Preliminary Safety, Efficacy, and Quality of Life Outcomes of Subcutaneous Lonigutamab (Anti–Insulin-Like Growth Factor 1 Receptor [IGF-1R]) from a Phase 1/2 Proof of Concept Study in Patients with Thyroid Eye Disease

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*At the time of the study.

Disclosures

- This study is sponsored by ACELYRIN, INC. Lonigutamab is an investigational therapy not approved by any regulatory authority
- All authors met the ICMJE authorship criteria and had full access to relevant data
- Jwu Jin Khong has received consulting fees from ACELYRIN, INC., and Amgen; received funding from the Centre for Eye Research Australia; participated in an advisory board for ACELYRIN, INC.; and served as a member on the RANZCO Victoria branch and the Royal Victorian Eye and Ear Hospital ethics committees
- David A. Kostick has served as a principal investigator for ACELYRIN, INC. Anita Grover, So Jung Imm, and Shephard Mpofu are employees and shareholders of ACELYRIN, INC. Sarah Chesler was an employee and shareholder of ACELYRIN, INC., at the time of the study. Shoaib Ugradar has received consulting fees from ACELYRIN, INC.
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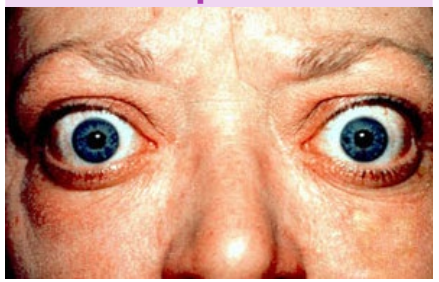
ICMJE, International Committee of Medical Journal Editors; RANZCO, Royal Australian and New Zealand College of Ophthalmologists.

Background: Thyroid Eye Disease

Proptosis



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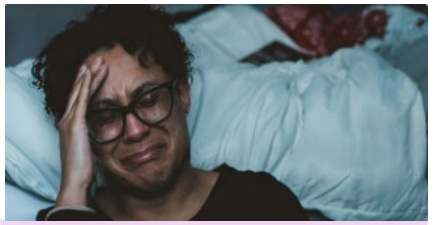


Patient QoL

Diplopia

Thyroid eye disease (TED) is a chronic, **debilitating, and vision-threatening** condition[1,2]

› Characterized by **progressive inflammation** resulting from aberrant stimulation of **IGF-1R/TSHR** signaling[1,2]

Limitations of available therapies:

› **Steroids**: variable efficacy, long-term safety limitations[3,4]

› **IV anti–IGF-1R**: limited durability of response, safety concerns, patient burden[2,5-9]

› **Surgery**: complex, does not address the underlying pathology of TED[3,4]

There is a current unmet medical need for an anti–IGF-1R with an improved therapeutic profile

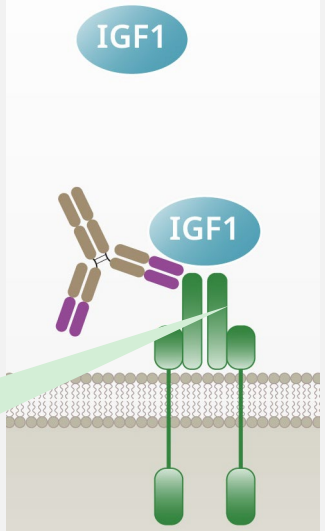
IGF-1R, insulin-like growth factor 1 receptor; IV, intravenous; QoL, quality of life; TSHR, thyroid-stimulating hormone receptor.

1. Smith TJ, et al. *Endocrine Rev*. 2019;40:236-67. 2. Men CJ, et al. *Ther Adv Ophthalmol*. 2021;13:25158414211027760. 3. Dosiou C, et al. *J Endocr Soc*. 2021;5:bvab034. 4. Kossler AL, et al. *J Clin Endocrinol Metab*. 2022;107(suppl 1):S36-46. 5. Kahaly G, et al. *Lancet Diabetes Endocrinol*. 2021;9:360-72. 6. Davis JB, et al. *J Neuroophthalmol*. 2024. doi:10.1097/WNO.0000000000002066. 7. Hwang CJ, et al. *Am J Ophthalmol*. 2023;263:152-9. 8. Shah SA, et al. *Ophthalmology*. 2024;131:458-67. 9. Davis JD, et al. *Clin Pharmacol Ther*. 2024;115:422-39.

Background: Lonigutamab

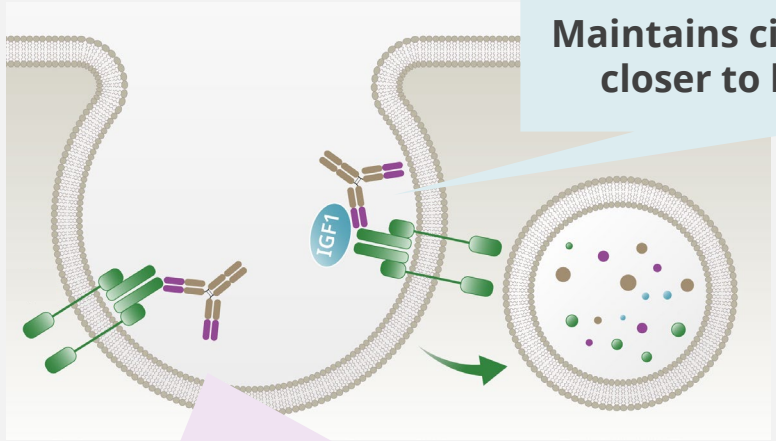
Lonigutamab is a **high-affinity** (30-pM binding affinity), humanized, **anti–IGF-1R** monoclonal antibody[1,2]

Unique Binding Epitope[2]



Peripheral to IGF-1 binding site; does not compete with IGF-1 binding

IGF-1R Internalization[1,2]



Maintains circulating IGF-1 levels closer to homeostatic range

Rapid internalization of IGF-1R within minutes

Lonigutamab Potential Therapeutic Benefits

Rapid Onset of Action

Improved Benefit/Risk Profile via Dose Optimization

SC Administration

IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; SC, subcutaneous.

1. Akla B, et al. *Mol Cancer Ther*. 2020;19:168-77. 2. Data on File. ACELYRIN, INC.

Phase 1/2 Study Design

NCT05683496[1]

Key Eligibility Criteria

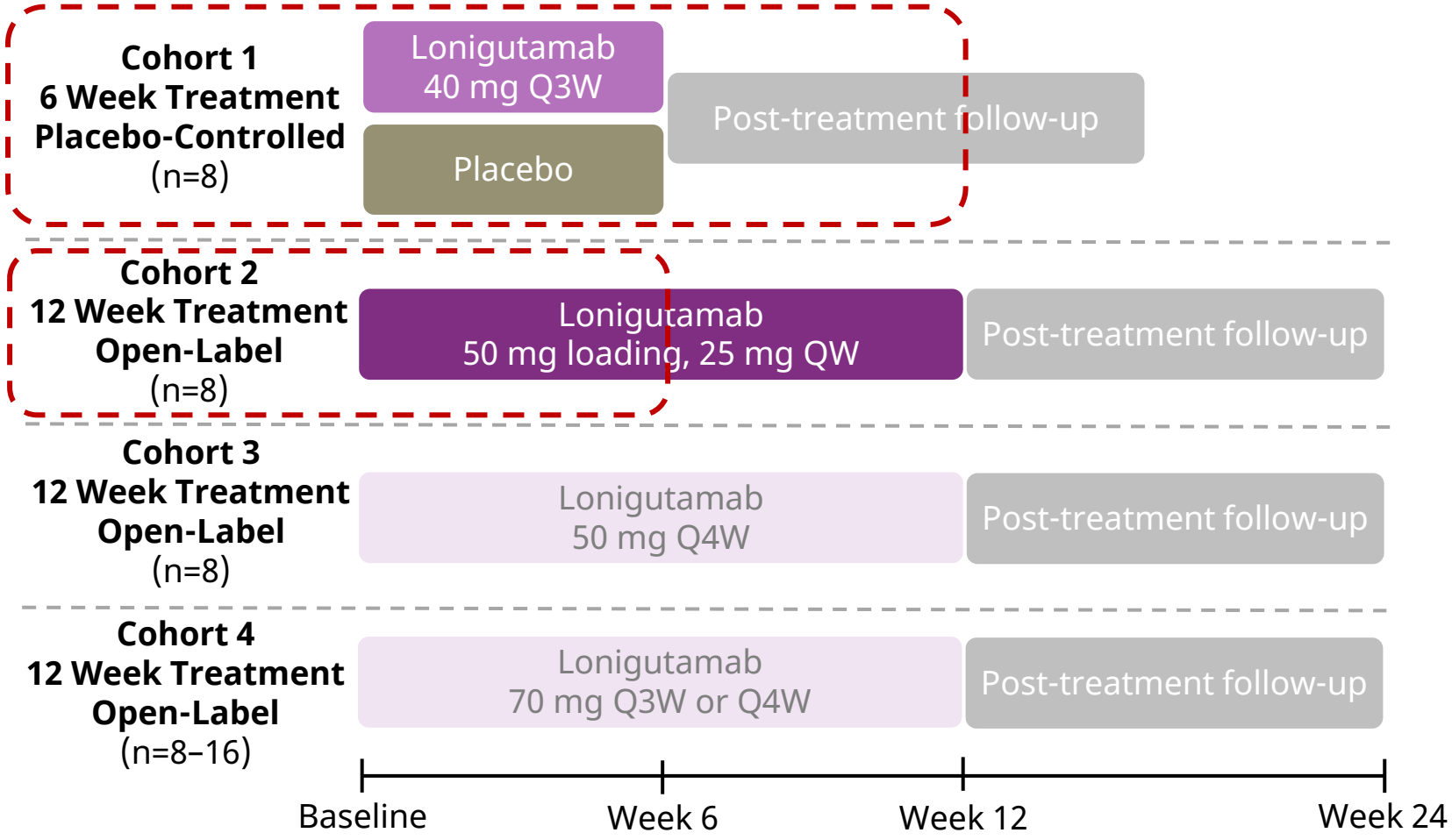
- Proptosis ≥3 mm above normal range in the study eye
- CAS ≥4 (using a 7-item scale) for the most severely affected eye

Efficacy Endpoints

- Proptosis response (≥2-mm reduction)
- CAS MCID (≥2-point improvement)
- Diplopia response (improvement in ≥1 Bahn-Gorman grade)
- GO-QoL (change from baseline)

Safety Endpoints

- Incidence and characterization of nonserious and serious TEAEs



For cohort 2, the treatment period is through week 12; week 6 data are currently available.
[1]https://clinicaltrials.gov/study/NCT05683496.
CAS, Clinical Activity Score; GO-QoL, Graves' Ophthalmopathy Quality of Life; MCID, minimal clinically important difference; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

Demographics and Baseline Characteristics

	Placebo (Cohort 1) n=2	Lonigutamab (Cohort 1: 40 mg Q3W) n=6	Lonigutamab (Cohort 2: 50 mg load, 25 mg QW) n=6
Age, mean (SD), years	49.5 (12.0)	43.8 (13.7)	43.3 (13.3)
Female, n (%)	2 (100.0)	5 (83.3)	4 (66.7)
White, n (%)	1 (50.0)	5 (83.3)	2 (33.3)
BMI, mean (SD), kg/m^2	28.6 (3.5)	26.6 (7.6)	26.2 (4.1)
Months since onset of TED, mean (SD)	14.6 (4.6)	10.2 (6.8)	10.0 (4.5)
Smoking status, n (%)			
Never	2 (100.0)	2 (33.3)	4 (66.7)
Past[a]	0	4 (66.7)	2 (33.3)
Proptosis for study eye, mean (SD), mm	26.0 (0)	26.2 (2.6)	23.2 (2.4)
CAS total score for study eye, mean (SD)	5.5 (2.1)	4.8 (1.0)	5.2 (0.8)
Diplopia at baseline, n (%)	2 (100.0)	4 (66.7)	5 (83.3)
GO-QoL at baseline, mean (SD)	54.7 (2.2)	53.4 (28.0)	62.9 (17.7)

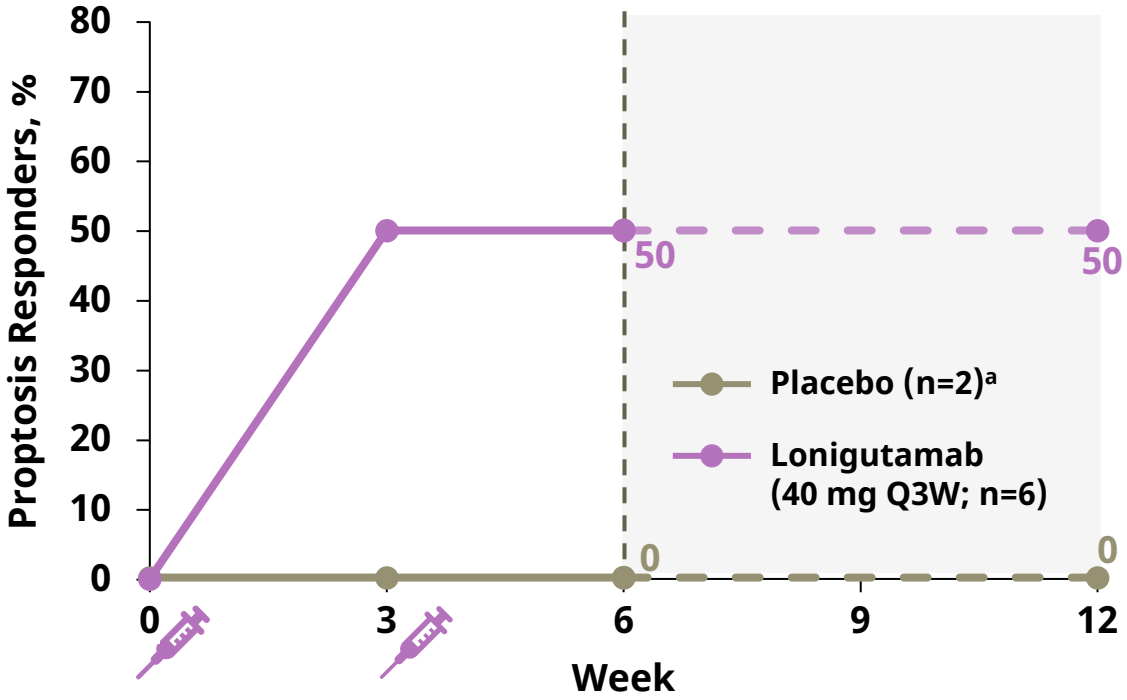
[a]No patients identified as current smokers.
BMI, body mass index; CAS, Clinical Activity Score; GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; SD, standard deviation; TED, thyroid eye disease.

Proptosis Response

≥2-mm Reduction in Proptosis

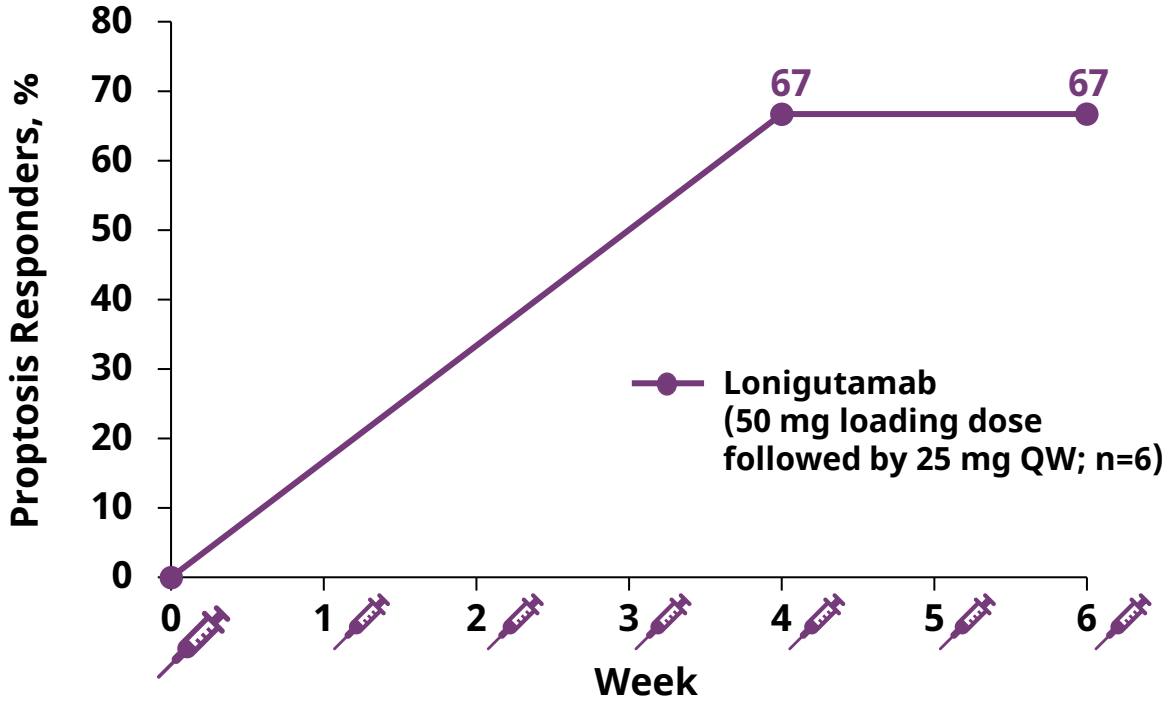
Cohort 1

50% of patients achieved a proptosis response within 3 weeks after a single 40 mg SC injection, which was maintained through week 12 (off-treatment)



Cohort 2

67% of patients achieved a proptosis response within 4 weeks



Cohort 1 data as of December 6, 2023; the gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. Cohort 2 data as of March 8, 2024; the treatment period is through week 12; week 6 data are currently available (week 4 is the earliest measured timepoint). Proptosis was measured by Hertel exophthalmometer.

[a]One patient in the placebo group had no post-baseline data and was imputed as a non-responder.

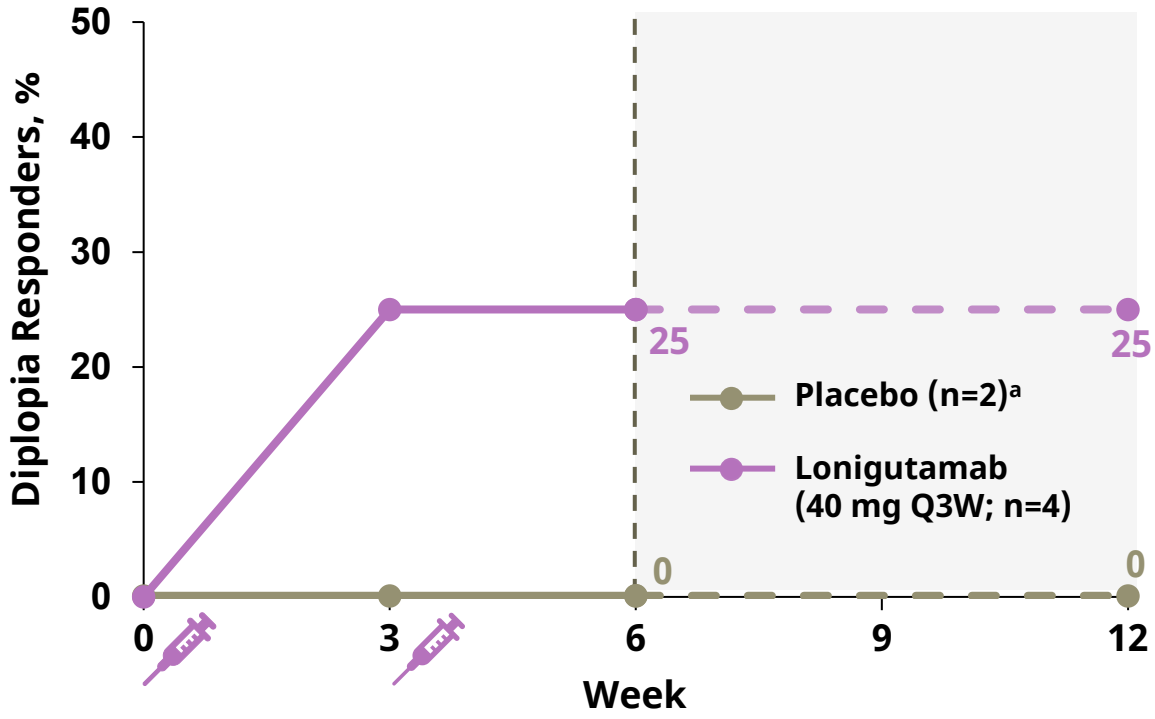
QW, every week; Q3W, every 3 weeks; SC, subcutaneous.

Diplopia Response in Patients with Baseline Diplopia >0

Improvement in ≥1 Bahn-Gorman Grade

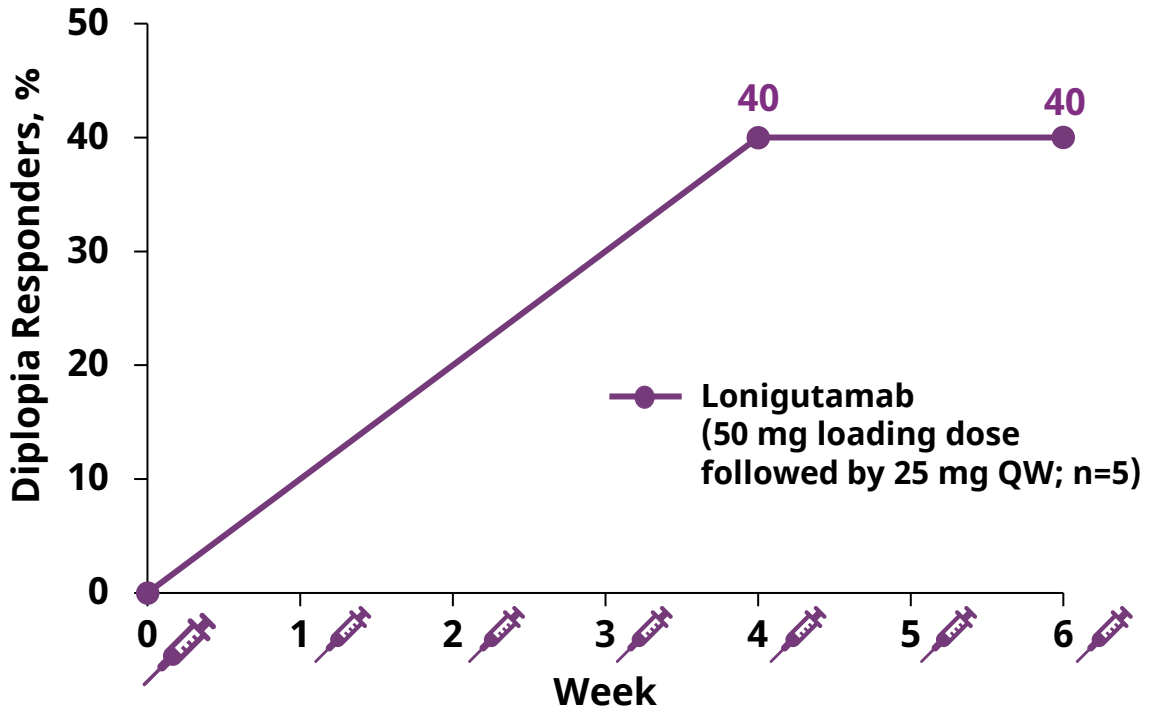
Cohort 1

Clinically meaningful diplopia response at week 3 was maintained through week 12 (off-treatment)



Cohort 2

Clinically meaningful diplopia responses within 4 weeks



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[a]One patient in the placebo group had no post-baseline data and was imputed as a non-responder.

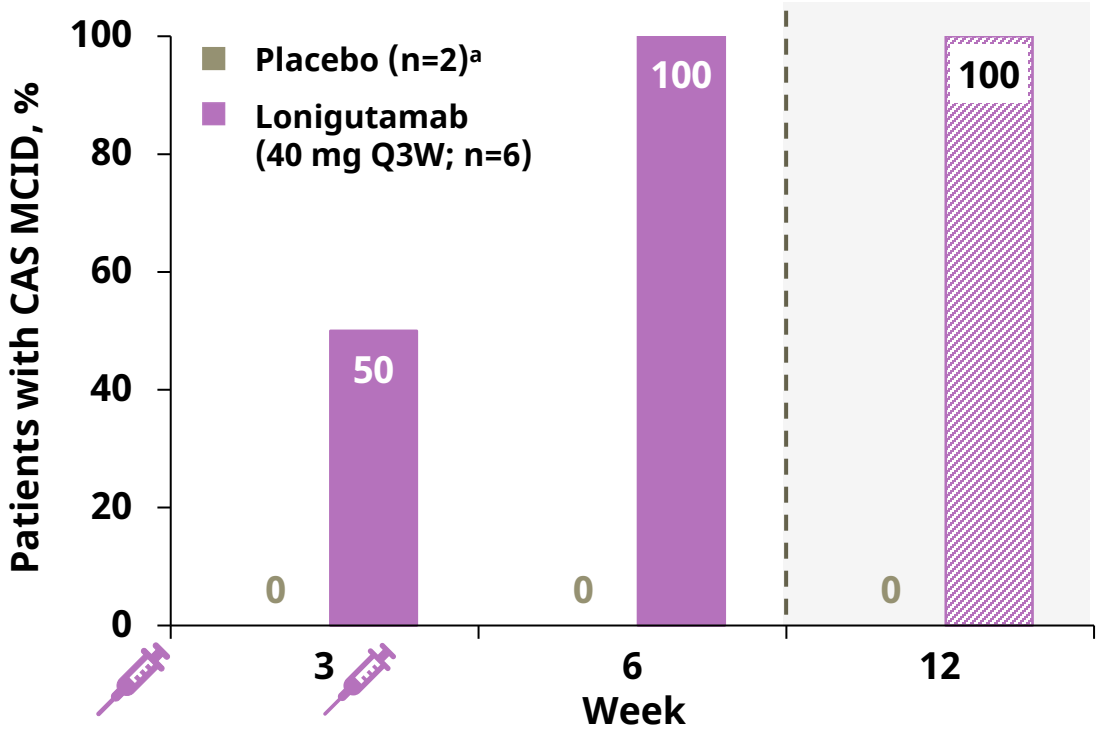
QW, every week; Q3W, every 3 weeks.

CAS Improvement, MCID

≥2-Point Reduction Is Considered Clinically Meaningful

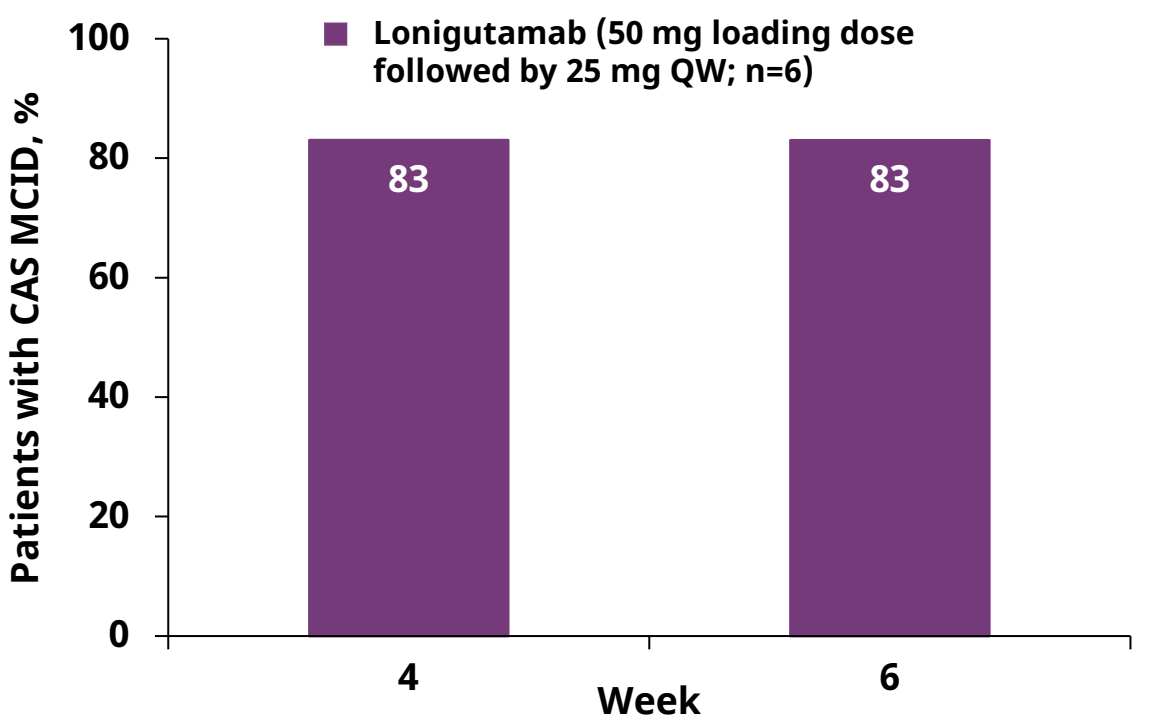
Cohort 1

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



Cohort 2

83% of patients achieved a clinically meaningful improvement in CAS within 4 weeks



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[a]One patient in the placebo group had no post-baseline data and was imputed as a non-responder.

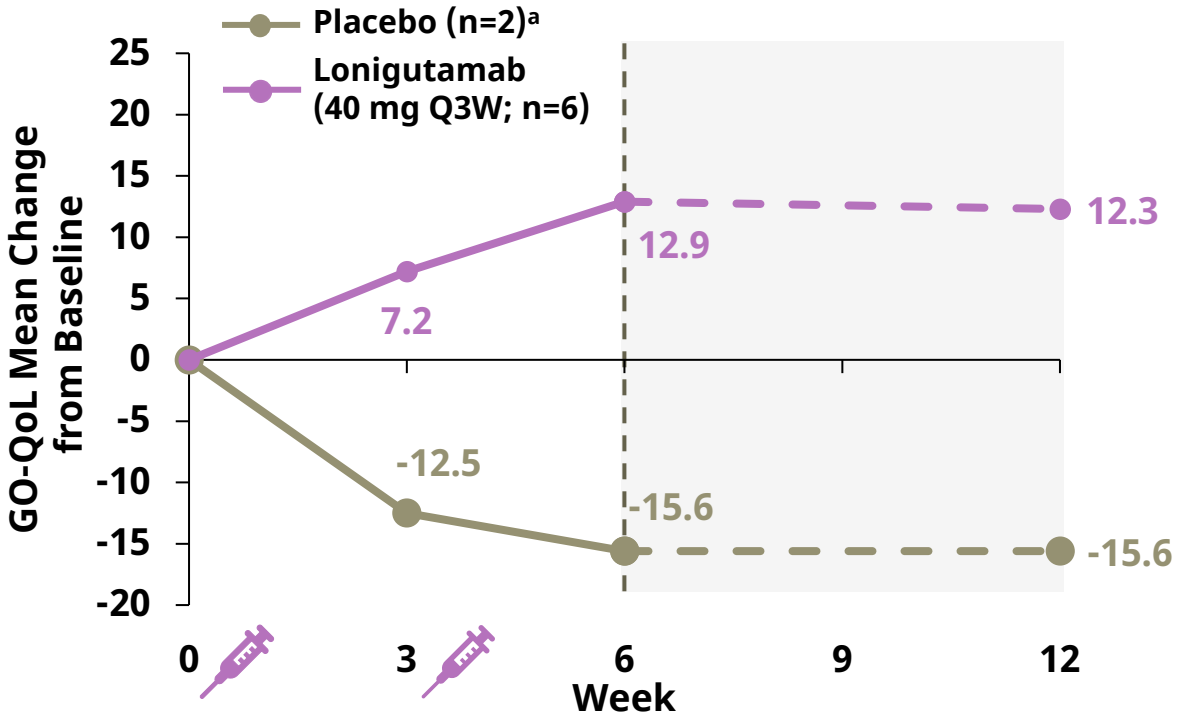
CAS, Clinical Activity Score; MCID, minimal clinically important difference; QW, every week; Q3W, every 3 weeks.

Graves' Ophthalmopathy Quality of Life

≥6-Point Improvement Is Considered Clinically Meaningful[1]; Higher Scores Indicate Better Health

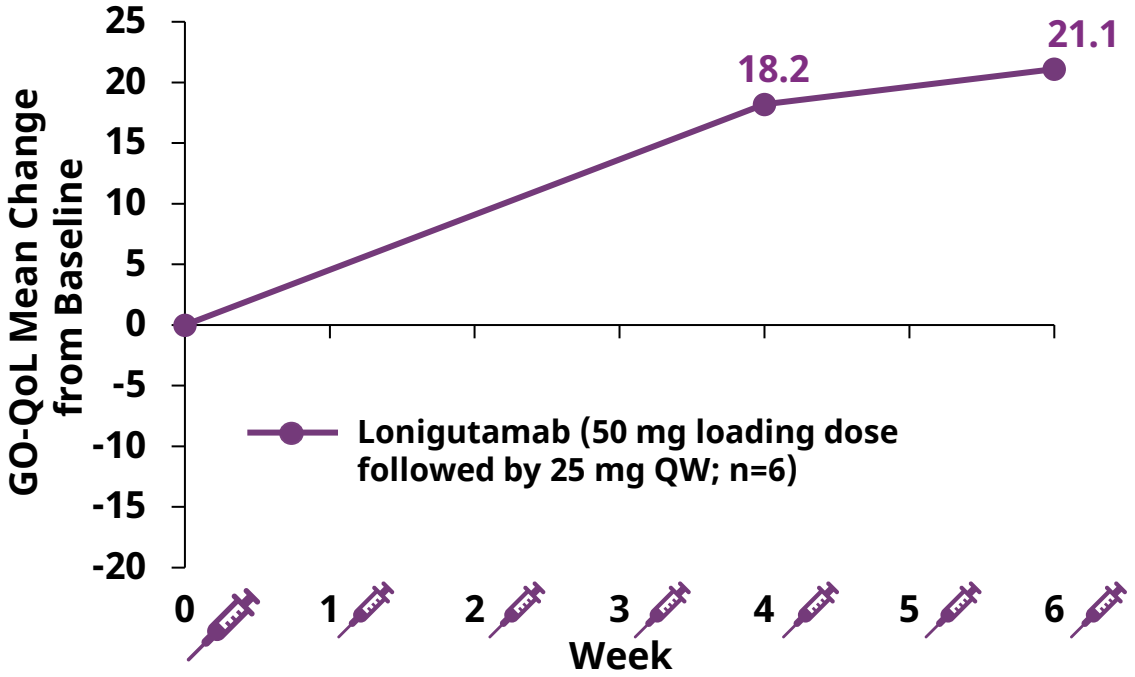
Cohort 1

Patients reported improved quality of life within 3 weeks after a single 40 mg SC injection, which was maintained through week 12 (off-treatment)



Cohort 2

Patients reported improved quality of life at week 4 (the earliest measured timepoint), with further increases through week 6



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[a]One patient in the placebo group had no post-baseline data.

GO-QoL, Graves' Ophthalmopathy Quality of Life; QW, every week; Q3W, every 3 weeks; SC, subcutaneous.

1. Douglas R, et al. *N Engl J Med*. 2020;382:341-52.

Safety: Cohorts 1 and 2

No audiology changes, no hyperglycemia events, and no serious adverse events

n (%)	Placebo (Cohort 1) n=2	Lonigutamab (Cohort 1: 40 mg Q3W) n=6	Lonigutamab (Cohort 2: 50 mg load, 25 mg QW) n=6
Any TEAEs	2 (100.0)	4 (66.7)	5 (83.3)
Serious	0	0	0
Grade 2 or higher	0	1 (16.7)	2 (33.3)
Any treatment-related TEAEs	0	3 (50.0)	4 (66.7)
Any AESIs	0	3 (50.0)	0
Tinnitus	0	3 (50.0)	0
Inflammatory bowel disease	0	0	0
Hyperglycemia	0	0	0
TEAEs leading to study drug discontinuation	1 (50.0)	0	0
Dysthyroid optic neuropathy	1 (50.0)	0	0

- Most events were mild in severity, with no serious TEAEs
- Injection-site reactions were all mild
- Three patients receiving lonigutamab had AESIs
  - All tinnitus (all transient and mild): no changes on audiogram
- One patient receiving placebo discontinued due to dysthyroid optic neuropathy

Cohort 1 data as of December 6, 2023. Cohort 2 data as of March 8, 2024.
AESI, adverse event of special interest; QW, every week; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

Conclusions

- These findings with lonigutamab represent the first reported proof-of-concept results of a subcutaneous anti–IGF-1R agent in patients with TED
- Patients in cohort 1 (40 mg Q3W) achieved early clinical responses across manifestations of disease
  - Responses were maintained through the timepoints evaluated, including week 12 (off-treatment), supporting the potential for longer dosing intervals
  - Improvements in patient-reported QoL occurred early (after a single dose) and were maintained over time
- Data from cohort 2 (50 mg loading dose followed by 25 mg QW) further substantiated the results seen in cohort 1
- Lonigutamab was well tolerated, with no serious adverse events, and warrants further investigation for the treatment of TED
- Further dose ranging is being explored in cohorts 3 and 4 to establish optimal dose selection for phase 3

ACKNOWLEDGMENTS: We thank the patients for their participation in the study, as well as site staff and principal investigators for their critical contributions.

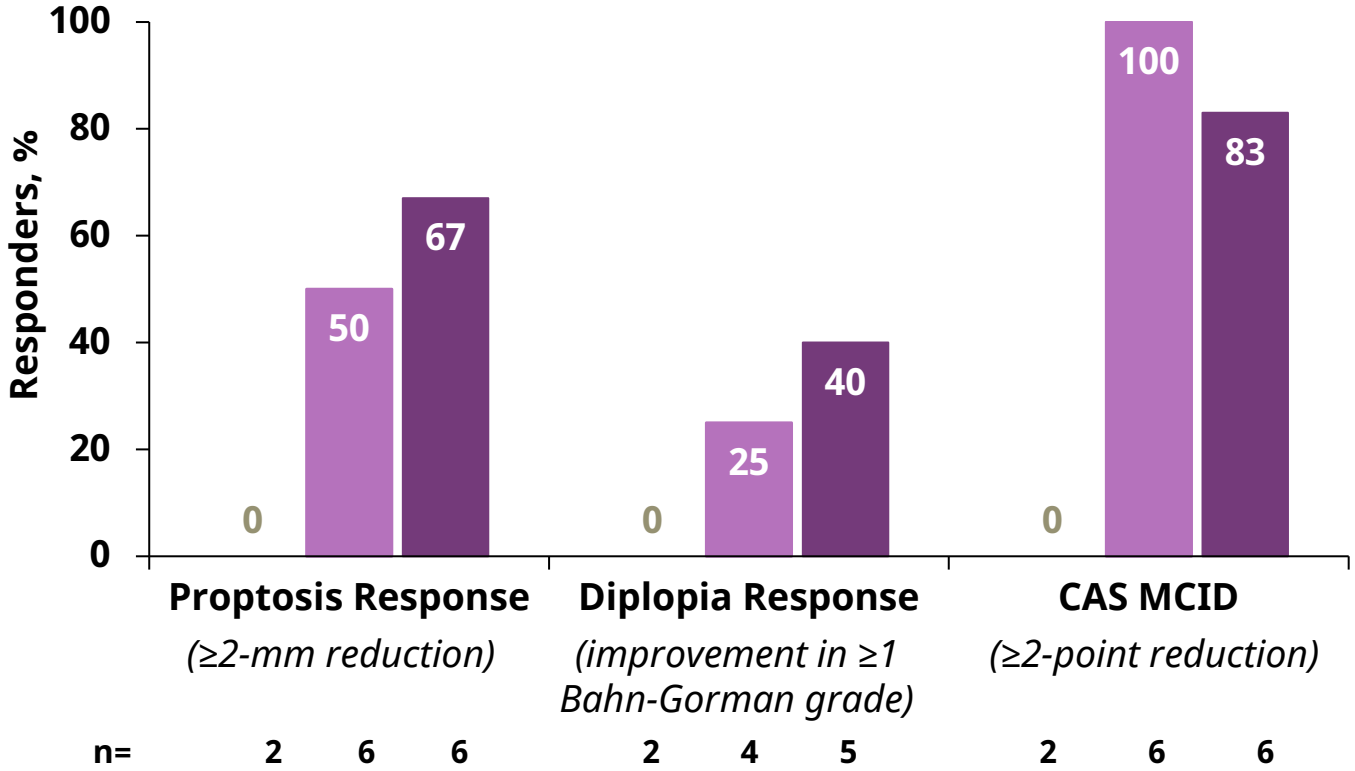
IGF-1R, insulin-like growth factor 1 receptor; QoL, quality of life; QW, every week; Q3W, every 3 weeks; TED, thyroid eye disease.

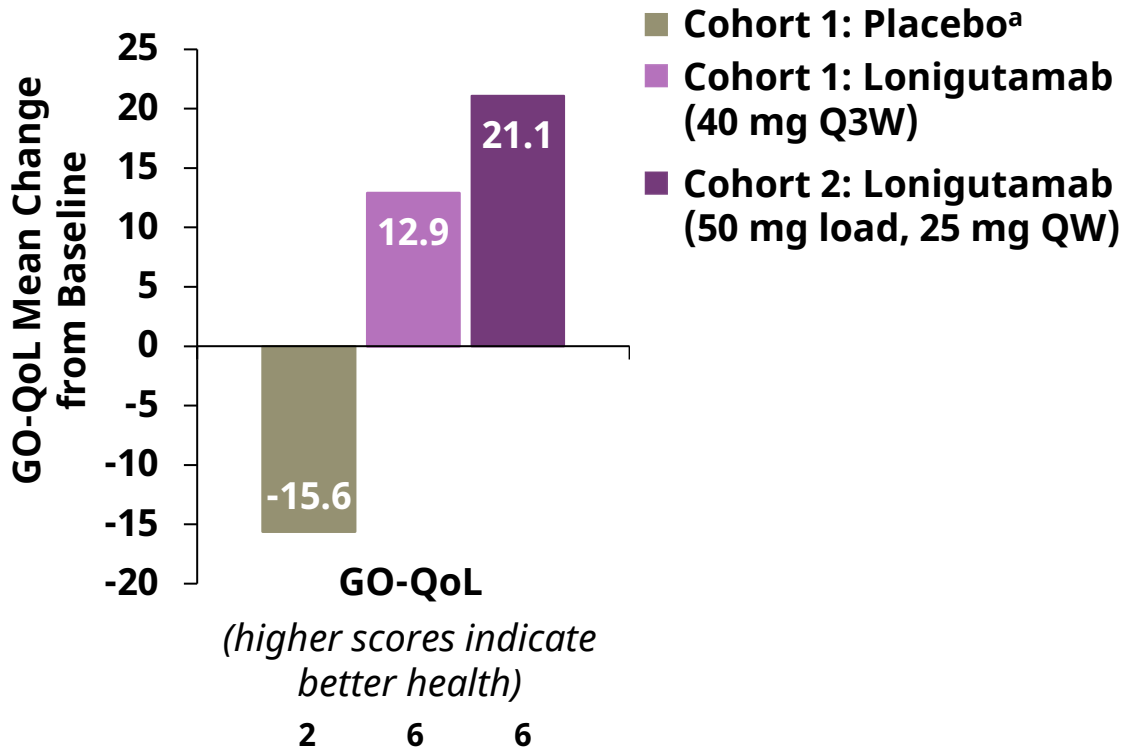
Backup

Responses at Week 6: Cohorts 1 and 2

Clinically meaningful results with lonigutamab across cohorts

Cohort 1 and Cohort 2 Responses at Week 6





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