Long-term safety and efficacy with garadacimab for hereditary angioedema prophylaxis in an open-label extension study

John Anderson[1], Donald S Levy[2], Gordon L Sussman[3], Joshua S Jacobs[4], Henriette Farkas[5], Maressa Pollen[6], Henrike Feuersenger[7], Timothy J Craig[8]

[1]AllerVie Clinical Research, Birmingham, AL, USA; [2]Division of Allergy and Immunology, University of California, Irvine, CA, USA; [3]Gordon Sussman Clinical Research Inc. and Department of Clinical Immunology and Allergy, St. Michael's Hospital, Toronto, ON, Canada; [4]Allergy & Asthma Clinical Research, Walnut Creek, CA, USA; [5]Department of Internal Medicine and Haematology, Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [6]CSL Behring, King of Prussia, PA, USA; [7]CSL Behring Innovation GmbH, Marburg, Germany; [8]Allergy, Asthma and Immunology, Department of Medicine and Pediatrics, Penn State University, Hershey, PA, USA.

CONCLUSIONS

- **Garadacimab demonstrated a favorable long-term safety profile in the ongoing open-label extension (OLE) study (NCT04739059),[1] generally consistent with the 6-month pivotal Phase 3 (VANGUARD) study[2]**
- **Garadacimab provided durable efficacy and sustained protection from hereditary angioedema (HAE) attacks over a median exposure of 13.8 months**

BACKGROUND

HAE[3–6]

- Causes recurrent, unpredictable, debilitating, and potentially life-threatening attacks
- Results from increased levels of bradykinin, a key mediator of HAE attacks
- The goals of HAE treatment are to achieve total control of the disease and to normalize patients' lives, which are currently achieved only by long-term prophylaxis (LTP)
- There is an unmet need for alternative LTP with improved efficacy, safety, and convenience of administration, and that provides choices for treatment optimization

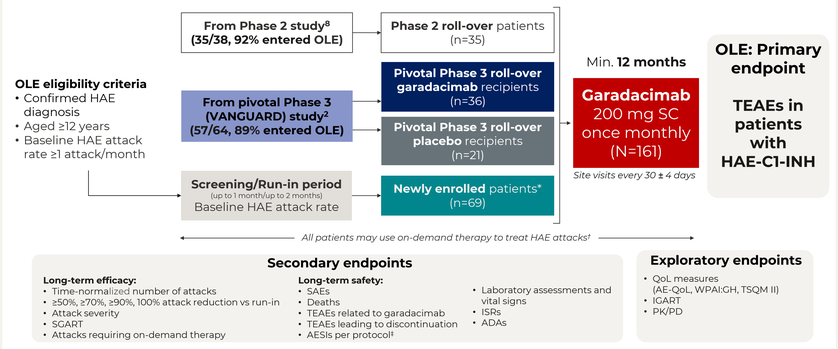
Garadacimab[1,2,7]

- First-in-class monoclonal antibody targeting activated factor XII, the key initiator of the contact system
- Fully human, high affinity/potency/specificity; regulates bradykinin production *in vitro*
- In the 6-month pivotal Phase 3 (VANGUARD) study, garadacimab significantly reduced the mean monthly number of attacks vs placebo (P<0.0001) with a favorable safety and tolerability profile
- Long-term evaluation of garadacimab for LTP against HAE attacks is ongoing in the Phase 3 (VANGUARD) OLE study (NCT04739059); recruitment for the OLE has completed

OBJECTIVE

- To report the long-term safety and efficacy results from the second interim analysis of the ongoing Phase 3 (VANGUARD) OLE study (data cut-off: February 13, 2023)

LONG-TERM PHASE 3 (VANGUARD) OLE STUDY DESIGN



*Newly enrolled patients received one 400 mg SC loading dose as their first dose; †Patients may use acute on-demand therapy to treat emerging episodes of edema if the medication has previously been shown to be effective; ‡Severe hypersensitivity including anaphylaxis, thromboembolic events, and abnormal bleeding events.
ADA, antidrug antibody; AE-QoL, Angioedema Quality of Life Questionnaire; AESI, adverse event of special interest; HAE, hereditary angioedema; HAE-C1-INH, HAE with C1 esterase inhibitor deficiency; IGART, investigator's global assessment of response to therapy; ISR, injection-site reaction; Min, minimum; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; QoL, quality of life; SAE, serious adverse event; SC, subcutaneous; SGART, subject's global assessment of response to therapy; TEAE, treatment-emergent adverse event; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI:GH, work productivity and activity impairment: general health.

RESULTS

Baseline demographics and characteristics of patients in the OLE

Characteristic	Garadacimab (N=161)
Mean (SD) age, years	42.3 (15.3)
Sex – Female, n (%)	101 (62.7)
Race, n (%)	
White	135 (83.9)
Asian	22 (13.7)
Black	2 (1.2)
Other*	2 (1.2)
Mean (SD) BMI, kg/m²†	28.1 (6.2)
HAE type, n (%)	
Type I	145 (90.1)
Type II	14 (8.7)
HAE-nC1-INH†	2 (1.2)
Mean (SD) number of HAE attacks per month during run-in‡	3.6 (2.4)
Median (IQR) garadacimab exposure in OLE, months	13.8 (11.9–16.3)
Patients with ≥12 months' exposure,§ n (%)	119 (73.9)

Most patients (74%) received at least 12 months of garadacimab in the OLE

*Includes Other and Multiple; †Two patients with HAE-nC1-INH were not included in the primary safety analysis and calculation of mean BMI; ‡All patients had their baseline attack rate measured during the run-in period; for roll-over patients, the run-in period was at the beginning of the first study the patient was enrolled in; §55/161 patients (34.2%) had ≥15 months' garadacimab exposure in the OLE.
BMI, body mass index; HAE, hereditary angioedema; HAE-nC1-INH, hereditary angioedema with normal levels of C1-esterase inhibitor; IQR, interquartile range; OLE, open-label extension; SD, standard deviation.

Garadacimab demonstrated a favorable long-term safety profile (primary endpoint) in the OLE

AEs, n (%)	Garadacimab (n=159)*
Patients with ≥1 TEAE	133 (84)
Related to garadacimab†	21 (13)
TEAEs leading to death	0
TEAEs leading to study discontinuation	1 (1)‡
TEAEs by severity	
Mild	99 (62)
Moderate	81 (51)
Severe	9 (6)
SAEs	3 (2)§
Related to garadacimab†	0
AESIs per protocol†¶	0
Most common TEAEs (AEs in ≥5% of patients), n (%)	
COVID-19	57 (36)
Nasopharyngitis	27 (17)
ISRs**	19 (12)
Injection-site erythema	11 (7)
pruritus	4 (3)
urticaria	2 (1)
bruising	1 (1)
hematoma	1 (1)
irritation	1 (1)
Influenza	11 (7)
Headache	10 (6)
Upper respiratory tract infection	9 (6)

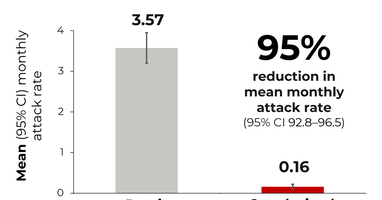
In the pivotal Phase 3 (VANGUARD) study:[2]
- Generally consistent safety profile with the OLE
- No TEAEs leading to death or study discontinuation
- No SAEs related to garadacimab
- No AESIs per protocol

In the OLE:
- ISRs were the most common garadacimab-related TEAE (36/52 events, 69%)
- 18/19 (95%) patients had mild ISRs; no severe ISRs were reported

*Two patients with HAE-nC1-INH were not included in the primary safety analysis; †As identified by investigator; ‡One garadacimab-related ISR leading to study discontinuation; §Three SAEs were reported 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; **TEAEs are categorized as ISRs based on medical review of relevant Preferred Terms.
AE, adverse event; AESI, adverse event of special interest; HAE, hereditary angioedema; HAE-nC1-INH, hereditary angioedema with normal levels of C1-esterase inhibitor; ISR, injection-site reaction; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Once-monthly garadacimab reduced the number of HAE attacks per month vs run-in (secondary endpoint) in the OLE

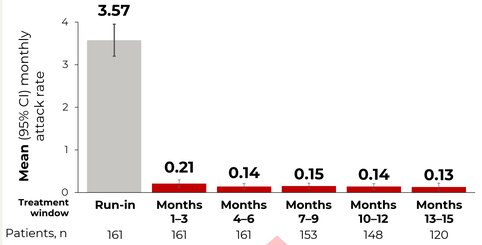
Median garadacimab exposure 13.8 months (N=161)



Over the 6-month pivotal Phase 3 (VANGUARD) study:[2]
- **0.27 vs 3.10** mean monthly attack rate with garadacimab vs run-in
- **91%** reduction (95% CI 83.4–97.9)

Durable efficacy of once-monthly garadacimab observed throughout the OLE

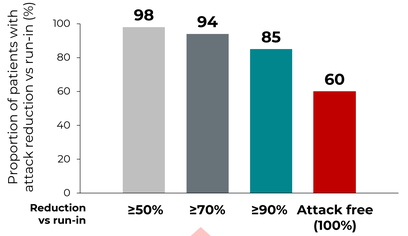
Mean monthly attack rate over 3-month intervals



In the OLE:
- **94%** reduction in mean monthly attack rate vs run-in was observed over Months 1–3
- Reduction sustained at ≥94% throughout the OLE

Attack free rate achieved in the pivotal Phase 3 (VANGUARD) study is sustained during the OLE

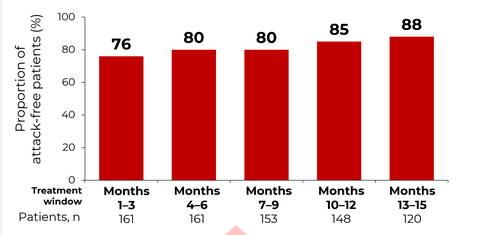
Median garadacimab exposure 13.8 months (N=161)



Over the 6-month pivotal Phase 3 (VANGUARD) study:[2]
- **62%** were attack free with garadacimab vs **0%** with placebo
- **74%** had ≥90% attack reduction with garadacimab vs **8%** with placebo

Consistent proportions of attack-free patients were observed over treatment intervals with garadacimab throughout the OLE

Percentage of attack-free patients by 3-month intervals



Over the 6-month pivotal Phase 3 (VANGUARD) study:[2]
- Months 1–3: **72%** were attack free with garadacimab vs **8%** with placebo
- Months 4–6: **69%** were attack free with garadacimab vs **9%** with placebo

CI, confidence interval; HAE, hereditary angioedema; OLE, open-label extension.

Western Society of Allergy, Asthma and Immunology| Koloa, HI| February 4-8, 2024

REFERENCES

1. ClinicalTrials.gov. NCT04739059. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04739059 (accessed October 2023); 2. Craig TJ et al. *Lancet* 2023;401:1079–1090; 3. Zanichelli A et al. *Expert Opin Emerg Drugs* 2022;27:103–110; 4. Busse P et al. *J Allergy Clin Immunol Pract* 2021;9:132–150.e3; 5. Zuraw B. *N Engl J Med* 2008;359:1027–1036; 6. Maurer M et al. *Allergy* 2022;77:1961–1990; 7. Cao H et al. *J Allergy Clin Immunol* 2018;142:1355–1358; 8. Craig T et al. *Lancet* 2022;399:945–955.

DISCLOSURES

This study was sponsored by CSL Behring. Writing support was provided by OPEN Health Communications.