Safety, Efficacy, and Quality of Life Outcomes of Subcutaneous Lonigutamab (Anti–IGF-1R): Week 12 Results from a Phase 1/2 Proof of Concept Study in Patients with Thyroid Eye Disease

Shoaib Ugradar[1], David A. Kostick[2], Jane Spadaro[3], Dinesh Selva[4], Jean-Louis deSousa[5], Krishna Tumuluri[6], Jwu Jin Khong[7]

[1]Private practice, Beverly Hills, CA, USA; [2]Florida Eye Specialists, Jacksonville, FL, USA; [3]Department of Ophthalmology, Corewell Health William Beaumont University Hospital, Royal Oak, MI, USA, and Kahana Oculoplastic and Orbital Surgery, Livonia, MI, USA; [4]Adelaide University, Adelaide, SA, Australia; [5]Lions Eye Institute, Nedlands, WA, Australia; [6]Westmead Hospital, Westmead, NSW, Australia, Macquarie University, Sydney, NSW, Australia, and Save Sight Institute, University of Sydney, Sydney, NSW, Australia; [7]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, VIC, Australia, and Department of Surgery, University of Melbourne, Melbourne, VIC, Australia.

American Society of Ophthalmic Plastic and Reconstructive Surgery

FINANCIAL DISCLOSURE

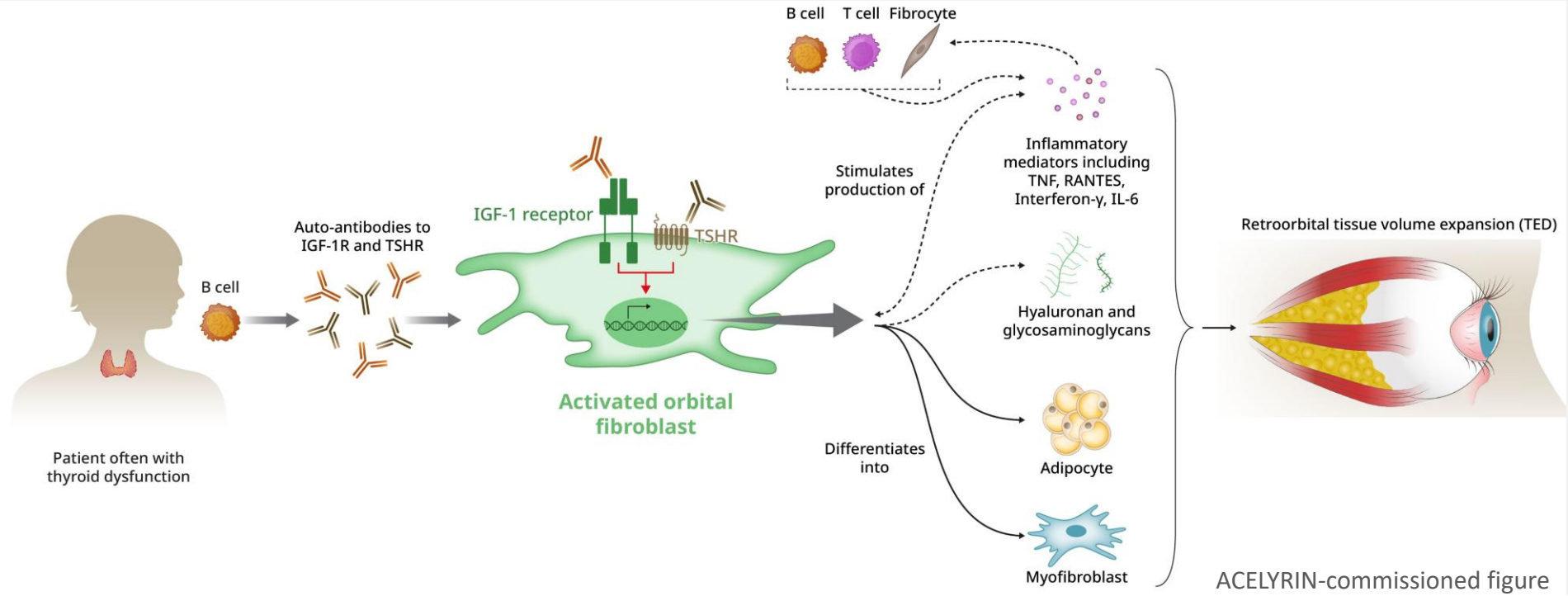
I/All authors have had the following financial relationships with ineligible companies in the past 24 months:

Name	Company	Relationship type	Ended/not ended
Shoaib Ugradar	ACELYRIN, INC.	Consultant/Advisor	No (not ended)
Shoaib Ugradar	Viridian Therapeutics	Consultant/Advisor	No (not ended)
David A. Kostick	Amgen	Speakers Bureau	No (not ended)
Krishna Tumuluri	Amgen	Consultant/Advisor	Yes (ended)
Jwu Jin Khong	ACELYRIN, INC.	Consultant/Advisor	No (not ended)
Jwu Jin Khong	Alkira Bio	Consultant/Advisor	No (not ended)
Jwu Jin Khong	Amgen	Consultant/Advisor	No (not ended)
Jwu Jin Khong	Centre for Eye Research Australia	Researcher	No (not ended)
Jwu Jin Khong	Roche	Consultant/Advisor	No (not ended)

This study was funded by ACELYRIN, INC., a wholly owned subsidiary of Alumis Inc.

Background

- **Thyroid eye disease (TED)** is a chronic, **debilitating**, and in the most severe cases, **vision-threatening** condition driven by aberrant stimulation of the IGF-1R pathway[1,2]
- **IGF-1R** is a clinically validated therapeutic target in **TED**[1-3]



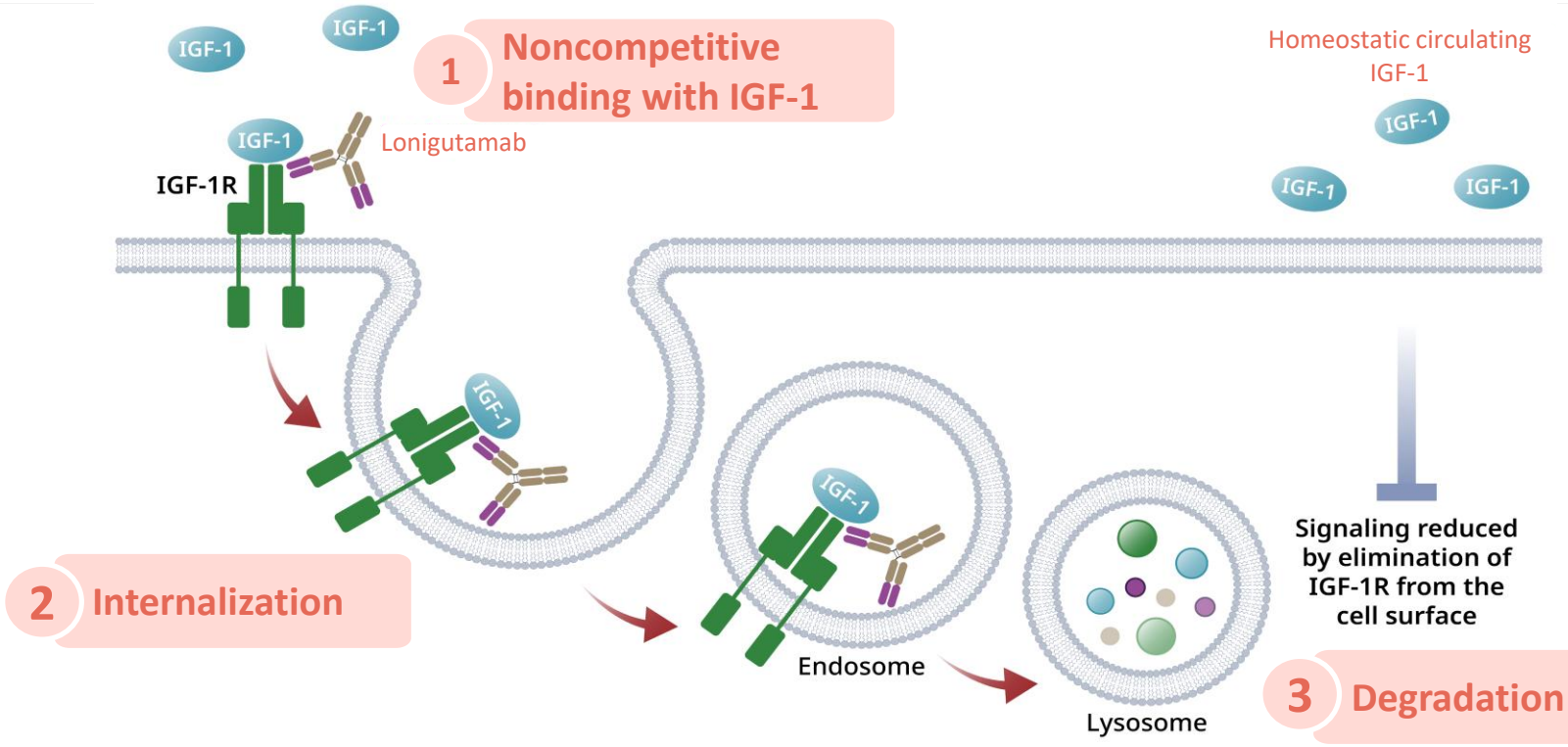
- Despite treatment advances, opportunity still exists for **durable multifaceted responses** and **a reduction in the treatment-limiting side effects** seen with anti–IGF-1Rs that directly compete with IGF-1 binding[4]

IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; IL-6, interleukin 6; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; TNF, tumor necrosis factor; TSHR, thyroid-stimulating hormone receptor.

1. Smith TJ, et al. *Endocr Rev*. 2019;40(1):236-67. 2. Men CJ, et al. *Ther Adv Ophthalmol*. 2021;13:25158414211027760. 3. Douglas RS, et al. *N Engl J Med.* 2020;382(4):341-52. 4. Wang X, et al. *Endocrine*. 2024;85(1):313-20.

Lonigutamab mechanism of action

〉 **Lonigutamab** is a novel, high-affinity, subcutaneously administered, **anti–IGF-1R monoclonal antibody** with a unique **noncompetitive** mechanism of action[1,2]



Potential Therapeutic Benefits of Lonigutamab

- Convenient Subcutaneous Administration
- Unique MoA
- Potentially Improved Benefit/Risk Profile

OBJECTIVE: To present week 12 data from 3 fully enrolled cohorts of a phase 1/2 dose-ranging study evaluating lonigutamab in patients with TED (NCT05683496)[3]

Figure created with BioRender.com. IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; MoA, mechanism of action; TED, thyroid eye disease.

1. Akla B, et al. *Mol Cancer Ther*. 2020;19(1):168-77. 2. Data on file. ACELYRIN, INC. a wholly owned subsidiary of Alumis Inc. 3. ClinicalTrials.gov identifier: NCT05683496. Updated July 1, 2025. Accessed August 5, 2025. https://clinicaltrials.gov/study/NCT05683496.

Phase 1/2 study design

NCT05683496[1]

Key eligibility criteria

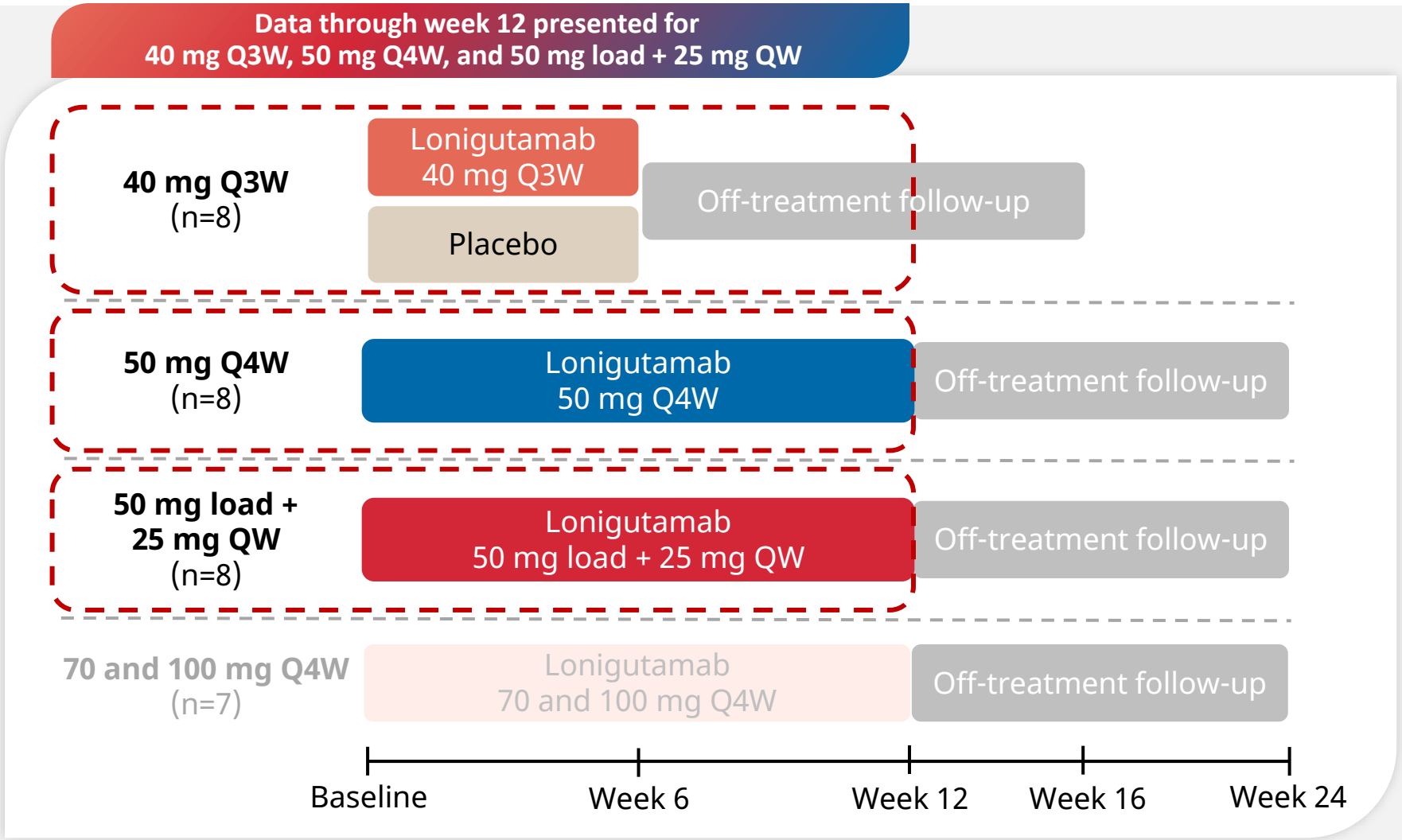
- Proptosis ≥3 mm above normal range in the study eye
- CAS ≥4 (using a 7-item scale) for the most severely affected eye
- Onset of active TED symptoms within 24 months before baseline/day 1

Efficacy endpoints

- Proptosis response (≥2-mm reduction in the study eye)
- CAS (≥2-point improvement; score of 0/1)
- Diplopia response (improvement in ≥1 Bahn-Gorman grade)
- GO-QoL (change from baseline)

Safety endpoints

- Incidence and characterization of nonserious and serious TEAEs



40 mg Q3W data as of December 6, 2023; 50 mg Q4W and 50 mg load + 25 mg QW data as of December 12, 2024.

CAS, Clinical Activity Score; GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

1. ClinicalTrials.gov identifier: NCT05683496. Updated July 1, 2025. Accessed August 5, 2025. https://clinicaltrials.gov/study/NCT05683496.

Demographics and baseline characteristics

	Placebo n=2	Lonigutamab (40 mg Q3W) n=6	Lonigutamab (50 mg Q4W) n=8	Lonigutamab (50 mg load + 25 mg QW) n=8
Age, mean (SD), years	49.5 (12.0)	43.8 (13.7)	45.6 (11.4)	42.1 (13.2)
Female, n (%)	2 (100.0)	5 (83.3)	3 (37.5)	5 (62.5)
White, n (%)	1 (50.0)	5 (83.3)	4 (50.0)	4 (50.0)
BMI, mean (SD), kg/m^2	28.6 (3.5)	26.6 (7.6)	28.1 (3.4)	26.6 (4.0)
Months since onset of TED, mean (SD)	14.6 (4.6)	10.2 (6.8)	11.8 (5.9)	10.4 (3.5)
Smoking status, n (%)				
Never	2 (100.0)	2 (33.3)	6 (75.0)	5 (62.5)
Past	0	4 (66.7)	1 (12.5)	3 (37.5)
Current	0	0	1 (12.5)	0
Proptosis for study eye[a], mean (SD), mm	26.0 (0)	26.2 (2.6)	24.4 (3.5)	22.5 (2.5)
CAS for study eye, mean (SD)	5.5 (2.1)	4.8 (1.0)	5.0 (1.1)	5.1 (0.8)
Diplopia at baseline, n (%)	2 (100.0)	4 (66.7)	5 (62.5)	6 (75.0)
GO-QoL total score at baseline, mean (SD)	54.7 (2.2)	53.4 (28.0)	60.2 (23.6)	60.2 (22.1)
Visual functioning	78.1 (22.1)	55.9 (45.1)	63.4 (22.4)	66.0 (29.1)
Appearance	31.3 (17.7)	50.0 (29.8)	57.0 (27.2)	54.7 (22.6)

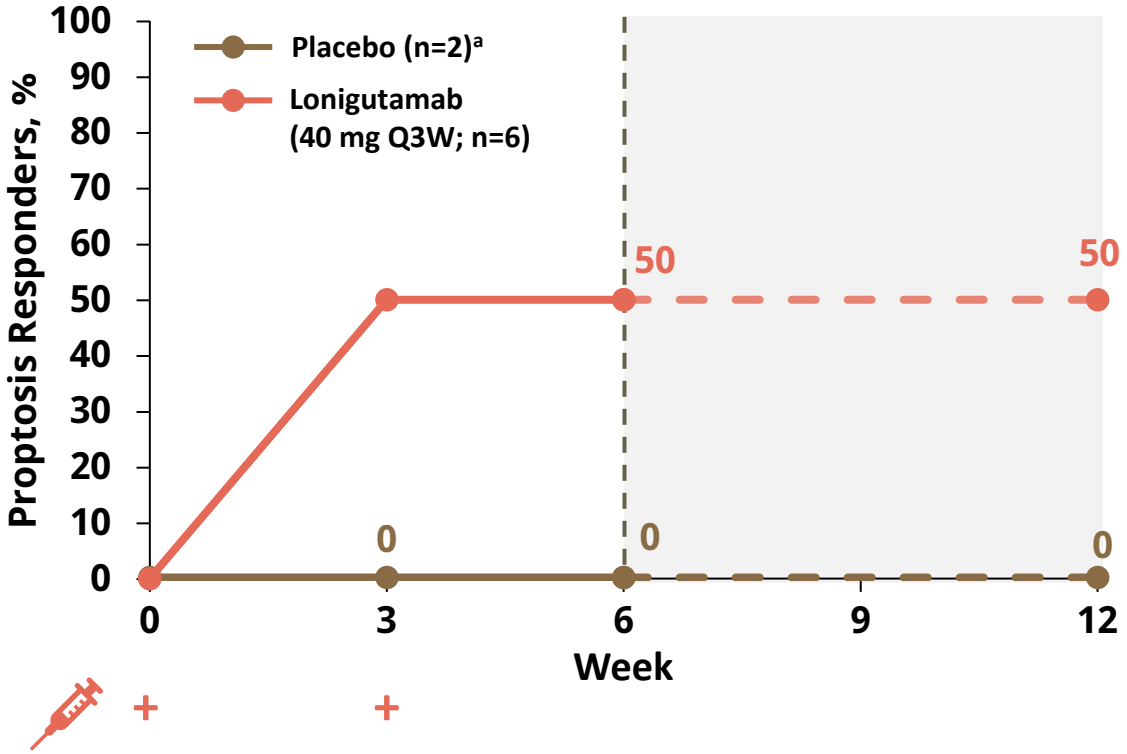
[a]Not age/sex/race adjusted.

BMI, body mass index; CAS, Clinical Activity Score; GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, standard deviation; TED, thyroid eye disease.

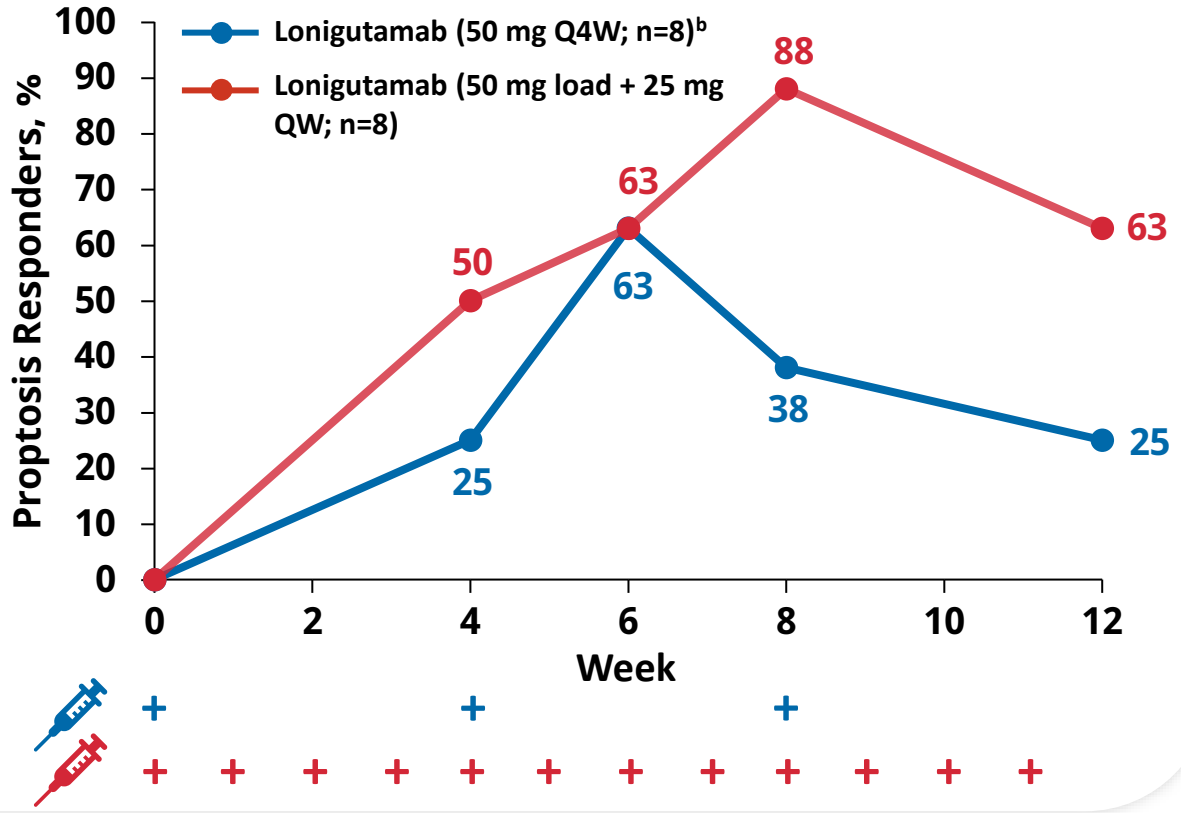
Proptosis response

(≥2-mm reduction in the study eye)

50% of patients in the 40 mg Q3W group achieved a proptosis response within 3 weeks, which was maintained through week 12 (off treatment)



63% of patients in the 50 mg load + 25 mg QW group achieved a proptosis response within 6 weeks, which was maintained through week 12

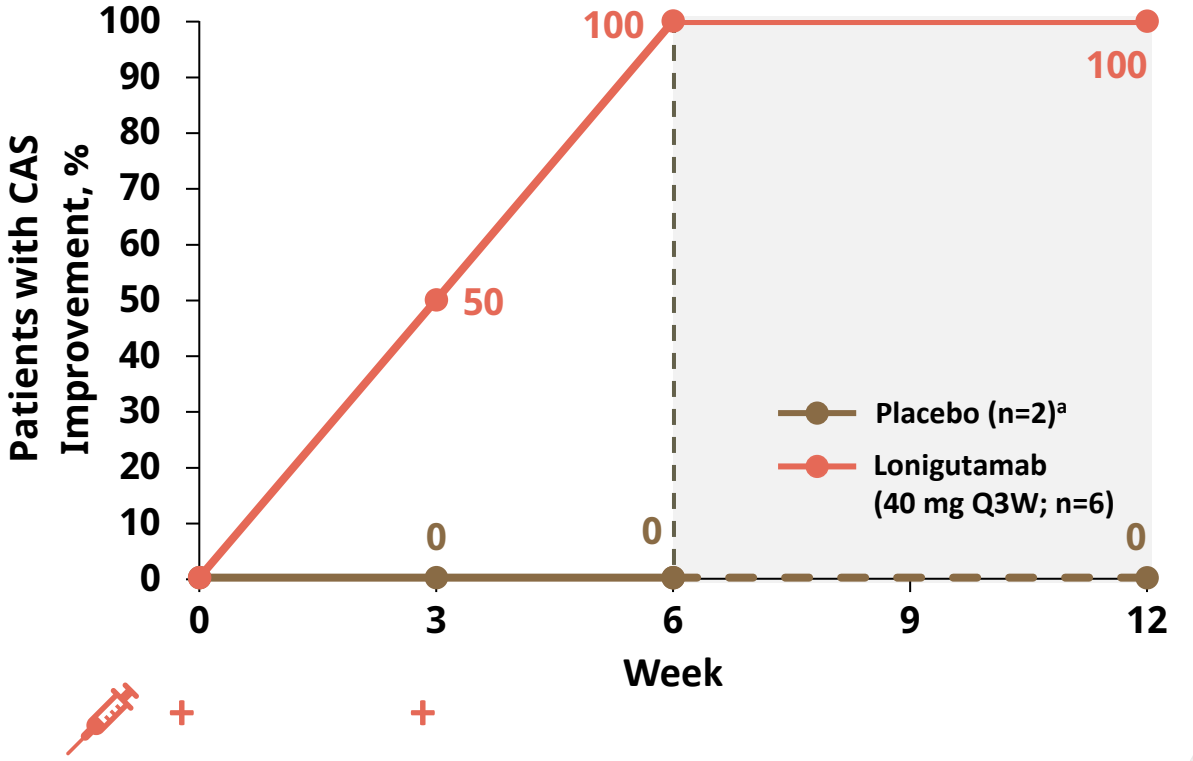


The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. For 50 mg Q4W and 50 mg load + 25 mg QW, the treatment period is through week 12; week 4 is the earliest measured time point. Proptosis was measured by Hertel exophthalmometer. [a]One patient in the placebo group had no postbaseline data and was imputed as a nonresponder. [b]One patient in the 50 mg Q4W group was missing week 12 data and imputed as a nonresponder.

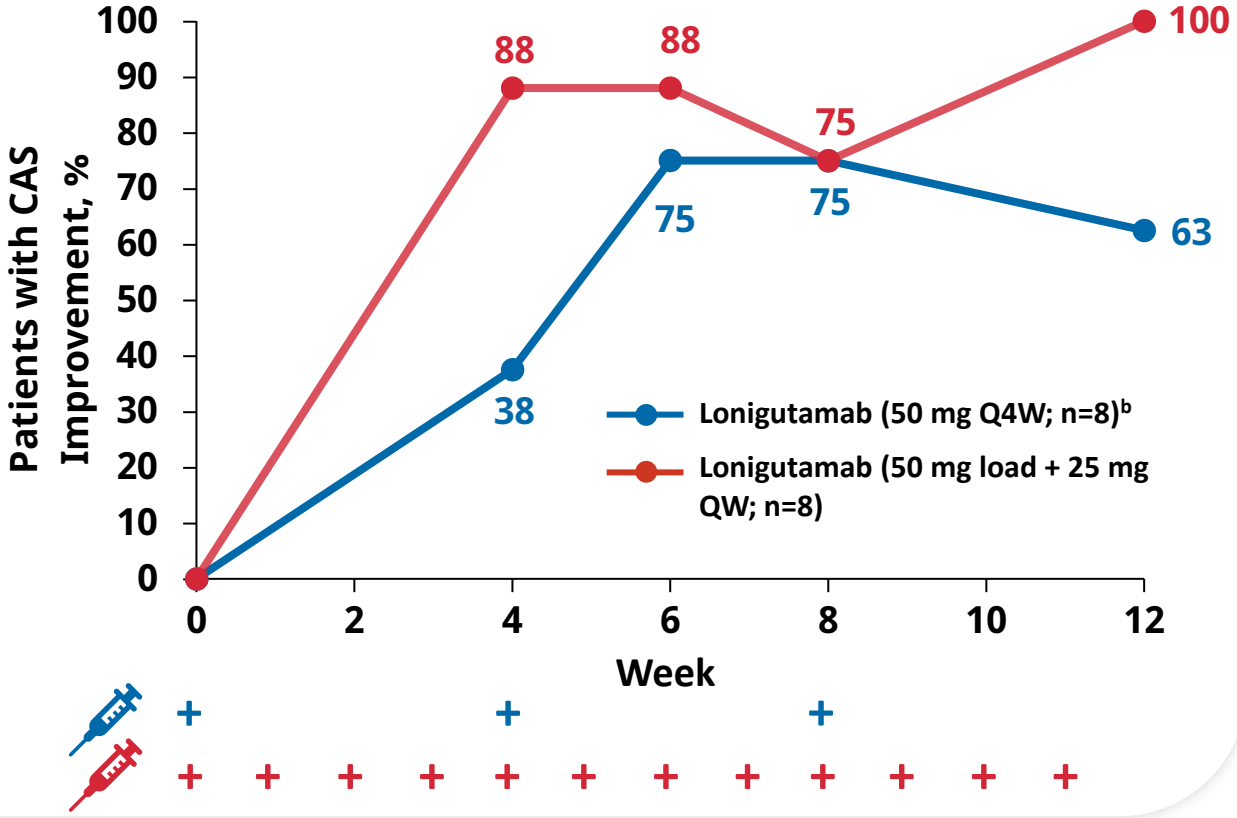
QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

CAS improvement
(≥2-point reduction)

100% of patients in the 40 mg Q3W group achieved a clinically meaningful improvement in CAS at week 6, which was maintained through week 12 (off treatment)



88% of patients in the 50 mg load + 25 mg QW group achieved a clinically meaningful improvement in CAS at week 6, which improved to 100% at week 12



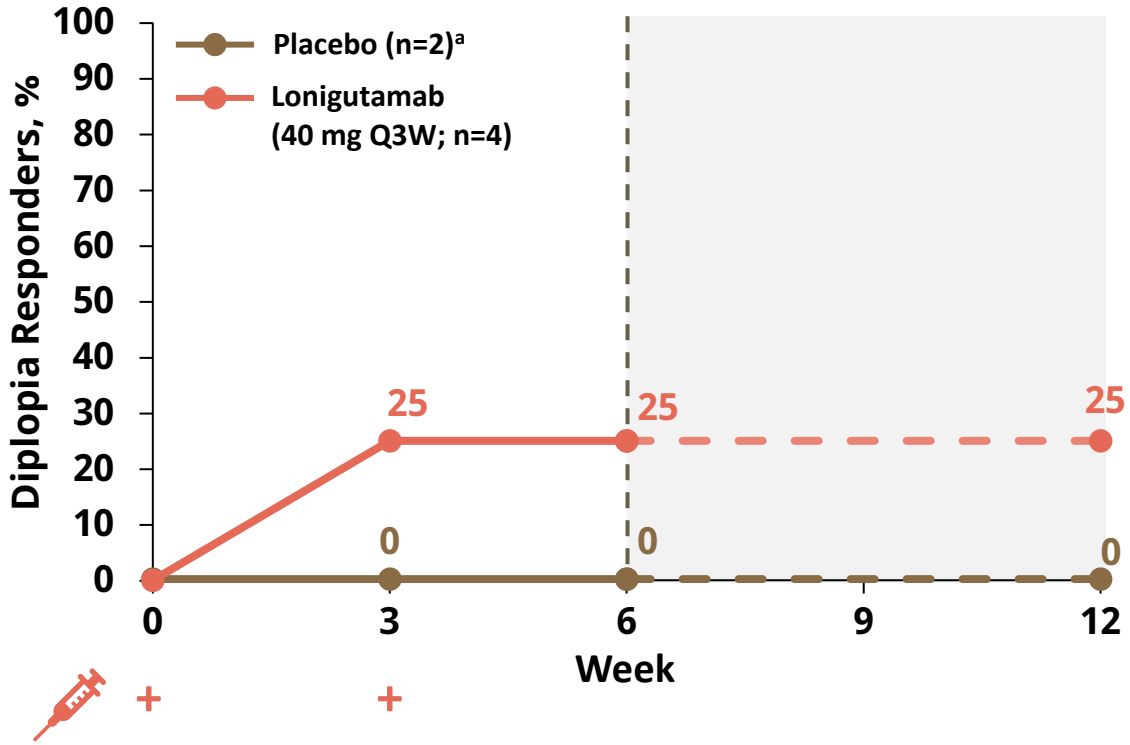
The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. For 50 mg Q4W and 50 mg load + 25 mg QW, the treatment period is through week 12; week 4 is the earliest measured time point. [a]One patient in the placebo group had no postbaseline data and was imputed as a nonresponder. [b]One patient in the 50 mg Q4W group was missing week 12 data and imputed as a nonresponder.

CAS, Clinical Activity Score; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

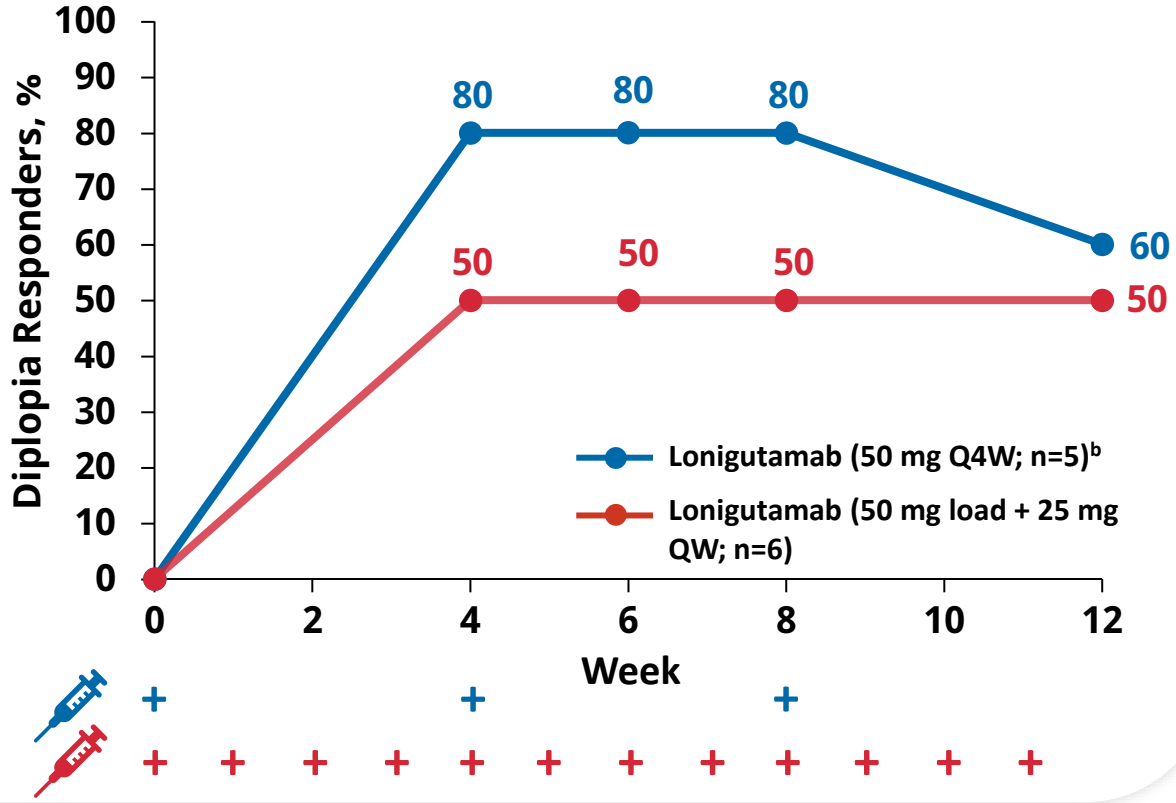
Diplopia response in patients with baseline diplopia >0

(Improvement in ≥1 Bahn-Gorman grade)

Clinically meaningful diplopia response in the 40 mg Q3W group at week 3 was maintained through week 12 (off treatment)



50% of patients in the 50 mg load + 25 mg QW group achieved clinically meaningful diplopia responses at week 4, which were maintained through week 12



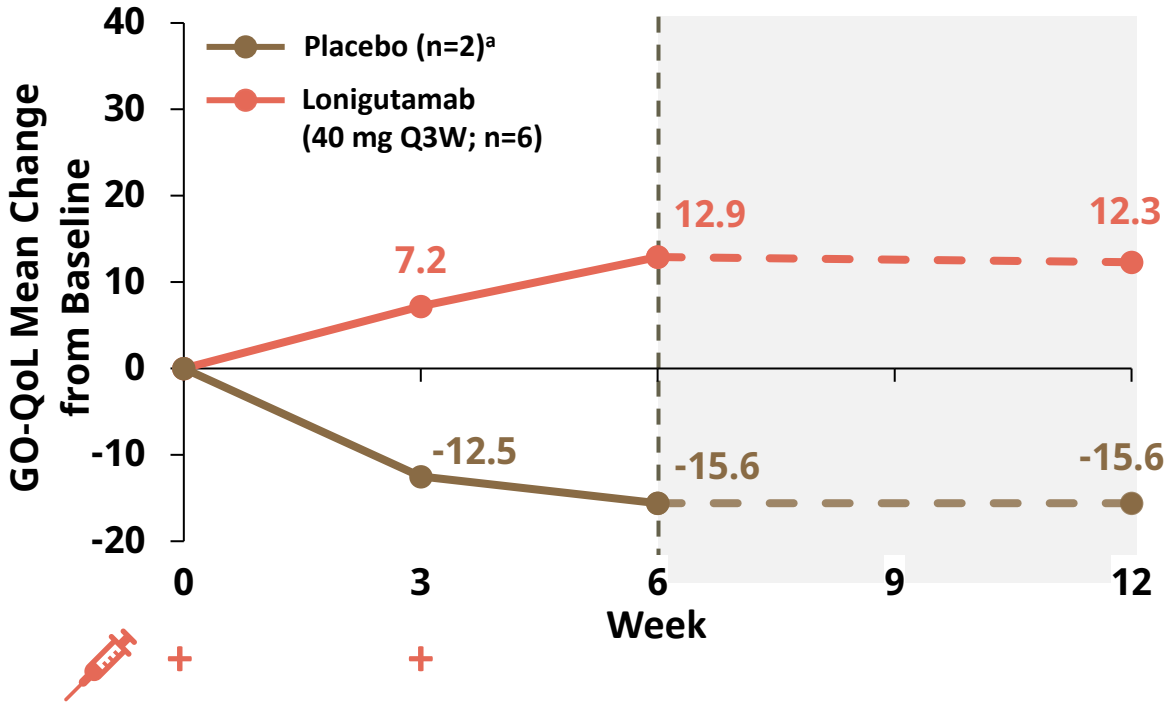
The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. For 50 mg Q4W and 50 mg load + 25 mg QW, the treatment period is through week 12; week 4 is the earliest measured time point. [a]One patient in the placebo group had no postbaseline data and was imputed as a nonresponder. [b]One patient in the 50 mg Q4W group was missing week 12 data and imputed as a nonresponder.

QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

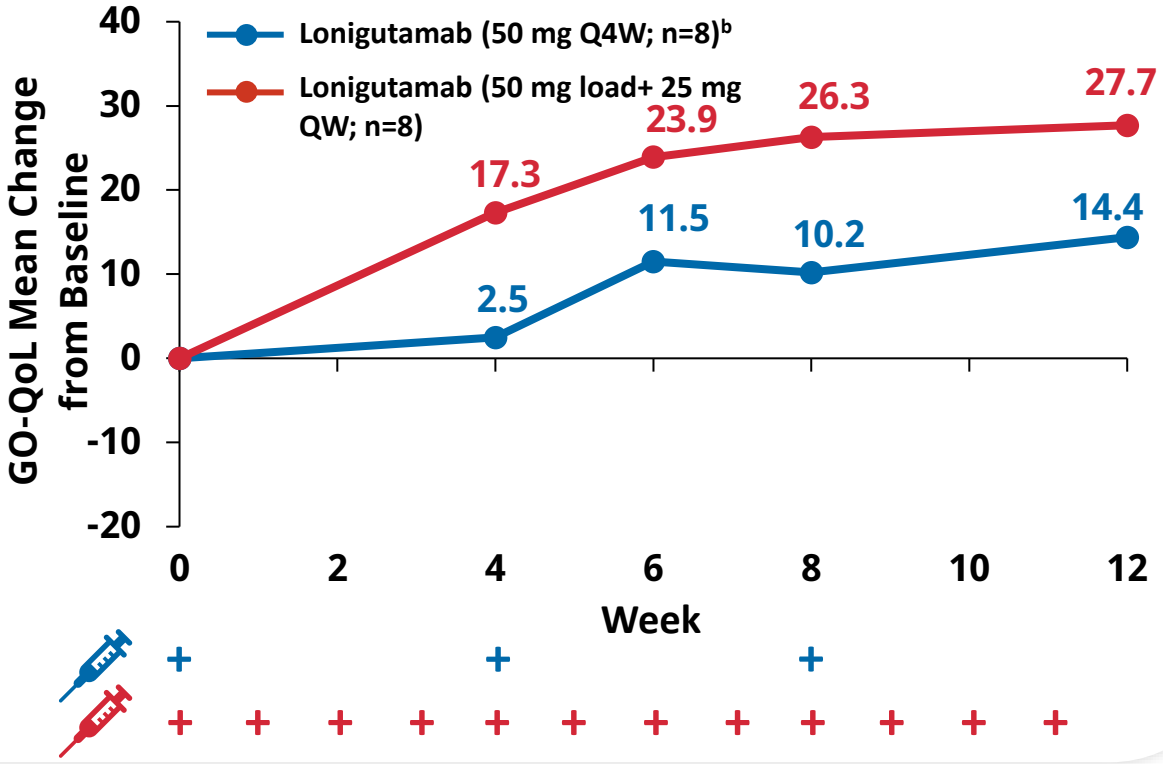
Graves' Ophthalmopathy Quality of Life

(≥6-point improvement is considered clinically meaningful[1]; higher scores indicate better health)

Patients in the 40 mg Q3W group reported improved quality of life within 3 weeks, which was maintained through week 12 (off treatment)



Patients in the 50 mg load + 25 mg QW group reported improved quality of life at week 4, with further increases through week 12

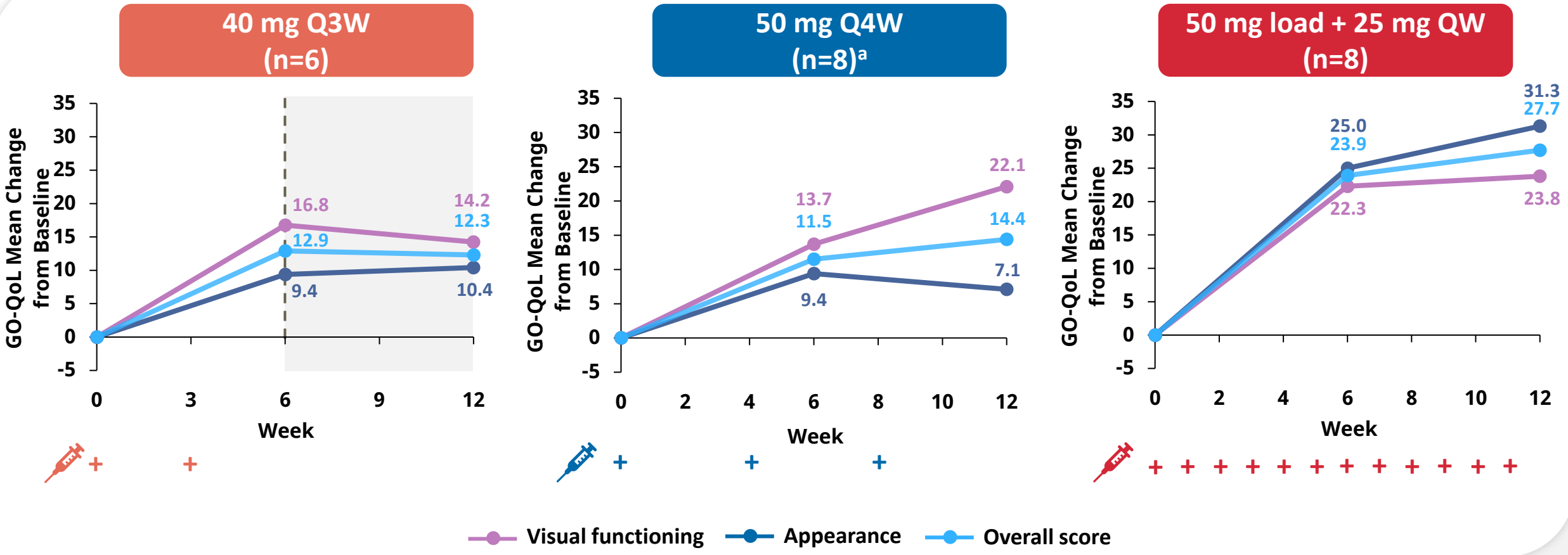


The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. For 50 mg Q4W and 50 mg load + 25 mg QW, the treatment period is through week 12; week 4 is the earliest measured time point. [a]One patient in the placebo group had no postbaseline data. [b]One patient in the 50 mg Q4W group was missing week 12 data. GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

1. Douglas RS, et al. *N Engl J Med*. 2020;382(4):341-52.

Graves' Ophthalmopathy Quality of Life

(Visual functioning and appearance subdomains; higher scores indicate better health)



The trend of improvement in GO-QoL over time was consistent across the 2 subdomains of visual functioning and appearance

The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. For 50 mg Q4W and 50 mg load + 25 mg QW, the treatment period is through week 12; week 4 is the earliest measured time point. [a]One patient in the 50 mg Q4W group was missing week 12 data.
GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

Summary of efficacy data at week 12

40 mg Q3W[a]		50 mg Q4W		50 mg load + 25 mg QW	
Proptosis	**CAS**	**Proptosis**	**CAS**	**Proptosis**	**CAS**
50% response ≥2 mm	**100%** ≥2-point improvement	**25%** response ≥2 mm	**63%** ≥2-point improvement	**63%** response ≥2 mm	**100%** ≥2-point improvement
−1.5 mm mean change	**67%** CAS 0/1 response	**−1.4 mm** mean change	**50%** CAS 0/1 response	**−1.9 mm** mean change	**38%** CAS 0/1 response
Diplopia	**GO-QoL**	**Diplopia**	**GO-QoL**	**Diplopia**	**GO-QoL**
25% response ≥1 Bahn-Gorman improvement	**12.3** points mean change overall	**60%** response ≥1 Bahn-Gorman improvement	**14.4** points mean change overall	**50%** response ≥1 Bahn-Gorman improvement	**27.7** points mean change overall

[a]Off-treatment follow-up.

CAS, Clinical Activity Score; CAS 0/1, CAS of 0 or 1; GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

Overall summary of TEAEs

- All events were mild or moderate in severity, with **no grade ≥3 or serious TEAEs**
- Injection-site reactions (erythema, swelling, pain) in 7 patients were all mild
- Four patients receiving lonigutamab had AESIs
  - Tinnitus (all mild)
  - **No audiology changes or events of hyperglycemia or IBD**
- One patient receiving placebo discontinued due to dysthyroid optic neuropathy

n (%)	Placebo n=2	Lonigutamab (40 mg Q3W) n=6	Lonigutamab (50 mg Q4W) n=8	Lonigutamab (50 mg load + 25 mg QW) n=8
Any TEAEs	2 (100.0)	4 (66.7)	6 (75.0)	8 (100.0)
Serious	0	0	0	0
Grade 2	0	1 (16.7)	0	3 (37.5)
Any treatment-related TEAEs	0	3 (50.0)	3 (37.5)	6 (75.0)
Any AESIs	0	3 (50.0)	1 (12.5)	0
Tinnitus	0	3 (50.0)	1 (12.5)	0
Inflammatory bowel disease	0	0	0	0
Hyperglycemia	0	0	0	0
TEAEs leading to study drug discontinuation	1 (50.0)	0	0	0
Dysthyroid optic neuropathy	1 (50.0)	0	0	0

The table reports the number and percentage of patient who experienced TEAEs through week 12.
AESI, adverse event of special interest; IBD, inflammatory bowel disease; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

Summary and conclusions

Lonigutamab, a high-affinity, next-generation, subcutaneously administered anti–IGF-1R monoclonal antibody with a noncompetitive binding mechanism, demonstrated proof of concept for clinical efficacy in patients with TED

Efficacy summary

- Clinical data suggest that **optimal clinical efficacy across multiple manifestations of TED** is achieved when minimal exposure is maintained above receptor saturation
  - A 50 mg loading dose followed by 25 mg every week demonstrated clinical efficacy, further supporting efficacy at exposures above the target-mediated drug disposition threshold (3 µg/mL)[1]
- Responses were maintained through the time points evaluated, including week 12 (off treatment for the 40 mg Q3W cohort)
- **Improvements in patient-reported quality of life occurred early** (after a single dose) and were maintained over time

Safety summary

- Evaluation of multiple dosing regimens showed that lonigutamab was **well tolerated with no serious adverse events**

IGF-1R, insulin-like growth factor 1 receptor; Q3W, every 3 weeks; TED, thyroid eye disease.

1. Keenan G, et al. Poster at NANOS Annual Meeting 2023; March 11-16. #293.