THRIVE-2 Phase 3 Trial of Veligrotug in Chronic Thyroid Eye Disease (TED): Efficacy, Safety, and Quality of Life at 15 Weeks

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KEY TAKEAWAYS

- The THRIVE-2 trial of **veligrotug** is the first global phase 3 RCT of IGF-1R inhibition in chronic TED to show significant improvement not only in proptosis but also in diplopia.
- Improvements in TED symptoms translated to rapid and clinically meaningful improvements in QoL on the GO-QOL scale; improvements were observed as early as 3-6 weeks and reached values well over the clinically meaningful threshold (8 points) at Week 15.
- **Veligrotug** was generally well tolerated, with mostly mild AEs and a low discontinuation rate.
- Results suggest **veligrotug** may become a promising new treatment option in TED.

INTRODUCTION

- TED remains a disease with significant unmet need, especially in the chronic phase. More treatment options are needed to improve convenience, efficacy, and/or safety.
- **Veligrotug**, a full antagonist humanized mAb to IGF-1R, was assessed in THRIVE-2 in chronic TED (onset >15 months, proptosis ≥3 mm above normal, and any CAS). Patients received either 10 mg/kg **veligrotug** or placebo given Q3W for a total of 5 IV infusions.
- Safety and efficacy including proptosis, diplopia, CAS, and GO-QOL were evaluated at Week 15.
  - CAS is a 7-point scale used to assess TED-related inflammatory activity.
  - GO-QOL is a disease-specific questionnaire that assesses QoL in TED.
- See RCOphth ePoster for THRIVE results in active TED.

BASELINE CHARACTERISTICS

	Veligrotug (n=125)	Placebo (n=63)
Age, mean years (SD)	50.5 (13.5)	50.7 (12.0)
Female, % (n)	76% (95)	73% (46)
Proptosis (Hertel), mean mm (SD)	24.3 (3.3)	23.8 (3.3)
CAS, mean (SD)	2.7 (1.9)	2.5 (1.8)
CAS 0 or 1, % (n)	35% (44)	35% (22)
CAS ≥3, % (n)	57% (71)	52% (33)
Diplopia at baseline, % (n)	52% (65)	59% (37)
Diplopia, mean Gorman score (SD)[1]	2.0 (0.8)	2.1 (0.9)
Time since onset of TED signs/symptoms, mean months (SD)	69.8 (78.9)	81.7 (83.7)
GO-QOL, mean overall score (visual function + appearance)	61.0	66.8
GO-QOL, mean visual function subscale score	77.1	77.2
GO-QOL, mean appearance subscale score	51.3	56.6

[1]In patients with diplopia at baseline.

EFFICACY AND SAFETY AT WEEK 15

Efficacy endpoints		Veligrotug (n=125)	Placebo (n=63)	p-value
Overall Response	Overall responder rate (MRI/CT)[1]	48%	3%	p < 0.0001
	Overall responder rate (Hertel)	56%	7%	p < 0.0001
Proptosis (Hertel)	Proptosis responder rate[2]	56%	8%	p < 0.0001
	Proptosis mean CFB, mm	-2.34	-0.46	p < 0.0001
Proptosis (MRI/CT)	Proptosis responder rate	48%	3%	p < 0.0001
	Proptosis mean CFB, mm	-2.07	-0.36	p < 0.0001
Diplopia	Diplopia complete resolution[3]	32%	14%	p = 0.0152
	Diplopia responder rate[4]	56%	25%	p = 0.0006
CAS *(prespecified exploratory endpoints)*	CAS 0 or 1[5]	54%	24%	p = 0.0060
	CAS mean CFB[5]	-2.9	-1.3	p < 0.0001

Endpoints shown are primary or secondary endpoints in at least one region, unless otherwise noted. Missing values were imputed using prespecified imputation methodology. Results were obtained from a GEE model with an unstructured covariance matrix. [1]Primary endpoint in Europe and Australia; percentage of participants with ≥2-mm reduction in proptosis (by MRI/CT) AND no worsening in CAS from baseline in the study eye, without corresponding deterioration (≥2-mm/point increase) in proptosis or CAS in the fellow eye of 0 at Week 15. [2]Primary endpoint in North America: percentage of participants with ≥2-mm reduction in proptosis from baseline in the study eye (by Hertel), without deterioration in the fellow eye (≥2-mm increase). [3]Percentage of participants reporting baseline diplopia (Gorman score >0) and a score of 0 at Week 15; [4]Percentage of participants reporting a score reduction of at least 1 on the Gorman subjective diplopia scale, among patients with diplopia at baseline. [5]Of participants with CAS ≥3 at baseline (n=71, veligrotug; n=33, placebo); CAS subpopulation analyses were prespecified exploratory endpoints and statistical p values are for descriptive purposes only.

AEs occurring at ≥10% frequency in either arm Patients, % (n)	Veligrotug (n=125)	Placebo (n=63)
Muscle spasms	36% (45)	6% (4)
Headache	14% (18)	13% (8)
Hearing impairment[1]	13% (16)	3% (2)
Fatigue[1]	12% (15)	8% (5)
Diarrhea	11% (14)	10% (6)
Hyperglycemia[1]	10% (13)	5% (3)
Menstrual disorders[1,2]	33% (16/48)	10% (2/20)

Three serious AEs in 3 **veligrotug** patients: Grade 3 vertigo (related), Grade 2 arthralgia (unrelated), Grade 2 metabolic encephalopathy (unrelated). Two serious AEs in 2 placebo patients: Grade 3 urticaria (related), Grade 3 fatigue (unrelated).
[1]Includes multiple terms aggregated using standard sets of MedDRA terms. [2]Reported as percentage of menstruating women.

- Most AEs were mild in both arms: 75% vs 73% for **veligrotug** vs placebo.
- There was a low treatment discontinuation rate of 6% in the **veligrotug** arm.
- Serious AEs occurred in 5 patients: 3 **veligrotug** and 2 placebo (1 treatment-related per arm).

GO-QOL OUTCOMES*

Overall

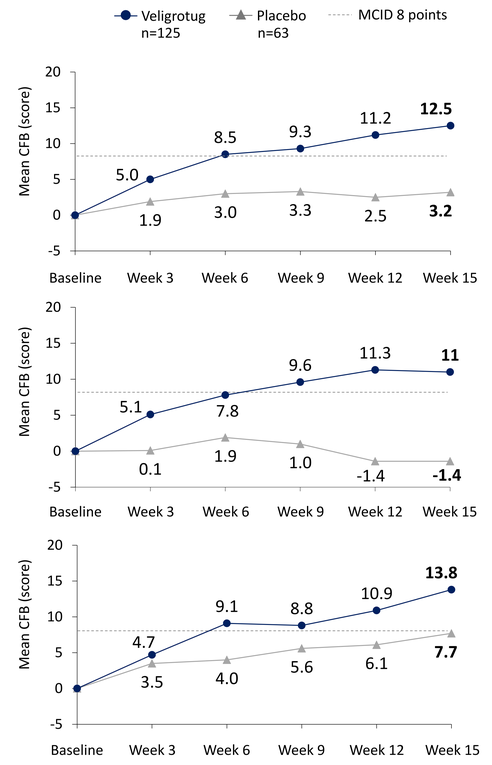
(comprised of 2 subscales, with 8 questions each [scale 0-100])

Visual function subscale

(limitations in activities: biking, walking, driving, reading, watching TV, moving around house, and hobbies)

Appearance subscale

(psychosocial influence: changed appearance, reactions from others, self-confidence, social activities, and relationships)



*Prespecified exploratory analysis at Week 15 and post hoc at earlier timepoints. GO-QOL MCID (minimal clinically important difference) vs baseline is 8 points. Nominal p <0.01 for all at Week 15.

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PDF of poster and additional information including THRIVE Study Group: Scan QR code.

Abbreviations used in poster: AE, adverse event; CAS, clinical activity score; CFB, change from baseline; GEE, generalized estimating equations; GO-QOL, Graves' Ophthalmopathy Quality of Life questionnaire; IGF-1R, insulin-like growth factor-1 receptor; IV, intravenous; mAb, monoclonal antibody; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; QoL, quality of life; Q3W, every 3 weeks; TED, thyroid eye disease.

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