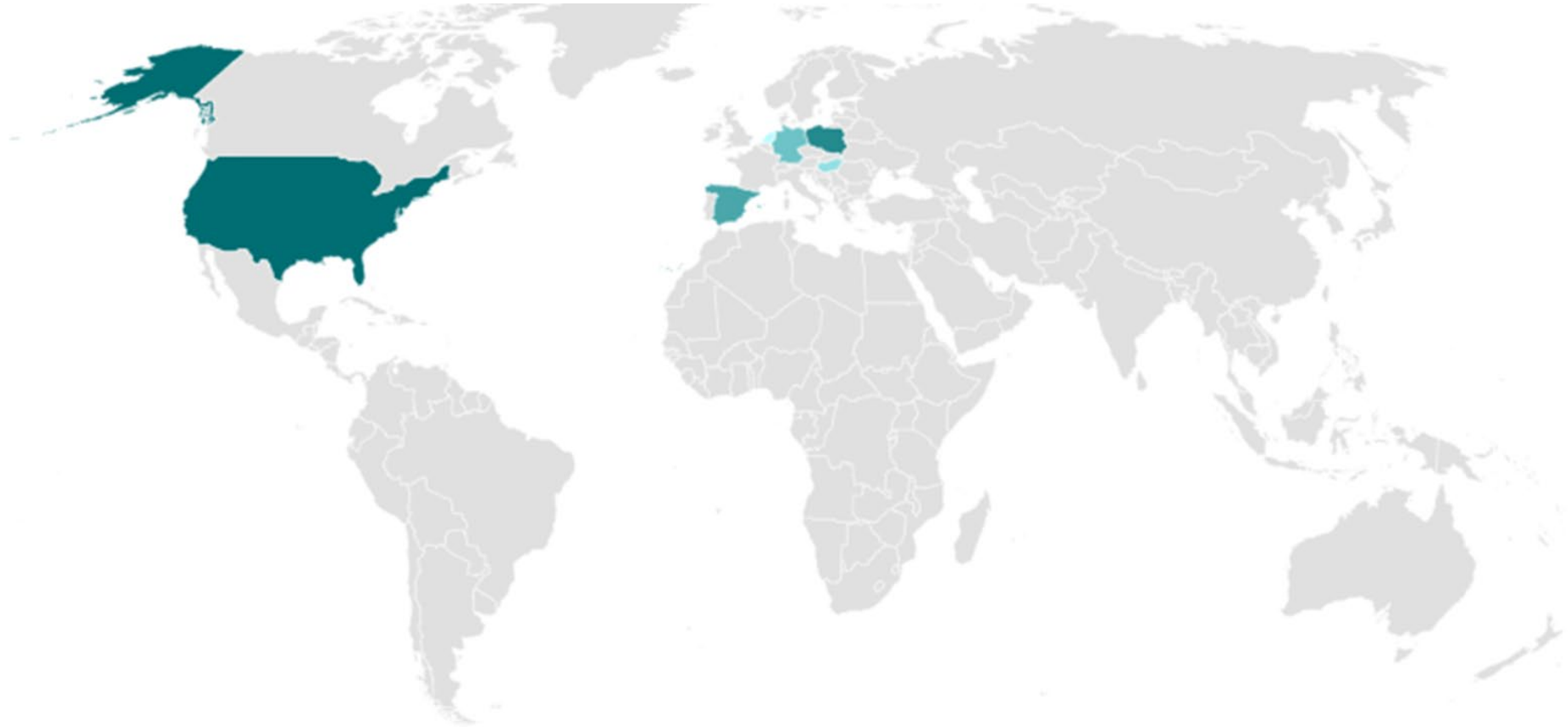
Primary efficacy endpoint in Europe: overall responder rate (proptosis reduction ≥2 mm vs baseline and either CAS reduction ≥2 points [REVEAL-1] or no worsening of CAS [REVEAL-2]) at 24 weeks

REVEAL-1 ACTIVE TED

REVEAL-2 CHRONIC TED

50 sites planned worldwide

- Germany
- Hungary
- Netherlands
- Poland
- Spain
- United States

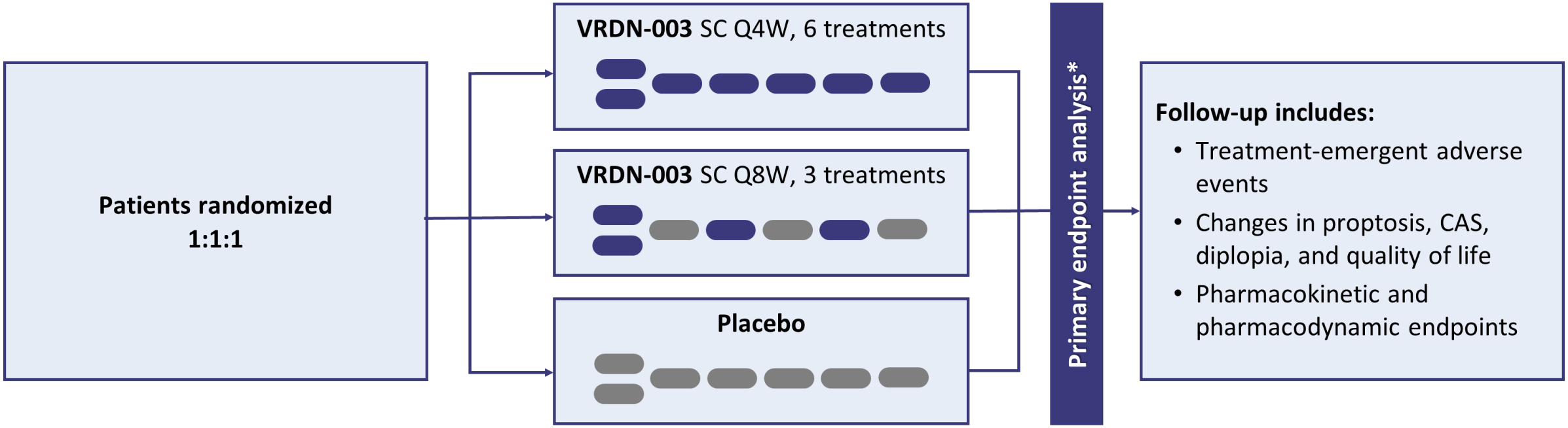


REVEAL-1 and REVEAL-2 trial design

Screening/Enrollment

Treatment Phase
(20 weeks treatment with primary endpoint at 24 weeks)

Follow-up
(through 52 weeks)



Day 1 loading dose given as two 300-mg SC injections
Each 300-mg SC injection is 2 mL

*Patients who do not meet responder criteria at 24 weeks may be eligible to receive a full course of open-label **VRDN-003** SC.

Conclusions

- Veligrotug phase 3 topline data support the potential for **VRDN-003** to demonstrate clinical activity when administered subcutaneously
- REVEAL-1 (active TED) and REVEAL-2 (chronic TED) are the first randomized, placebo-controlled double-masked phase 3 trials designed to assess the safety and efficacy of **VRDN-003** SC injections in TED
  - Both studies are currently enrolling
  - Both studies will test 2 different dosing regimens, Q4W and Q8W for 24 weeks; nonresponders at 24 weeks may be eligible for open-label **VRDN-003** SC
- **VRDN-003** SC has the potential to reduce treatment burden via convenient, infrequent administration

Thank you!
Questions?

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Primary and key secondary outcomes 15 weeks (5 infusions)

THRIVE Clinical Trial

		Veligrotug (n=75)	Placebo (n=38)	p-value
Proptosis	**Primary Endpoint:** Proptosis responder rate (Hertel)[1]	70%	5%	p < 0.0001
	Proptosis mean change from baseline (Hertel)	-2.89 mm	-0.48 mm	p < 0.0001
Diplopia	Diplopia complete resolution[2]	54%	12%	p < 0.0001
	Diplopia responder rate[3]	63%	20%	p < 0.0001
CAS	Clinical activity score (CAS) 0 or 1	64%	18%	p < 0.0001
	CAS mean change from baseline	-3.4	-1.7	p < 0.0001
Overall Response	Overall responder rate (ORR)[4]	67%	5%	p < 0.0001

[1] Percentage of participants with ≥2 mm reduction in proptosis from baseline in the study eye, without deterioration in the fellow eye (≥2 mm increase);
[2] Percentage of participants with baseline diplopia (Gorman Score >0) and a score of 0 at Week 15;
[3] Percentage of participants achieving a reduction of at least 1 on the Gorman subjective diplopia scale at week 15, among patients with diplopia at baseline;
[4] Percentage of participants with ≥2 mm reduction in proptosis AND ≥2-point reduction in CAS from baseline in the study eye, without corresponding deterioration [≥2 mm/point increase] in proptosis or CAS in the fellow eye. CAS = clinical activity score.

Most common adverse events

15 weeks (5 infusions)

	Veligrotug n=75, n (%)	**Placebo** n=38, n (%)
Participants with any AE	**66 (88%)**	**24 (63%)**
AEs occurring at ≥10% frequency in either arm		
Muscle spasms	32 (43%)	2 (5%)
Headache	16 (21%)	5 (13%)
Infusion related reaction (IRR)	13 (17%)	1 (3%)
Hearing impairment[1]	12 (16%)	4 (11%)
Hyperglycemia[1]	11 (15%)	2 (5%)
Fatigue[1]	10 (13%)	6 (16%)
Nausea	10 (13%)	3 (8%)
Ear discomfort	9 (12%)	1 (3%)
Diarrhea	8 (11%)	1 (3%)
Alopecia	6 (8%)	4 (11%)
Menstrual disorders[1,2]	8 / 34 (24%)	1 / 12 (8%)

[1] Includes multiple terms aggregated using standard sets of MedRA terms;
[2] Reported as percentage of menstruating women
AE = adverse event