Efficacy and safety of subcutaneous garadacimab for the prophylaxis of hereditary angioedema (HAE) attacks in adult and adolescent patients with HAE: results from a multicenter, placebo-controlled Phase 3 trial

Timothy J Craig[1], Markus Magerl[2], Avner Reshef[3], H Henry Li[4], Joshua S Jacobs[5], Jonathan A Bernstein[6,7], Henriette Farkas[8], William H Yang[9], Erik S G Stroes[10], Isao Ohsawa[11], Raffi Tachdjian[12], Michael E Manning[13], William R Lumry[14], Inmaculada Martinez Saguer[15], Emel Aygören-Pürsün[16], Bruce Ritchie[17], Gordon L Sussman[18], John Anderson[19], Kimito Kawahata[20], Yusuke Suzuki[21], Petra Staubach[22], Regina Treudler[23], Henrike Feuersenger[24], Lolis Wieman[25], and Iris Jacobs[25]

[1]Allergy, Asthma and Immunology, Department of Medicine and Pediatrics, Penn State University, Hershey, PA, USA; [2]Institute of Allergology, Charité-Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [3]Allergy, Immunology and Angioedema Center, Barzilai University Hospital, Ashkelon, Israel; [4]Institute for Asthma and Allergy, Chevy Chase, MD, USA; [5]Allergy and Asthma Clinical Research, Walnut Creek, CA, USA; [6]University of Cincinnati, Department of Internal Medicine, Division of Rheumatology, Allergy and Immunology, Cincinnati, OH, USA; [7]Bernstein Clinical Research Center, Cincinnati, OH, USA; [8]Department of Internal Medicine and Hematology, Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [9]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [10]Department of Vascular Medicine, Amsterdam UMC, Amsterdam, the Netherlands; [11]Department of Nephrology, Saiyu Soka Hospital, Saitama, Japan; [12]Division of Allergy and Clinical Immunology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; [13]Allergy, Asthma and Immunology Associates, Ltd., Internal Medicine, UA College of Medicine – Phoenix, Phoenix, AZ, USA; [14]AARA Research Center, Dallas, TX, USA; [15]HZRM Hemophilia Center Rhein Main, Mörfelden-Walldorf, Germany; [16]Klinikum der Johann Wolfgang-Goethe Universität, Klinik für Kinder- und Jugendmedizin, Frankfurt, Germany; [17]Division of Hematology, Department of Medicine, University of Alberta, Edmonton, AB, Canada; [18]Gordon Sussman Clinical Research Inc. and Department of Clinical Immunology and Allergy, St. Michael's Hospital, Toronto, ON, Canada; [19]AllerVie Clinical Research, Birmingham, AL, USA; [20]St. Marianna University School of Medicine, Kawasaki-shi, Kanagawa, Japan; [21]Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan; [22]Department of Dermatology and Allergy, University Medical Center Mainz, Mainz, Germany; [23]University Leipzig Medical Faculty, Department of Dermatology, Venereology and Allergology, Leipzig Interdisciplinary Center for Allergology – CAC, Leipzig, Germany; [24]CSL Behring Innovation GmbH, Marburg, Germany; [25]CSL Behring, King of Prussia, PA, USA. **Corresponding author: Dr Timothy J. Craig, DO. Email:** tcraig@pennstatehealth.psu.edu

CONCLUSIONS

- **Once-monthly subcutaneous (SC) garadacimab elicited significant reductions in HAE attack rate per month (100% reduction in median attack rate vs placebo)**
- **Garadacimab demonstrated early onset and sustained control of HAE attacks (71.8% attack free in first 3 months and 61.5% attack free over 6-month treatment period)**
- **Favorable safety profile observed with no reported abnormal bleeding or thrombotic adverse events (AESIs per protocol)**
- **Long-term efficacy and safety are currently under evaluation in an open-label extension study (ClinicalTrials.gov identifier: NCT04739059)**

BACKGROUND

- HAE is a rare, often debilitating, potentially fatal disease characterized by unpredictable swellings (HAE attacks)[1,2]
- Most patients with HAE display deficiency (type I) or dysfunction (type II) of C1-INH, causing contact system dysregulation leading to uncontrolled bradykinin production via the kallikrein–kinin pathway[1-3]
- FXIIa is an initiator of the contact system, which includes production of bradykinin, a key mediator of vascular permeability, vasodilation, and fluid efflux[3,4]
- Garadacimab is a fully human, immunoglobulin G4, monoclonal antibody that inhibits FXIIa at the origin of the contact system cascade, reducing bradykinin production[5,6]

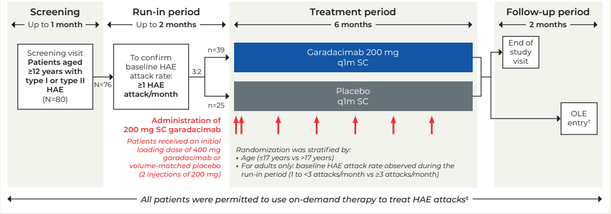
OBJECTIVE

- To report the efficacy and safety of once-monthly SC 200 mg garadacimab in patients with type I/II HAE from the global VANGUARD Phase 3, randomized, double-blind, placebo-controlled, multicenter study (NCT04656418)

METHODS

- Key eligibility criteria and study design shown in **Figure 1**
- Primary endpoint and three secondary endpoints were hierarchically tested
- **Primary endpoint:** time-normalized number of HAE attacks through Day 182 (HAE attack rate per month) (**H01**)
  - **Key secondary endpoints supporting hierarchical testing:** time-normalized number of HAE attacks at various time-points during treatment period (supporting **H02:** reduction in mean number of HAE attacks vs placebo), reduction in HAE attack rate vs run-in period (supporting **H03:** number of patients who do not experience an HAE attack within first 3 months), SGART (supporting **H04:** percent of patients with 'good' or better SGART responses at Day 182)
  - **Secondary endpoints:** time-normalized number of HAE attacks requiring on-demand therapy, time-normalized number of moderate/severe HAE attacks
  - **Exploratory efficacy endpoints:** time to first HAE attack, AE-QoL score
- Safety endpoints were serious AEs, TEAEs and AESIs per protocol

Figure 1. VANGUARD study design (conducted at 28 sites across 7 countries)*



*Efficacy and safety data were monitored by an Interim Analyses and Data Monitoring Committee; †Entry into Phase 3b OLE study (NCT04739059); ‡If that medication had previously been shown to be effective.

RESULTS

- 64 patients (including 6 adolescents) were randomized to garadacimab (n=39) or placebo (n=25) and entered treatment (**Table 1**)
  - Demographics and baseline characteristics were generally comparable across treatment arms

Table 1. Demographics and baseline characteristics

Characteristics	Placebo q1m (n=25)	Garadacimab 200 mg q1m (n=39)
Age, years, mean (SD)	37.8 (12.80)	43.3 (17.45)
Female, n (%)	14 (56.0)	24 (61.5)
Race, n (%)		
White	22 (88.0)	33 (84.6)
Asian	2 (8.0)	4 (10.3)
Other*	1 (4.0)	2 (5.2)
BMI, kg/m^2, mean (SD)	28.4 (7.56)	27.9 (6.02)
HAE type I, n (%)	22 (88.0)	34 (87.2)
HAE attack rate per month during run-in period		
Mean (95% CI)	2.52 (2.13, 2.91)	3.07 (2.41, 3.73)
Median (IQR)	2.23 (1.40)	2.61 (1.75)

*Including American Indian, Alaska Native, Black or African American, Native Hawaiian, or Pacific Islander.

Time-normalized number of HAE attacks through Day 182 (primary endpoint)

- **H01:** Mean 95% CI: 0.27 (0.05, 0.49) in garadacimab arm vs 2.01 (1.44, 2.57) in placebo arm (p<0.001) (**Figure 2**)
  - Least square mean (95% CI): 0.22 (0.11, 0.47) in garadacimab arm vs 2.07 (1.49, 2.87) in placebo arm
- Median (IQR) HAE attack rate per month: 0.00 (0.31) in garadacimab arm vs 1.35 (2.2) in placebo arm (**Figure 2**)

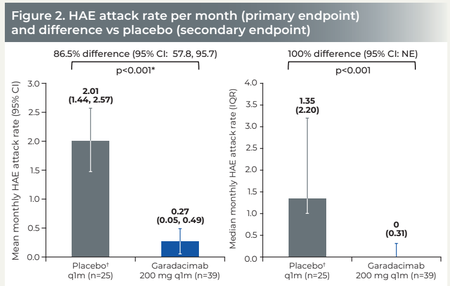
Percentage reduction in time-normalized number of HAE attacks through Day 182 vs placebo (secondary endpoint)

- **H02:** Mean HAE attack rate: 86.5% reduction (95% CI 57.8, 95.7) (**Figure 2**)
  - Least squares mean: 89.2% reduction (95% CI 75.6, 95.2)
- Median HAE attack rate: 100% reduction (95% CI not estimable) (**Figure 2**)

Reduction in HAE attack rate vs run-in period (secondary endpoint)

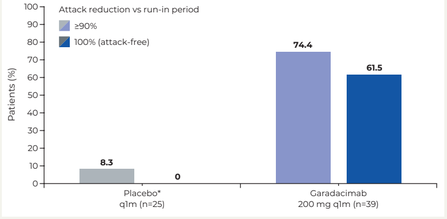
- **H03:** Attack-free patients within first 3 months: 28 patients (71.8%) for garadacimab vs 2 (8.3%) for placebo (p<0.001)
- Attack-free patients over entire 6-month treatment period: 24 patients (61.5%) for garadacimab vs none for placebo (**Figure 3 and 4**)
- ≥90% reduction in HAE attack rate over entire 6-month treatment period: 29 patients (74.4%) for garadacimab vs 2 (8.3%) for placebo (**Figure 3**)

Figure 2. HAE attack rate per month (primary endpoint) and difference vs placebo (secondary endpoint)



*Two-sided Wilcoxon test; †One patient receiving placebo with <30 days in the study period was excluded from the analysis; ‡Difference in LSM number of HAE attacks per month using a generalized linear model (sensitivity analysis).

Figure 3. Percentage of patients with 100% or ≥90% reduction in number of HAE attacks per month vs run-in period throughout 6-month treatment period (secondary endpoint)



*One patient receiving placebo with <30 days in the study period was excluded from the analysis.

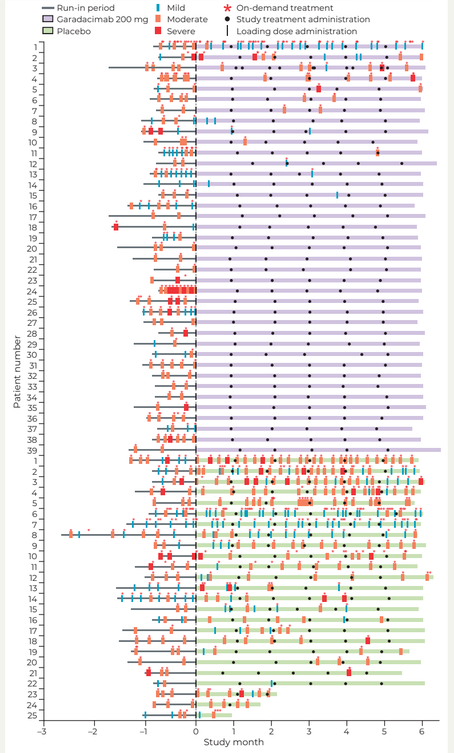
Number of moderate/severe HAE attacks per month (secondary endpoint)

- Mean (95% CI): 0.13 (0.03, 0.22) in garadacimab arm vs 1.35 (0.86, 1.84) for placebo (90.4% reduction) (**Figure 4**)

Time to first HAE attack (exploratory endpoint)

- Time to first HAE attack for 75% of patients (or attack free): ≥72 days in garadacimab arm vs ≥5 days in placebo arm

Figure 4. HAE attacks during the run-in and treatment periods



AE-QoL score (exploratory endpoint)

- Clinically meaningful quality of life improvement (AE-QoL score reduction ≥6 points): Mean (SD) total score reduction was -26.5 (17.9) from baseline to Day 182 in garadacimab arm vs -2.2 (19.1) in placebo arm

Safety

- Rates of TEAEs comparable between garadacimab and placebo: 64.1% vs 60.0%, respectively (**Table 2**)
- Most common TEAEs are shown in **Table 2**
- No deaths or AEs leading to discontinuation
- One serious, severe AE occurred in the garadacimab arm (laryngeal attack managed with overnight hospitalization and assessed as not related to garadacimab by the investigator)
- No AESIs per protocol, such as anaphylaxis, thromboembolic events, and abnormal bleeding were identified

Table 2. Safety results during the 6-month treatment period

TEAEs, n (%)*	Placebo q1m (n=25)	Garadacimab 200 mg q1m (n=39)
Patients experiencing ≥1 TEAE	15 (60.0)	25 (64.1)
Any serious TEAE	0	1† (2.6)
TEAE leading to study discontinuation	0	0
AESI per protocol	0	0
TEAE related to study treatment	3 (12.0)	4 (10.3)
Most common TEAEs in ≥5% of patients MedDRA Preferred Term		
Upper-respiratory tract infections	2 (8.0)	4 (10.3)
Nasopharyngitis	1 (4.0)	3 (7.7)
Headache	4 (16.0)	3 (7.7)
Injection-site reactions‡	3 (12.0)	2 (5.1)

*Number of patients with at least one AE; †One severe, serious TEAE (not related to study treatment) due to overnight hospital observation for a laryngeal HAE attack; ‡Injection-site reactions is a virtual system organ class including injection-site erythema (one patient in garadacimab arm and two in placebo arm), bruising (one patient in the garadacimab arm), and pruritus (one patient in the garadacimab arm).

References

1. Busse P3 et al. *J Allergy Clin Immunol Pract* 2021;9:132–150.e3;
2. Maurer M et al. *Allergy* 2022;77:1961–1990;
3. Davis AE 3rd et al. *Mol Immunol* 2008;45:4057–4063;
4. Björkqvist J et al. *Thromb Haemost* 2013;110:399–407;
5. McKenzie A et al. *Clin Transl Sci* 2022;15:626–637;
6. Craig T et al. *Lancet* 2022;399:945–955.

Acknowledgments

The authors thank all the study investigators, trial site coordinators, and patients who participated in this trial.

Disclosures

CSL Behring provided funding for the trial, as well as for medical writing assistance. Writing support was provided by OPEN Health Communications and Meridian HealthComms.

AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; CI, confidence interval; HAE, hereditary angioedema; IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Affairs; NE, not estimable; OLE, open-label extension; q1m, once monthly; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event.