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Integrated safety and efficacy of garadacimab for hereditary angioedema prophylaxis across 3 clinical trials: Phase 2, pivotal Phase 3, and open-label extension studies

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Disclosures

Timothy J. Craig is a speaker for Astria Therapeutics, BioMarin, CSL Behring, Grifols, Takeda, and Regeneron and has received research and consultancy grants from Astria Therapeutics, BioCryst, BioMarin, CSL Behring, Intellia Therapeutics, Ionis, KalVista, GSK, Pharvaris, and Takeda. He is a member of the US Hereditary Angioedema Association Medical Advisory Board, and Director of the ACARE International Angioedema Center at Penn State University in Hershey, PA, USA.

HAE is a rare and potentially life-threatening genetic condition[1–3]

- HAE attacks are recurrent, unpredictable, and debilitating[1–3]
- HAE treatment goals are to achieve total disease control and normalize patients' lives[4]
- There is an unmet need for:[1,4]
  - Improved efficacy, safety, and convenience of administration
  - Novel treatments offering a variety of choices for treatment optimization

HAE, hereditary angioedema.

1. Zanichelli A et al. *Expert Opin Emerg Drugs* 2022;27:103–110; 2. Busse P et al. *J Allergy Clin Immunol Pract* 2021;9:132–150.e3; 3. Zuraw B. *N Engl J Med* 2008;359:1027–1036; 4. Maurer M et al. *Allergy* 2022;77:1961–1990.

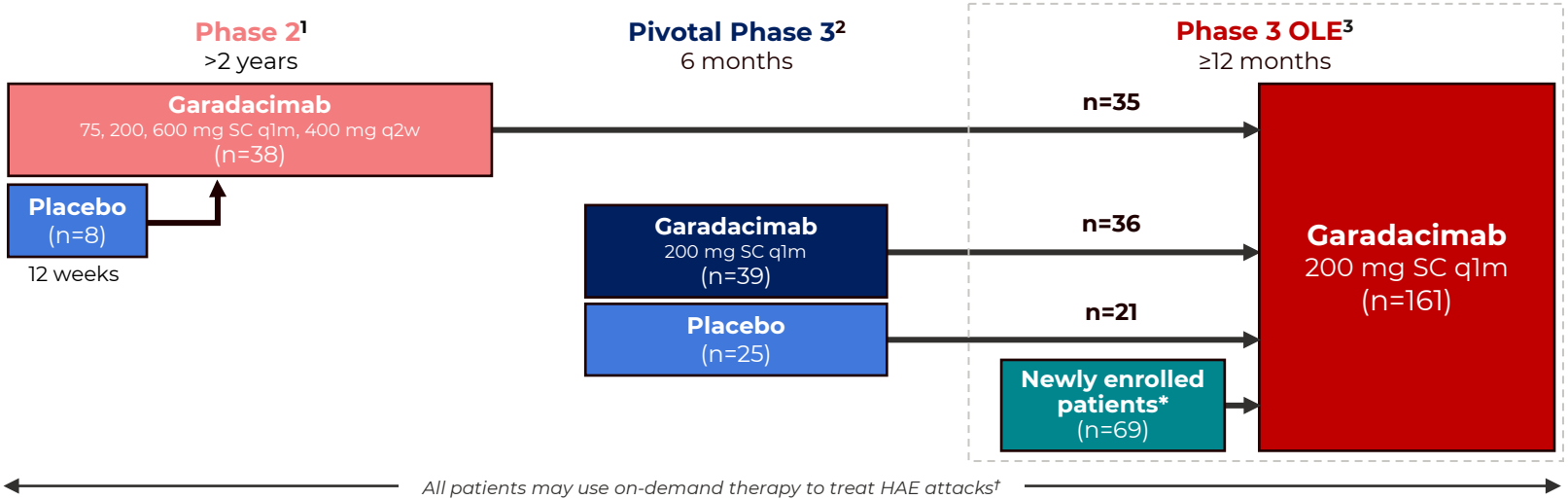
Garadacimab has been evaluated in a comprehensive clinical program as LTP for HAE attacks

- Garadacimab (first-in-class, fully human mAb targeting FXIIa) has been evaluated in **Phase 2**, **pivotal Phase 3,** and ongoing **Phase 3 OLE** studies as LTP for HAE attacks[1–4]
  - Garadacimab demonstrated **durable efficacy with a favorable safety profile**[2,4] in:
    - Pivotal Phase 3* with **91% reduction in HAE attacks vs run-in),** and
    - Phase 3 OLE studies (**95% reduction in HAE attacks** vs run-in

Results from the integrated safety and efficacy analysis of Phase 2, pivotal Phase 3, and ongoing OLE studies evaluating garadacimab are presented

Data cut-off: Feb 13, 2023.
*Primary endpoint: time-normalized number of HAE attacks per month; the mean number of HAE attacks per month was 0.27 with garadacimab vs 2.01 with placebo, P<0.0001.
FXIIa, activated Factor XII; HAE, hereditary angioedema; LTP , long-term prophylaxis; mAb, monoclonal antibody; OLE, open-label extension.
1. Craig TJ et al. *Lancet* 2022;399:945–955; 2. Craig TJ et al. *Lancet* 2023;401:1079–1090;
3. ClinicalTrials.gov. NCT04739059. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04739059 (accessed January 2024);
4. Anderson J et al. Ann. Allergy Asthma Immunol. 2023;131:S3–S13 (Abstract A016), Presented at American College for Asthma, Allergy & Immunology Annual Scientific Meeting; Nov 9–13, 2023; Anaheim, CA, USA.

A comprehensive, multi-study clinical program is evaluating garadacimab SC once-monthly as LTP for HAE attacks



	Phase 2	Pivotal Phase 3	Phase 3 OLE
Eligibility criteria	• Confirmed HAE diagnosis • Aged 18–65 years • Baseline HAE attack rate ≥2 attacks/month	• Confirmed HAE type I/II diagnosis • Aged ≥12 years • Baseline HAE attack rate ≥1 attack/month	• Confirmed HAE diagnosis • Aged ≥12 years • Baseline HAE attack rate ≥1 attack/month
Primary endpoint	Time-normalized number of HAE attacks/month		TEAEs in patients with HAE-C1-INH

Data cut-off: Feb 13, 2023.

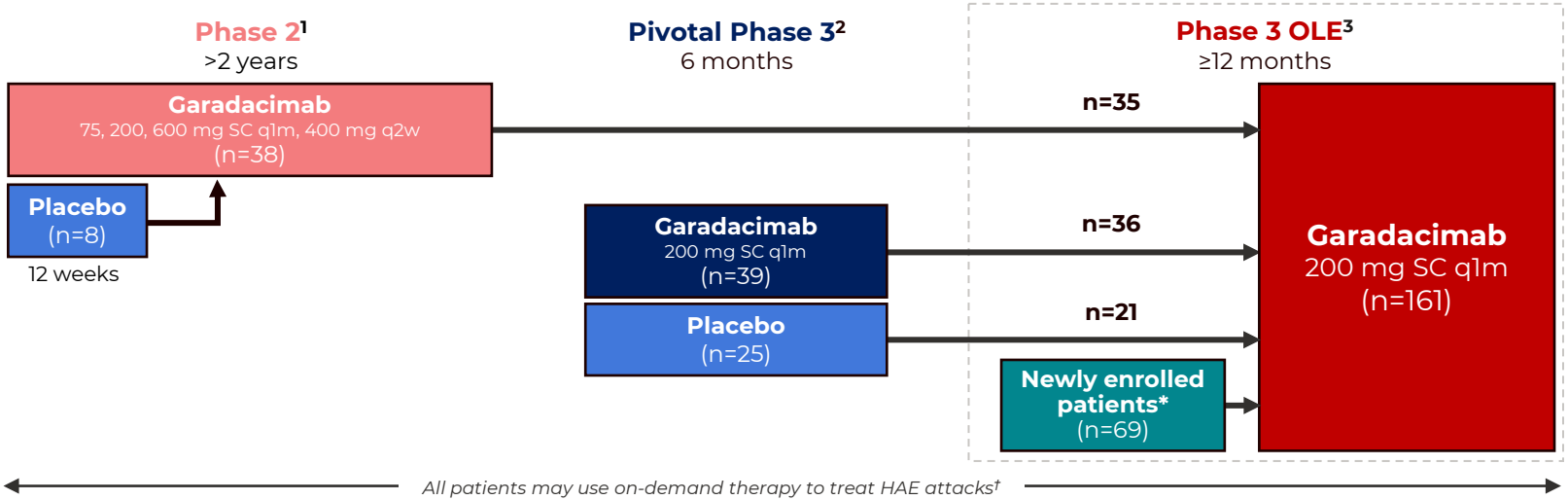
*Newly enrolled patients received one 400 mg SC loading dose as their first dose; †Patients may use acute on-demand therapy to treat emerging HAE attacks if the medication has previously been shown to be effective.

HAE, hereditary angioedema; HAE-C1-INH, HAE with C1-inhibitor deficiency or dysfunction; LTP, long-term prophylaxis; OLE, open-label extension; q1m, once-monthly (Phase 2 = 28 ± 2 days; Phase 3 = 30 ± 4 days); q2w, every 2 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.

1. Craig TJ et al. *Lancet* 2022;399:945–955; 2. Craig TJ et al. *Lancet* 2023;401:1079–1090; 3. Anderson J et al. Ann. Allergy Asthma Immunol. 2023;131:S3–S13 (Abstract A016), Presented at American College for Asthma, Allergy & Immunology Annual Scientific Meeting; Nov 9–13, 2023; Anaheim, CA, USA.

Integrated safety set

Integrated safety analysis set: Long-term safety data



Assessment of safety

Patients who received ≥1 garadacimab dose: **Garadacimab n=172; Placebo n=33**

- **Any dose** (75–600 mg) received in the clinical program
- Up to **4.2 years' (50.4 months) exposure** across three clinical trials

Data cut-off: Feb 13, 2023.

*Newly enrolled patients received one 400 mg SC loading dose as their first dose; †Patients may use acute on-demand therapy to treat emerging HAE attacks if the medication has previously been shown to be effective.

HAE, hereditary angioedema; OLE, open-label extension; q1m, once-monthly (Phase 2 = 28 ± 2 days; Phase 3 = 30 ± 4 days); q2w, every 2 weeks; SC, subcutaneous.

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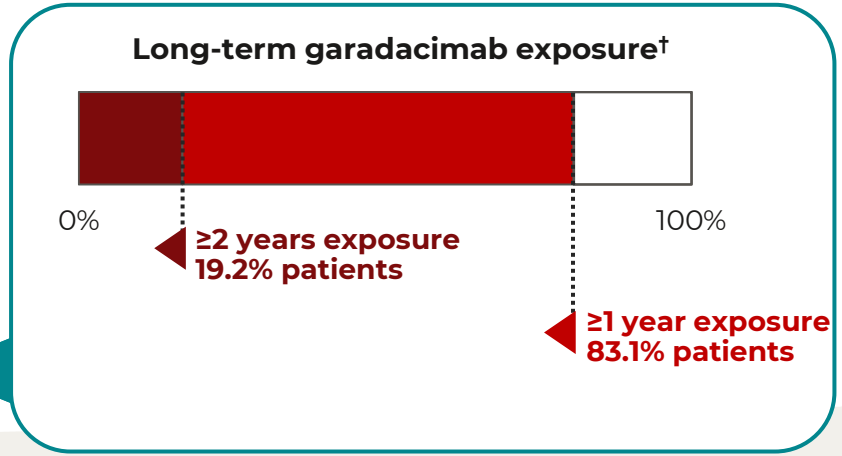
Integrated safety analysis set: Baseline characteristics and exposure

Integrated safety set

Characteristic	Placebo n=33	Garadacimab n=172
Mean age, years (SD)	38.6 (12.6)	41.2 (15.2)
Sex, n (%)		
Female	18 (55)	111 (65)
Male	15 (45)	61 (35)
Race, n (%)		
White	29 (88)	142 (83)
Asian	2 (6)	24 (14)
Black	1 (3)	3 (2)
Other*	1 (3)	3 (2)
Mean BMI, kg/m^2 (SD)	28.4 (6.7)	28.2 (6.6)
HAE type, n (%)		
Type I	29 (88)	153 (89)
Type II	4 (12)	13 (8)
HAE-nC1-INH	0	6 (3)
Median exposure, years (IQR)	**0.5 (0.3–0.5)**	**1.3 (1.1–1.8)**
Range exposure, years	**0.1–0.7**	**0.2–4.2**



Data cut-off: Feb 13, 2023.
*Includes other (including Native Hawaiian or Other Pacific Islander) and multiple; †16.9% of patients receiving garadacimab had <1 year exposure.
BMI, body mass index; HAE, hereditary angioedema; HAE-nC1-INH, hereditary angioedema with normal levels of C1-esterase inhibitor; IQR, interquartile range; SD, standard deviation.

Garadacimab demonstrated a favorable long-term safety profile across the clinical program

Integrated safety set

Median exposure:	0.5 years	1.3 years
AEs, n (%)	**Placebo, n=33**	**Garadacimab, n=172**
Patients with ≥1 TEAE	21 (64)	148 (86)
Related to garadacimab/placebo*	5 (15)	40 (23)
TEAEs leading to death	0	0
TEAEs leading to study discontinuation	0	1 (1)
TEAEs by severity		
Mild	20 (61)	121 (70)
Moderate	9 (27)	103 (60)
Severe	0	15 (9)
SAEs	0	7 (4)†
Related to garadacimab/placebo*	0	0
AESIs per protocol*‡	0	1 (1)§

ISR, moderate severity, garadacimab-related (abdomen irritation at injection site)

HAE attacks, n=3; COVID-19, n=2; asthma, n=1; diverticular perforation, n=1

Epistaxis, not related to garadacimab

Data cut-off: Feb 13, 2023.

*As identified by investigator; †Seven SAEs were reported (one in the placebo-controlled period of the Phase 2 study: facial/abdominal severe HAE attack n=1; two in the open-label period of the Phase 2 study: Diverticular perforation, n=1; asthma, n=1; one in the pivotal Phase 3 study [laryngeal attack n=1]; three in the OLE: COVID-19, n=2; abdominal HAE attack, n=1); none were related to garadacimab; ‡Severe hypersensitivity, including anaphylaxis, thromboembolic events, and abnormal bleeding events; §Phase 2, 600 mg: epistaxis, not garadacimab-related.

AE, adverse event; AESI, adverse event of special interest; HAE, hereditary angioedema; ISR, injection site reaction; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment emergent adverse event.

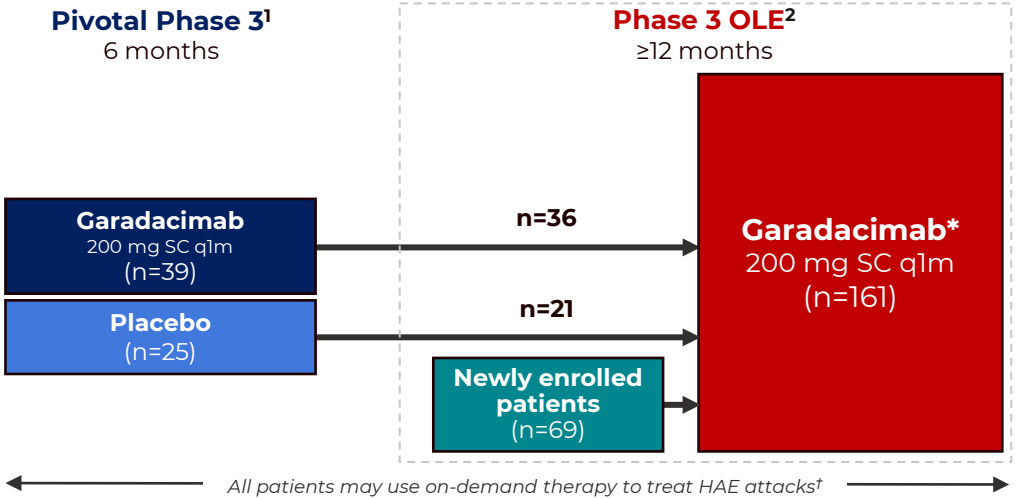
Integrated safety set

Most common TEAEs across all studies

Median exposure:	0.5 years	1.3 years	
AEs in ≥5% of patients, n (%)	**Placebo, n=33**	**Garadacimab, n=172**	
		Any TEAE	**Related to garadacimab**
COVID-19	3 (9)	60 (35)	0
Nasopharyngitis	1 (3)	32 (19)	0
Injection site reactions *(mild severity unless specified)*			
Injection-site erythema	4 (21)	17 (10)	17 (10)
pain	0	4 (2)	3 (2)
urticaria	0	3 (2)	2 (1)
bruising	0	3 (2)	2(1)
reaction	0	3 (2)	1 (1)
swelling	0	1 (1)*	1(1)*
hematoma	0	1 (1)	0
irritation	0	1 (1)*	1(1)*
Headache	4 (12)	23 (13)	6 (4)
URTI	4 (12)	19 (11)	0
Influenza	0	12 (7)	0
Sinusitis	0	12 (7)	0

Data cut-off: Feb 13, 2023.
*Moderate severity.
AE, adverse event; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Integrated efficacy analysis set: Long-term efficacy data



Assessment of efficacy

Garadacimab n=164, Placebo n=25

- **200 mg SC q1m** dose
- **1.2 years' (14.9 months') median exposure**

Data cut-off: Feb 13, 2023.

*Of the 161 patients in the OLE, 35 rolled over from the Phase 2 study where they had previously received garadacimab; †Patients may use acute on-demand therapy to treat emerging HAE attacks if the medication has previously been shown to be effective.

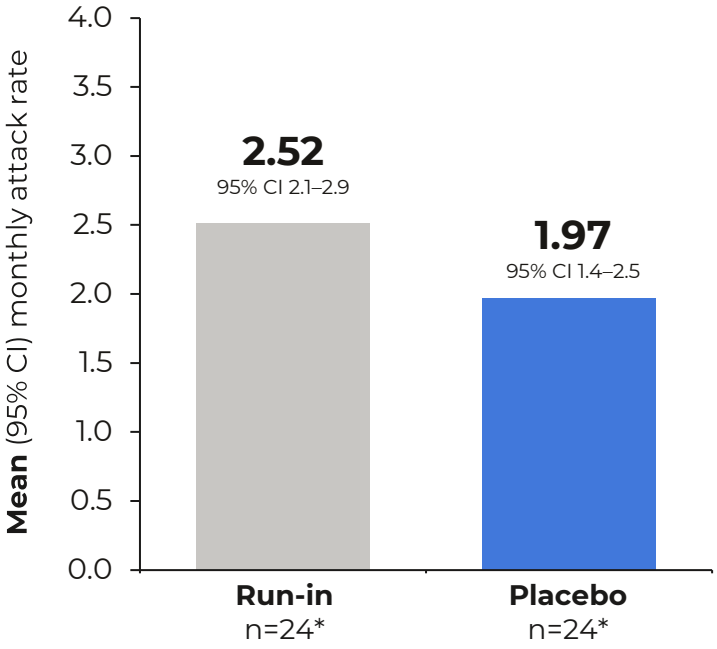
HAE, hereditary angioedema; OLE, open-label extension; q1m, once-monthly (Phase 2 = 28 ± 2 days; Phase 3 = 30 ± 4 days); SC, subcutaneous.

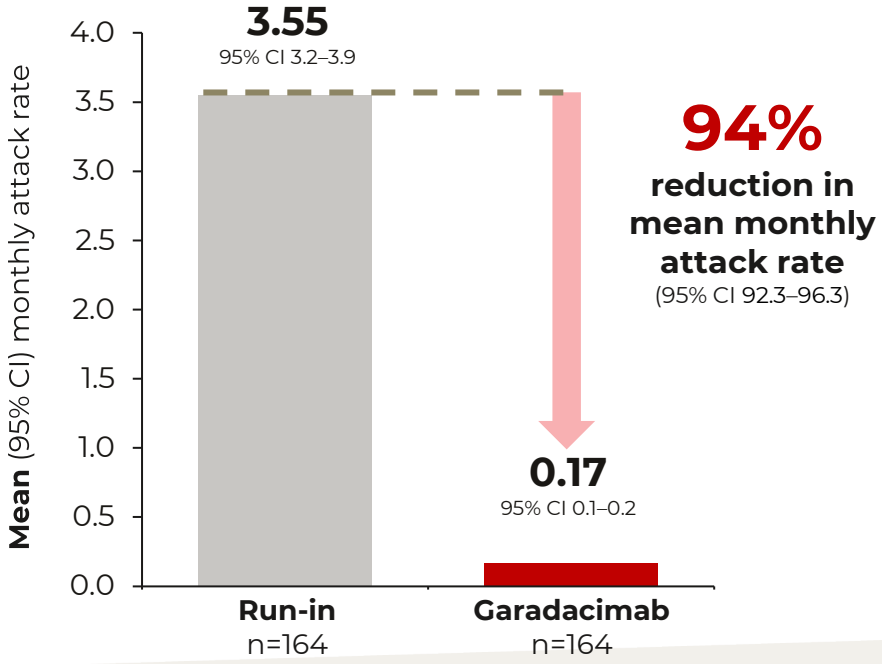
1. Craig TJ et al. *Lancet* 2023;401:1079–1090; 2. Anderson J et al. Ann. Allergy Asthma Immunol. 2023;131:S3–S13 (Abstract A016), Presented at American College for Asthma, Allergy & Immunology Annual Scientific Meeting; Nov 9–13, 2023; Anaheim, CA, USA.

Long-term once-monthly garadacimab reduced mean HAE attack rate vs run-in across the clinical program

Integrated efficacy set

Median garadacimab exposure: 1.2 years (n=164)





Data cut-off: Feb 13, 2023.

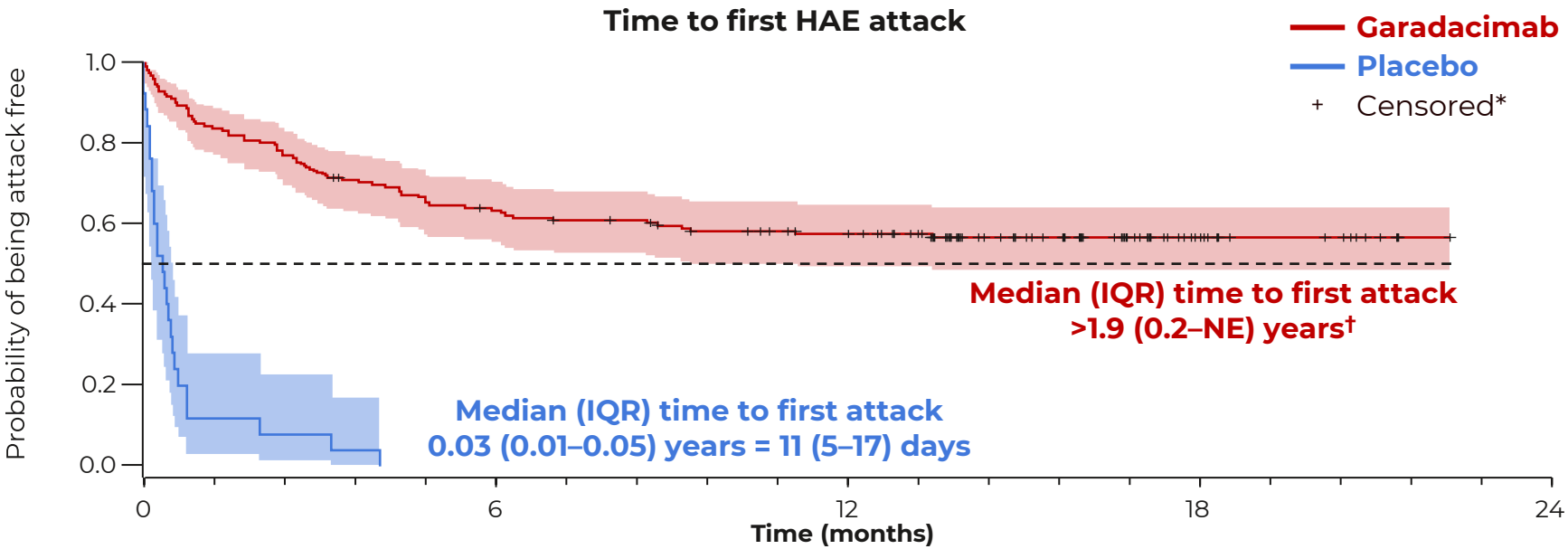
*One patient in the placebo arm was excluded from efficacy analysis as they received treatment for <30 days.

CI, confidence interval; HAE, hereditary angioedema.

Garadacimab delayed time to first attack across the long-term clinical program

Integrated efficacy set

Median garadacimab exposure: 1.2 years (n=164)



Data cut-off: Feb 13, 2023

*If the event is not observed, subjects are considered censored at the date of the End of Treatment visit and the maximum attack-free time is equal to the observed time in the Treatment Period; †Median and upper IQR values could not be calculated as >50% of patients were still attack free at data cut-off.

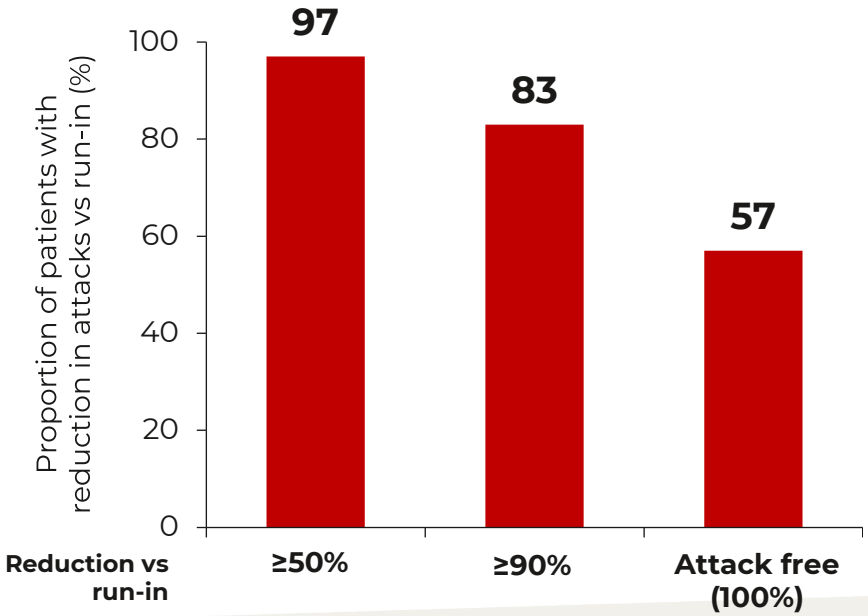
HAE, hereditary angioedema; IQR, interquartile range; NE, not estimable.

Most patients were attack free for >1 year across the clinical program

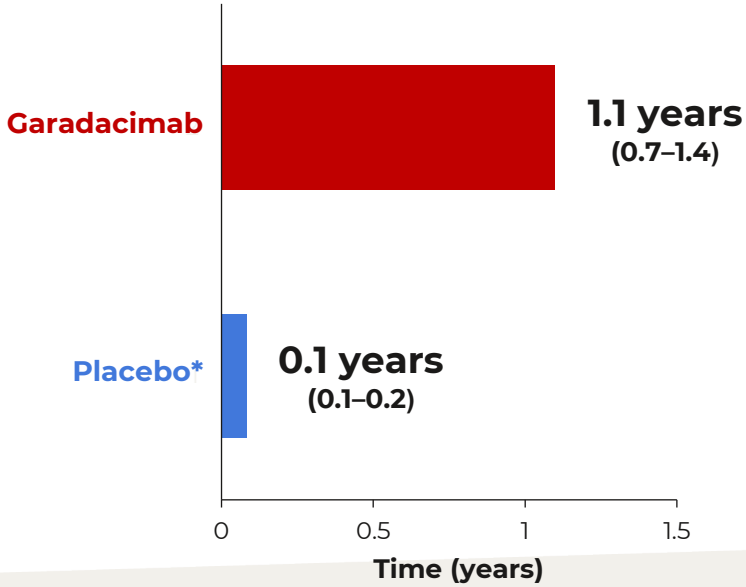
Integrated efficacy set

Median garadacimab exposure: 1.2 years (n=164)

Reduction in attacks vs run-in for patients receiving garadacimab



Longest duration that patients were attack free, median (IQR)



Data cut-off: Feb 13, 2023.
*None of the patients receiving placebo (n=25) were attack free at data cut-off.
IQR, interquartile range.

Garadacimab 200 mg SC once-monthly showed durable efficacy with a favorable long-term safety profile across the clinical program

- **Favorable long-term safety profile over a median exposure of 1.3 years**
  - 86% of patients with ≥1 TEAE, 23% related to garadacimab
  - Most common TEAEs (≥5%): COVID-19, nasopharyngitis, ISRs, headache, URTI, influenza and sinusitis
  - Seven SAEs*, none related to garadacimab: HAE attacks n=3, COVID-19 n=2, asthma n=1, diverticular perforation n=1
  - One garadacimab-related TEAE (ISR) leading to study discontinuation
  - No TEAEs leading to death, no garadacimab-related AESIs† per protocol
- **Durable efficacy over a median exposure of 1.2 years for HAE LTP**
  - 94% reduction in number of attacks vs run-in
  - 83% of patients had ≥90% reduction in HAE attacks vs run-in
  - 57% of patients remained attack free across the studies analyzed

Data cut-off: Feb 13, 2023.
*Seven SAEs were reported (one in the placebo-controlled period of the Phase 2 study: Facial and abdominal severe HAE attack; two in the open-label period of the Phase 2 study: Diverticular perforation, n=1; asthma, n=1; one in the pivotal Phase 3 study [laryngeal attack]; three in the OLE: COVID-19, n=2; abdominal HAE attack, n=1); none were related to garadacimab; †Severe hypersensitivity including anaphylaxis, thromboembolic events, and abnormal bleeding events.
AESI, adverse event of special interest; HAE, hereditary angioedema; ISR, injection site reaction; LTP, long-term prophylaxis; OLE, open-label extension; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.