Safety and Efficacy of Garadacimab for Hereditary Angioedema Prophylaxis in Patients Aged ≥65 Years

Joshua S Jacobs[1], William R Lumry[2], Hilary Longhurst[3], William H Yang[4], Jonathan A Bernstein[5], Constance H Katelaris[6], Bruce Ritchie[7], Iris Jacobs[8], John-Philip Lawo[9], Harsha Shetty[8], and Markus Magerl[10–12]

[1]Allergy & Asthma Clinical Research, Walnut Creek, CA, USA; [2]AARA Research Center, Dallas, TX, USA; [3]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [4]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [5]University of Cincinnati, Department of Internal Medicine Division of Rheumatology, Allergy and Immunology and the Bernstein Clinical Research Center Cincinnati, Cincinnati, OH, USA; [6]Campbelltown Hospital and Western Sydney University Sydney, New South Wales, Australia; [7]Division of Hematology, Department of Medicine, University of Alberta, Edmonton, AB, Canada; [8]CSL Behring, King of Prussia, PA, USA; [9]CSL Innovation GmbH, Marburg, Germany; [10]Institute of Allergology, Charité–Universitätsmedizin Berlin, Berlin, Germany; [11]Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [12]Immunology and Allergology, Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP), Berlin, Germany.

CONCLUSIONS

- **Garadacimab demonstrated long-term efficacy and a favorable safety profile in patients with hereditary angioedema (HAE) aged ≥65 years**
- **The outcomes observed in patients aged ≥65 years were consistent with those of the overall population previously analyzed**

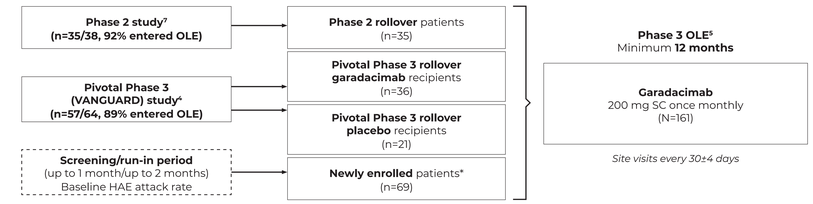
BACKGROUND

- HAE is a genetic disorder that causes recurrent, unpredictable, debilitating, and potentially life-threatening attacks of angioedema, requiring lifelong treatment[1–3]
- Garadacimab is a first-in-class, fully human, anti-activated factor XII monoclonal antibody under evaluation for the long-term prophylaxis of HAE attacks[4–7]
- Garadacimab has demonstrated early and durable efficacy, and a favorable long-term safety profile in the Phase 2, pivotal Phase 3 (VANGUARD), and Phase 3 open-label extension (OLE) studies[4–7]
- Patients with HAE aged ≥65 years may have specific challenges and concerns derived from their life-long experience with this condition, such as increased attack frequency or severity, changes due to menopause, treatment access issues, and changing perspectives on HAE management. Their disease and treatment burdens may be increased by comorbidities and polypharmacy. Evaluating treatment response in this population can inform clinical decision making and help maximize patient outcomes[8,9]

OBJECTIVE

- To evaluate the long-term safety and efficacy of garadacimab in patients with HAE aged ≥65 years, using integrated analyses of data from the Phase 2, pivotal Phase 3 (VANGUARD), and ongoing Phase 3 OLE (data cutoff: February 13, 2023) studies

GARADACIMAB CLINICAL STUDY PROGRAM AND ANALYSIS SETS



	Phase 2	Pivotal Phase 3	Pivotal 3 OLE
Eligibility criteria	• Confirmed HAE diagnosis • Aged 18–65 years • Baseline HAE attack rate ≥2 attacks/month	• Confirmed HAE-C1INH-Type1/2 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 (HAE attack rate)		TEAEs in patients with HAE-C1INH

Integrated safety set — **Phase 2, pivotal Phase 3,** and **Phase 3 OLE** studies
Patients treated with ≥1 dose of garadacimab once monthly‡ (any dose investigated)
- Overall population (garadacimab n=172; placebo n=33)
- **Patients aged ≥65 years (garadacimab n=13; placebo n=0)§**

Integrated efficacy set — **Pivotal Phase 3** and **Phase 3 OLE**¶ studies
Patients treated with ≥1 dose of garadacimab 200 mg SC once monthly‡
- Overall population (garadacimab n=164; placebo n=24)
- **Patients aged ≥65 years (garadacimab n=14; placebo n=0)§**

*Newly enrolled patients received a garadacimab loading dose (two 200 mg SC injections) as first administration; †Patients were permitted to use ODT to treat emerging HAE attacks, if the therapy had previously been shown to be effective; ‡Once monthly: Phase 2 = 28±2 days; Phase 3 = 30±4 days; §Only data from patients aged ≥65 years at study enrolment were part of the integrated analyses. One patient, aged 64 years in the Phase 2 study, became aged 65 years when rolling over to the Phase 3 OLE. For this reason, this patient's data were not part of the integrated safety analysis (Phase 2, pivotal Phase 3 [VANGUARD] and Phase 3 OLE studies, n=13) but were included in the integrated efficacy analysis (pivotal Phase 3 [VANGUARD] and Phase 3 OLE studies, n=14); ¶The analysis also included the Phase 3 OLE data from patients who rolled over from the Phase 2. C1INH, C1 inhibitor; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema due to normal C1INH; ODT, on-demand treatment; OLE, open-label extension; SC, subcutaneous; TEAE, treatment-emergent adverse event.

RESULTS

Baseline characteristics, garadacimab exposure and concomitant medications

Integrated safety set*

Baseline characteristics

Characteristic	Overall population		≥65 years
	Placebo (n=33)	Garadacimab (n=172)	Garadacimab (n=13)
Mean age, years (SD)	38.6 (12.6)	41.2 (15.2)	67.6 (2.7)
Sex, n (%)			
Female	18 (54.5)	111 (64.5)	6 (46.2)
Male	15 (45.5)	61 (35.5)	7 (53.8)
Race/ethnicity, n (%)			
White	29 (87.9)	142 (82.6)	12 (92.3)
Asian	2 (6.1)	24 (14.0)	0
Black	1 (3.0)	3 (1.7)	0
Other†	1 (3.0)	3 (1.7)	1 (7.7)
Mean BMI, kg/m² (SD)	28.4 (6.7)	28.2 (6.6)	29.5 (5.3)
HAE type, n (%)			
Type 1	29 (87.9)	153 (89.0)	12 (92.3)
Type 2	4 (12.1)	13 (7.6)	1 (7.7)
HAE-nC1INH	0	6 (3.5)	0
Most common comorbidities (in ≥4 patients aged ≥65 years), n (%)			
Hypercholesterolemia	0	8 (4.7)	4 (30.8)
Hypertension	4 (12.1)	23 (13.4)	4 (30.8)
Asthma	3 (9.1)	21 (12.2)	4 (30.8)

Garadacimab exposure and concomitant medication use

Characteristic	Overall population		≥65 years
	Placebo (n=33)	Garadacimab (n=172)	Garadacimab (n=13)
Median garadacimab exposure, years (IQR)	**0.5 (0.3–0.5)**	**1.3 (1.1–1.8)**	**1.4 (1.2–1.4)**
Range of exposure, years	**0.1–0.7**	**0.2–4.1**	**1.1–4.1**
Patients exposed to garadacimab for ≥1 year, n (%)	-	143 (83.1)	13 (100)
Patients exposed to garadacimab for ≥2 years, n (%)	-	33 (19.2)	1 (7.7)
Most common concomitant medications (in ≥4 patients aged ≥65 years), n (%)‡			
Atorvastatin	0	10 (5.8)	4 (30.8)
Pravastatin	0	4 (2.3)	4 (30.8)
Tozinameran	10 (30.3)	57 (33.1)	7 (53.8)
Paracetamol	5 (15.2)	57 (33.1)	5 (38.5)
Levothyroxine sodium	2 (6.1)	8 (4.7)	4 (30.8)

Statins were the most common concomitant medications used during garadacimab treatment among patients aged ≥65 years, with 69.2% of patients (n=9/13) in this age group using them compared with 11.6% of patients (n=20/172) in the overall population

*Integrated safety set: Phase 2, pivotal Phase 3 (VANGUARD), and Phase 3 OLE studies; †Includes any other race (Native Hawaiian or Other Pacific Islander) and multiple; ‡Includes concomitant medications and medications initiated prior to study treatment that were taken concomitantly. BMI, body mass index; HAE, hereditary angioedema; HAE-nC1INH, hereditary angioedema due to normal C1INH; IQR, interquartile range; OLE, open-label extension; SD, standard deviation.

Garadacimab demonstrated a favorable long-term safety profile in patients aged ≥65 years

Integrated safety set*

Overview of TEAEs

TEAEs, n (%)	Overall population		≥65 years
	Placebo (n=33)	Garadacimab (n=172)	Garadacimab (n=13)
Patients with ≥1 TEAE	21 (63.6)	148 (86.0)	11 (84.6)
Related to placebo/garadacimab†	5 (15.2)	40 (23.3)	5 (38.5)
TEAEs leading to death	0	0	0
TEAEs leading to study discontinuation	0	1 (0.6)‡	0
TEAEs by severity			
Mild	20 (60.6)	121 (70.3)	8 (61.5)
Moderate	9 (27.3)	103 (59.9)	8 (61.5)
Severe	0	15 (8.7)	1 (7.7)
SAEs	0	7 (4.1)§	0
Related to placebo/garadacimab†	0	0	0
AESIs per protocol¶§	0	1 (0.6)**	0
Injection-site reactions	4 (12.1)	33 (19.2)	4 (30.8)

There were 12 TEAEs related to garadacimab in patients aged ≥65 years:
- 8 × mild injection-site urticaria (7.7%; n=1/13)
- 2 × mild injection-site erythema (15.4%; n=2/13)
- 1 × mild injection-site bruising (7.7%; n=1/13)
- 1 × moderate headache (7.7%; n=1/13)

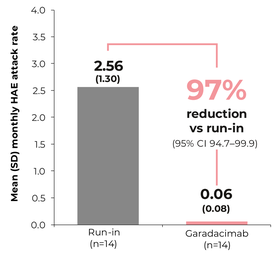
No TEAEs leading to death/discontinuation, SAEs, or AESIs per protocol were reported in patients aged ≥65 years treated with garadacimab

*Integrated safety set: Phase 2, pivotal Phase 3 (VANGUARD), and Phase 3 OLE studies; †As identified by investigator; ‡One moderate injection-site reaction (abdominal irritation) related to garadacimab (occurred after 4 months of treatment within 24 hours of injection; recovered/resolved after 13 days); §Seven SAEs were reported (one in the placebo-controlled period of the Phase 2 study [facial/abdominal 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 Phase 3 OLE study [COVID-19, n=2; abdominal HAE attack, n=1]), none of which were related to garadacimab; ¶Severe hypersensitivity, including anaphylaxis, thromboembolic events, and abnormal bleeding events; **Phase 2, 600 mg: epistaxis, not related to garadacimab.
AESI, adverse event of special interest; HAE, hereditary angioedema; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Garadacimab demonstrated early and durable protection from HAE attacks in patients aged ≥65 years, consistent with previously reported data for the overall population

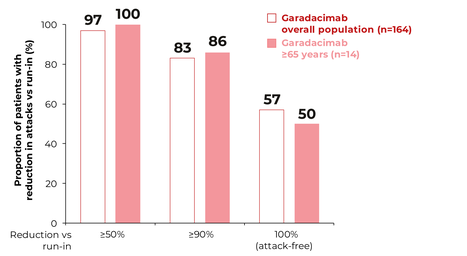
Integrated efficacy set*

Monthly HAE attack rate vs run-in in patients aged ≥65 years



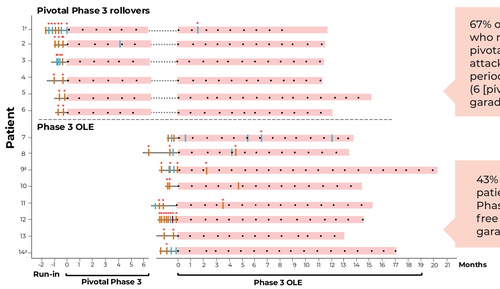
The reduction in monthly HAE attack rate with garadacimab in patients aged ≥65 years was consistent with that of the overall population

Proportion of patients with ≥50%, ≥90%, and 100% reduction in HAE attack rate



The proportions of patients in the ≥65-year subgroup with ≥50%, ≥90%, and 100% reduction in HAE attack rate with garadacimab were consistent with those of the overall population

Treatment and HAE attacks for each patient aged ≥65 years



67% of patients (n=4/6) who rolled over from the pivotal Phase 3 study were attack free for a cumulative period of ≥17 months ([6 [pivotal]+ 11 [OLE]) after garadacimab initiation

43% of newly enrolled patients (n=3/7) in the Phase 3 OLE were attack free for ≥12 months after garadacimab initiation

*Integrated efficacy set: Pivotal Phase 3 (VANGUARD) and Phase 3 OLE studies; †Patient discontinued upon physician decision, not due to TEAEs; ‡Patients 9 and 14 received garadacimab 200 mg SC once monthly in the Phase 3 OLE after rolling over from the Phase 2 study. Patient 14 was not included in the integrated safety analysis due to being aged <65 years when first enrolled in the Phase 2 study.
CI, confidence interval; HAE, hereditary angioedema; ODT, on-demand treatment; OLE, open-label extension; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event.

Scan the QR code to access the poster

REFERENCES:
1. Maurer M et al. *Allergy* 2022;77:1961–1990; 2. Busse PJ et al. *J Allergy Clin Immunol Pract* 2021;9:132–150.e3; 3. Davis AE 3rd. *Transfus Apher Sci* 2003;29:195–203; 4. Craig TJ et al. *Lancet* 2023;401:1079–1090; 5. Reshef A et al. *Allergy* 2025;80:545–556; 6. Craig TJ et al. *Lancet Haematol* 2024;11:e436–e447; 7. Craig TJ et al. *Lancet* 2022;399:945–955; 8. Kingston A et al. *Age Ageing* 2018;47:374–380; 9. Baptist AP et al. *Ann Allergy Asthma Immunol* 2024;132:76–81.e2.

DISCLOSURES:
This study was funded by CSL Behring LLC. Medical writing support was provided by Grant Kirkpatrick, MSc, and Anita Toscani, PhD, of Helix, OPEN Health Communications, and was funded by CSL Behring, in accordance with Good Publication Practice guidelines (GPP 2022).