Preliminary Safety and Efficacy of Subcutaneous Lonigutamab (Anti–IGF-1R) From a Phase 1/2 Proof of Concept Study in Patients with Thyroid Eye Disease

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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

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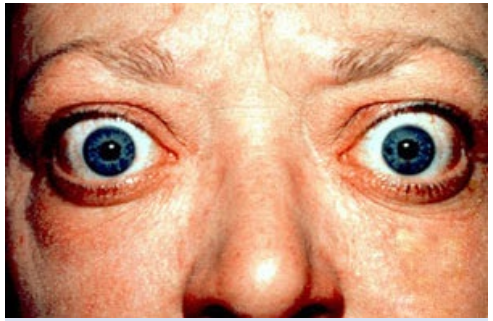
ICMJE, International Committee of Medical Journal Editors.

BACKGROUND: THYROID EYE DISEASE



Proptosis

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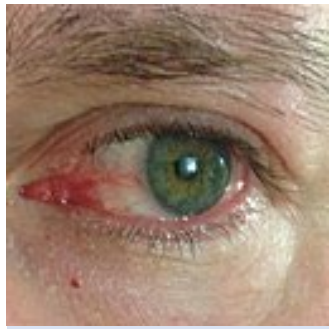

Redness

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Diplopia

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

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

Limitations of available therapies:

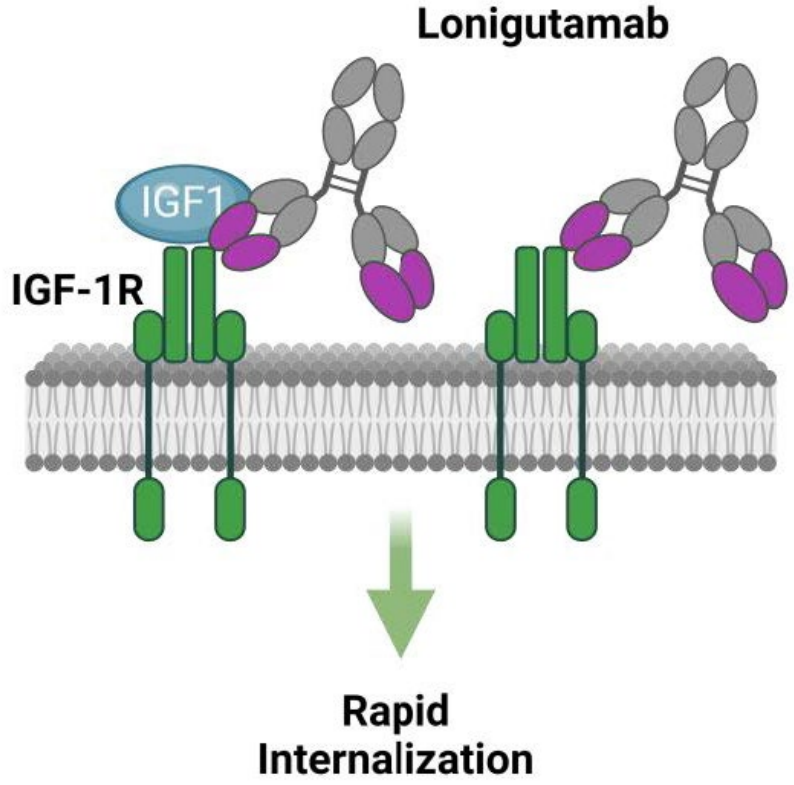
- **Steroids**: variable efficacy, long-term safety limitations[3,4]
- **IV anti–IGF-1R**: limited durability of response, safety concerns, patient burden[2,5-9]
- **Surgery**: complex, does not address the underlying pathology of TED[3,4]

Current unmet medical need for an anti–IGF-1R with an improved therapeutic profile

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

1. Smith TJ, et al. *Endocrine Rev*. 2019;40(1):236-67. 2. Men CJ, et al. *Ther Adv Ophthalmol*. 2021;13:25158414211027760. 3. Dosiou C, et al. *J Endocr Soc*. 2021;5(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(6):360-72. 6. Davis JB, et al. *J Neuroophthalmol*. 2024. doi: 10.1097/WNO.0000000000002066. 7. Hwang CJ, et al. *Am J Ophthalmol*. 2023 doi: 10.1016/j.ajo.2023.12.001. 8. Shah SA, et al. *Ophthalmology*. 2024;131(4):458-67. 9. Davis JD, et al. *Clin Pharmacol Ther*. 2024;115(3):422-39.

BACKGROUND: LONIGUTAMAB



The Molecule

Lonigutamab is a **high-affinity**, humanized, **anti–IGF-1R** monoclonal antibody[1]

- High binding affinity (30 pM)[2]
- Unique binding epitope peripheral to the IGF-1 binding site[2]
- Efficient receptor internalization within minutes[1]

Objective: To provide proof of concept of efficacy and safety of SC lonigutamab from an ongoing phase 1/2 dose-ranging study in patients with TED

IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; SC, subcutaneous; TED, thyroid eye disease.

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

PHASE 1/2 STUDY DESIGN

NCT05683496

Key Eligibility Criteria

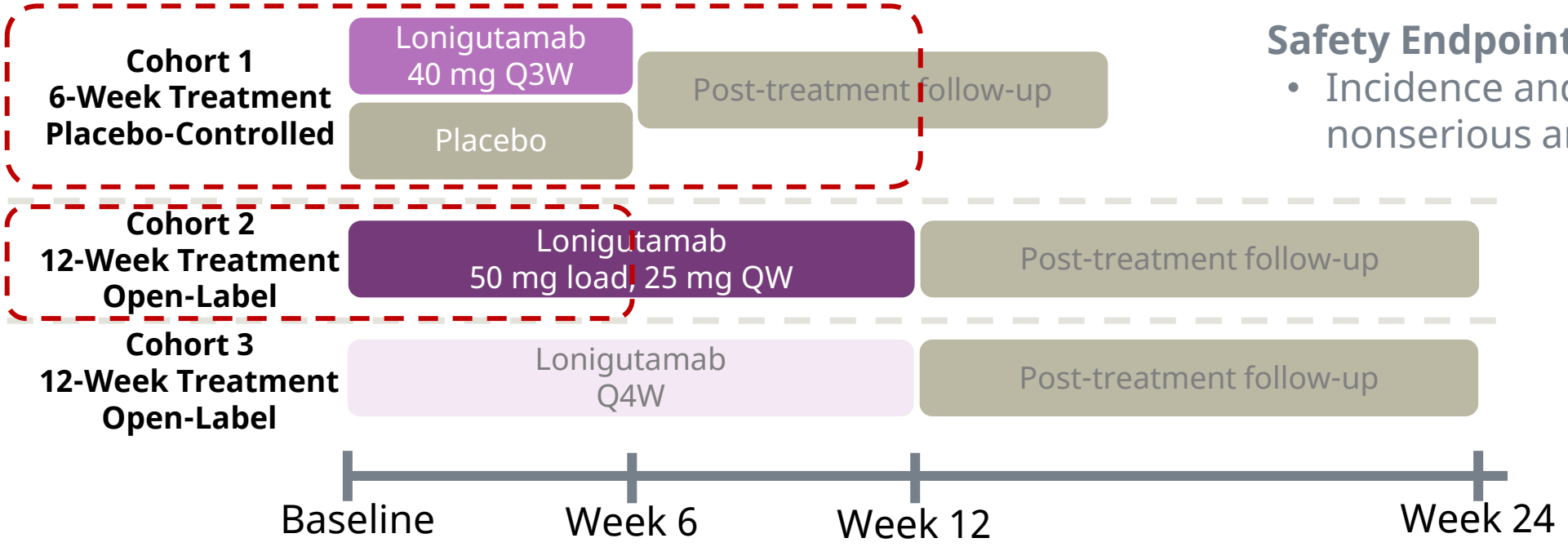
- Proptosis ≥3 mm above normal range in the study eye
- CAS ≥4 (using a 7-item scale) for the most severely affected eye

Efficacy Endpoints

- Proptosis response (≥2-mm reduction)
- CAS MCID (≥2-point improvement)
- Diplopia response (improvement in ≥1 Bahn Gorman grade)

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.
CAS, Clinical Activity Score; 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)	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)

[a]No patients identified as current smokers.
BMI, body mass index; CAS, Clinical Activity Score; QW, every week; Q3W, every 3 weeks; SD, standard deviation; TED, thyroid eye disease.

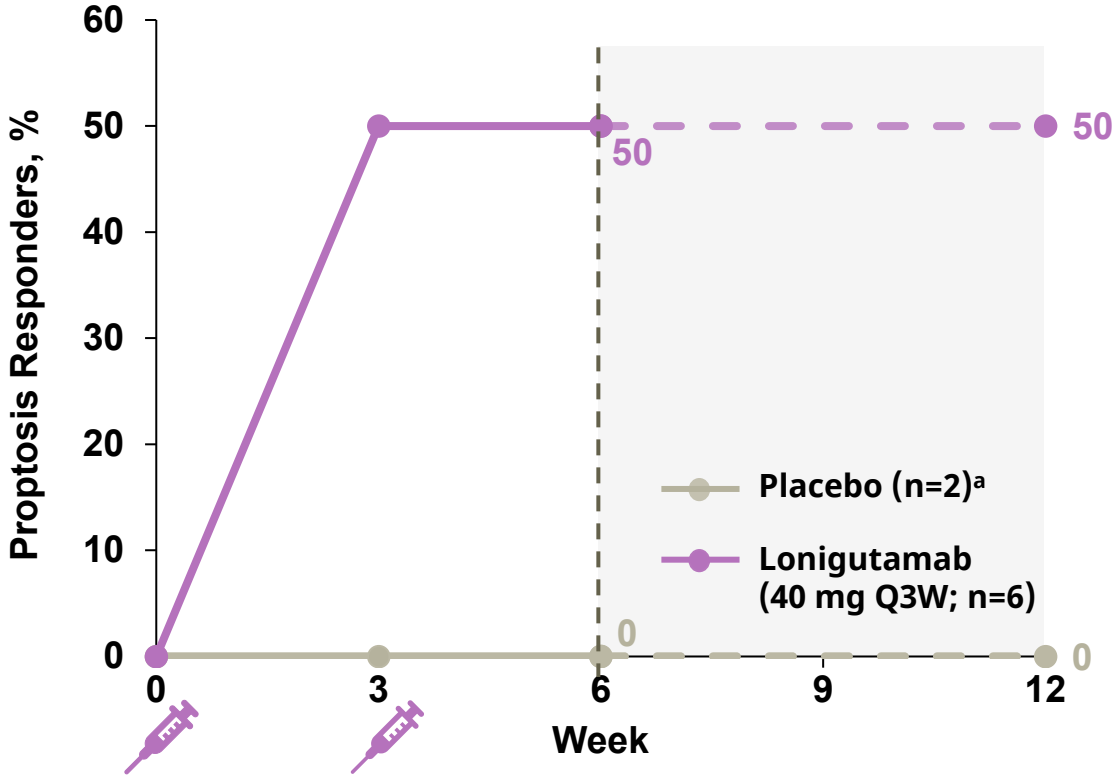
PROPTOSIS RESPONSE: COHORT 1

Treatment period through week 6 / off-treatment through week 12

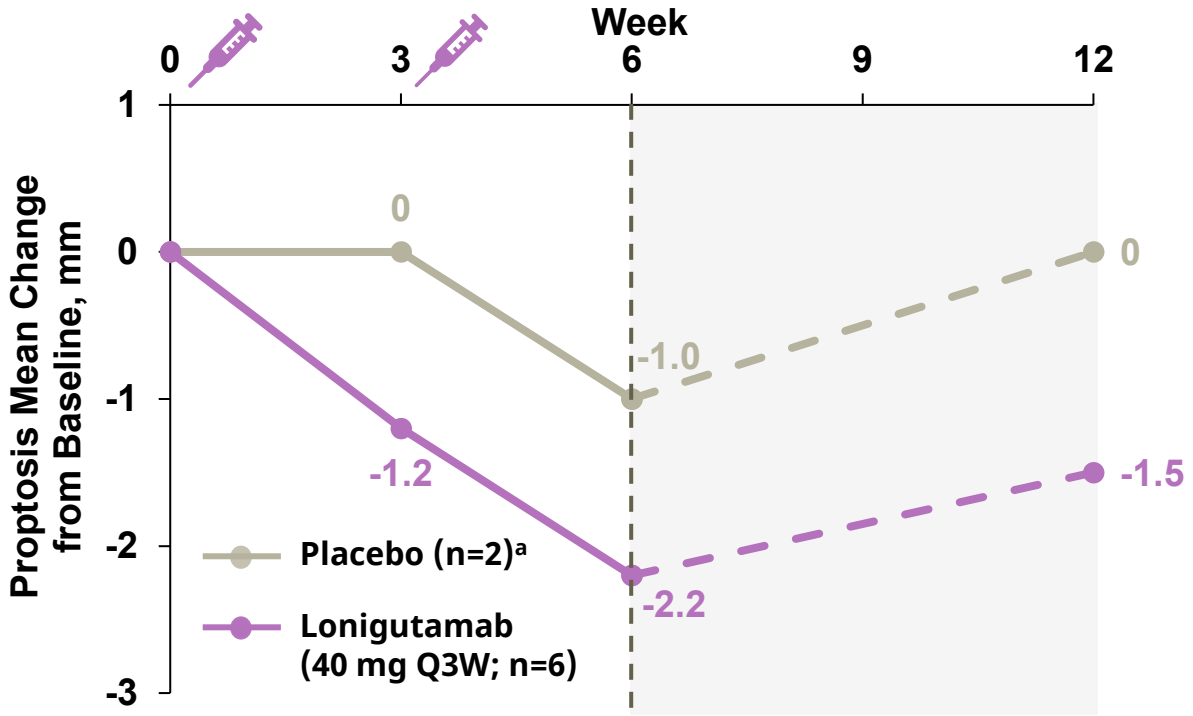
50% of patients achieved a proptosis response within 3 weeks after a single 40-mg SC injection, which was maintained through week 12 (off-treatment)

Proptosis Response

(defined as a ≥2-mm reduction in proptosis)



Proptosis Mean Change from Baseline



Data as of December 6, 2023. The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively. 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.

Q3W, every 3 weeks; SC, subcutaneous.

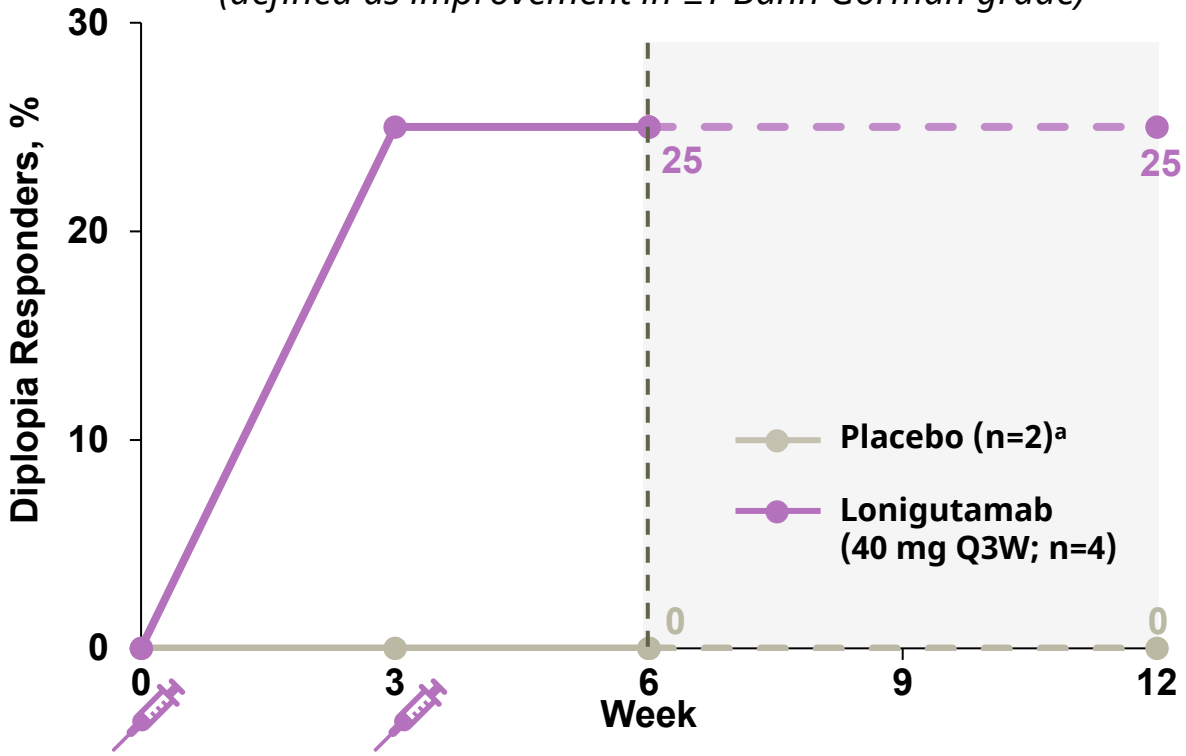
DIPLOPIA AND CAS: COHORT 1

Treatment period through week 6 / off-treatment through week 12

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

Diplopia Response in Patients with Baseline Diplopia >0

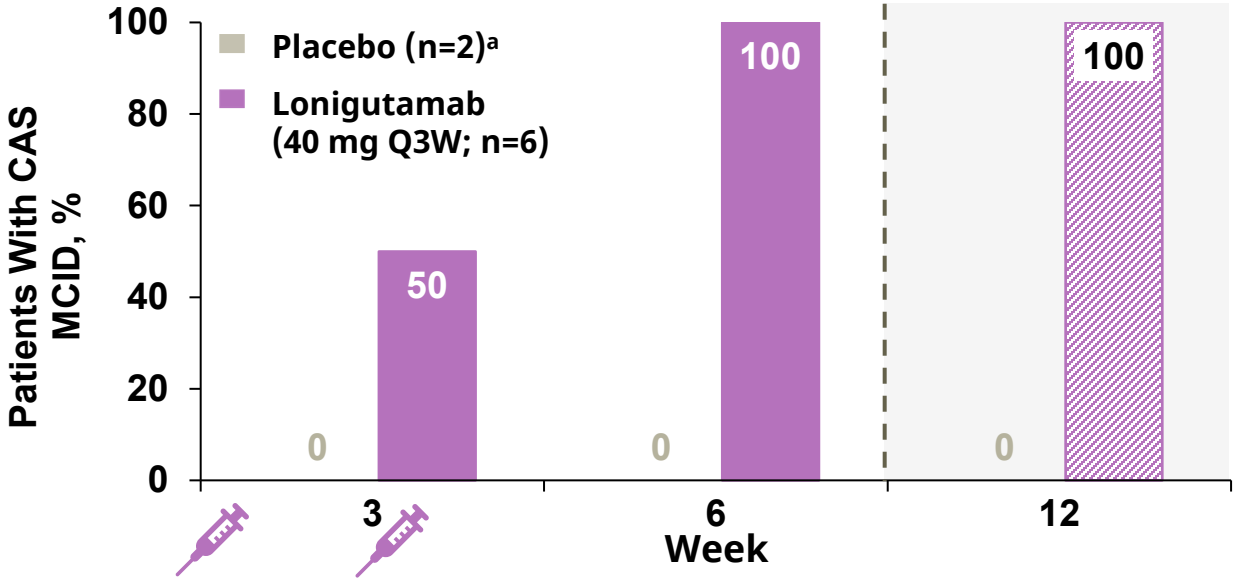
(defined as improvement in ≥1 Bahn Gorman grade)



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

CAS Improvement, MCID

(a ≥2-point reduction is considered clinically meaningful)

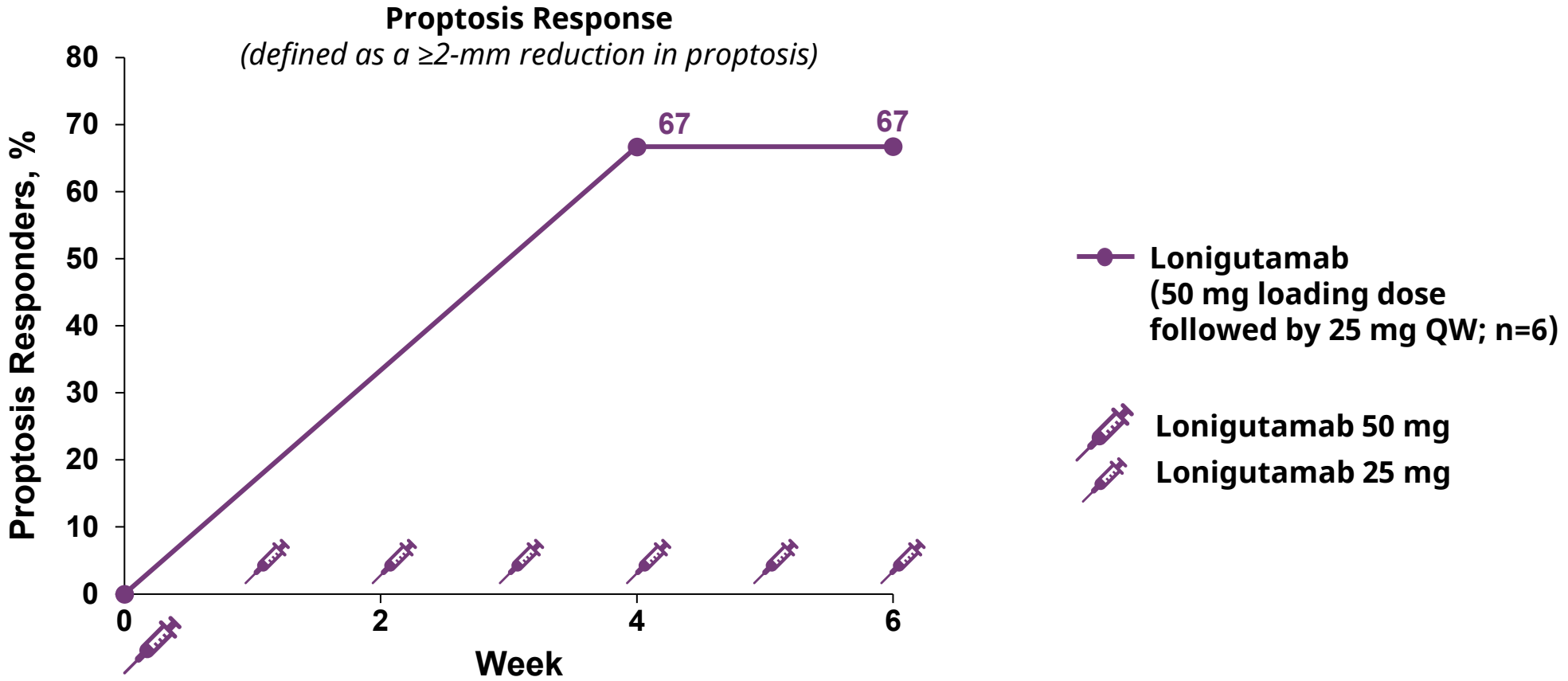


Mean CAS Change from Baseline	Week 3	Week 6	Week 12
Placebo[a]	0	0	−1.0
Lonigutamab	−2.2	−3.5	−3.7

Data as of December 6, 2023. The gray dashed line and shading indicate the end of treatment and off-treatment follow-up period, respectively.
[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; Q3W, every 3 weeks.

PROPTOSIS RESPONSE: COHORT 2

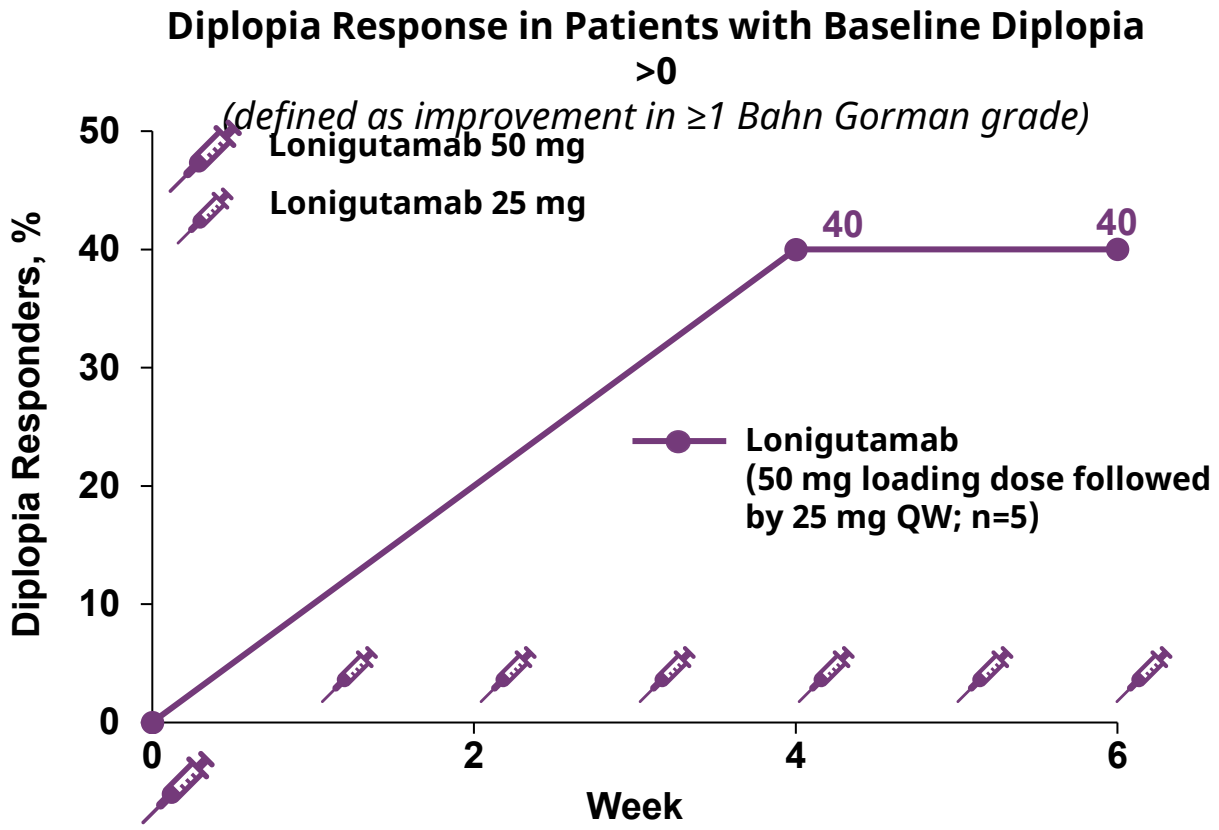
67% of patients achieved a proptosis response within 4 weeks



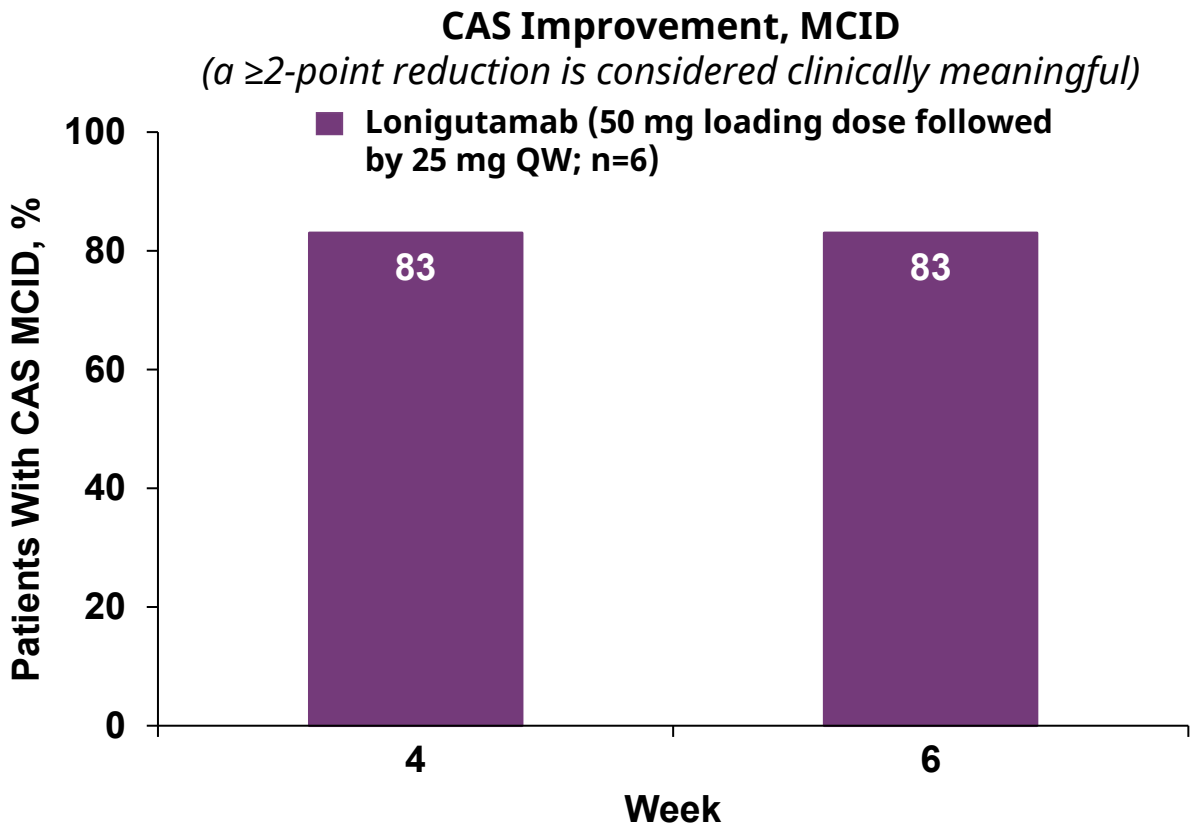
Week 4 is the earliest measured time point. The treatment period is through week 12; week 6 data are currently available. Data as of March 8, 2024. Proptosis was measured by Hertel exophthalmometer.
QW, every week.

DIPLOPIA AND CAS: COHORT 2

Clinically meaningful diplopia responses within 4 weeks



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



Week 4 is the earliest measured time point. Treatment period is through week 12; week 6 data are currently available. Data as of March 8, 2024.
CAS, Clinical Activity Score; MCID, minimal clinically important difference; QW, every week.

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 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 achieved early clinical responses across manifestations of disease
  - Responses were maintained through the time points evaluated, including week 12 (off-treatment), supporting the potential for longer dosing intervals
- Data from cohort 2 further substantiated the results seen in cohort 1
- Lonigutamab was well tolerated and warrants further investigation for the treatment of TED

ACKNOWLEDGMENTS

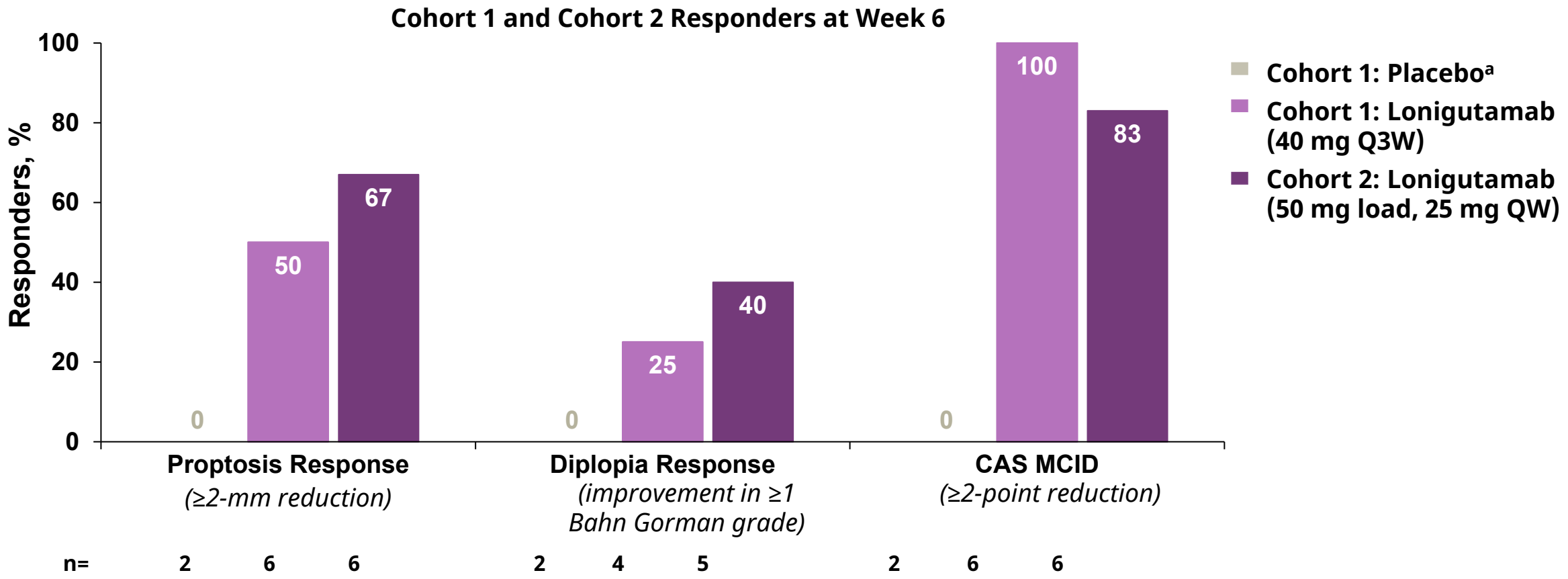
We thank the patients for their participation in the study, as well as site staff and principal investigators for their critical contributions.

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

BACKUP

RESPONSES AT WEEK 6: COHORTS 1 AND 2

Clinically meaningful results with lonigutamab across cohorts



Cohort 1 data as of December 6, 2023. Cohort 2 data as of March 8, 2024. Proptosis was measured by Hertel exophthalmometer. Diplopia response was assessed in patients with baseline diplopia >0.
[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.