Garadacimab for hereditary angioedema (HAE) prophylaxis: long-term efficacy and safety from the Phase 3 VANGUARD trial and first interim analysis of the open-label extension trial

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CONCLUSIONS

- **In the OLE, the median garadacimab exposure was 9.5 months, with some patients receiving garadacimab for upwards of 12 months**
- **Once-monthly garadacimab reduced the mean monthly attack rate vs run-in period by 94%, and 63% of patients were attack free in the OLE**
- **Garadacimab had a favorable safety profile with no related SAEs or AESIs per protocol reported**
- **Results are generally consistent with the pivotal Phase 3 study results and demonstrate the sustained efficacy of garadacimab as routine prophylaxis to prevent HAE attacks**

BACKGROUND

- Garadacimab is a novel, first-in-class, fully human monoclonal antibody against FXIIa[1]
- Garadacimab SC 200 mg administered once monthly showed significant and clinically meaningful improvements in HAE attack rates in a 6-month pivotal Phase 3 study:
  - HAE attack rate was significantly lower with garadacimab vs placebo[1]
  - 62% of patients receiving garadacimab were attack free over the entire 6 months vs no patients receiving placebo[1]
  - Garadacimab demonstrated a favorable safety and tolerability profile[1]
- Following the 6-month pivotal Phase 3 study, patients rolled over into an OLE[1]

OBJECTIVE

- To evaluate the long-term efficacy and safety of once-monthly SC garadacimab 200 mg in an OLE study

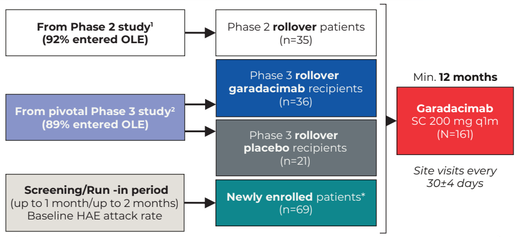
METHODS

- The OLE is evaluating long-term efficacy and safety of once-monthly SC garadacimab 200 mg for ≥12 months, including patients rolled over from the Phase 2 and pivotal Phase 3 studies, and newly enrolled garadacimab-naïve patients. Key eligibility criteria and study design are shown in **Figure 1**

Figure 1. Study design

OLE eligibility criteria
- Confirmed HAE
- Aged ≥12 years
- Baseline HAE attack rate ≥1 attack/month

Primary endpoints
- Safety: TEAEs (incl. TEAE rates per injection and per patient year) in patients with HAE-C1-INH



Secondary endpoints

Long-term efficacy
- Time-normalized number of attacks
- ≥50%, ≥70%, ≥90%, 100% reduction vs run-in
- Attack severity
- SGART
- HAE attack requiring on-demand therapy

Long-term safety
- SAEs
- Deaths
- TEAEs leading to discontinuation
- Laboratory assessments and vital signs
- AESIs per protocol
- ISRs
- ADAs
- TEAEs for HAE-nC1-INH patients

Exploratory endpoints
- QoL measures, (AE-QoL, WPAI:GH, TSQM)
- IGART
- PK/PD

*Newly enrolled patients received one SC 400 mg 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; ‡The efficacy analysis is exploratory, and no statistical tests are planned; §AESIs in this study were thromboembolic events, bleeding events and severe hypersensitivity, including anaphylaxis.

RESULTS

Table 1. Patient characteristics and garadacimab exposure

Characteristic	Garadacimab (N=161)
Mean (SD) age, years	42.3 (15.3)
Sex – female, n (%)	101 (62.7)
Race, n (%) White Asian Black or African American Other*	 135 (83.9) 22 (13.7) 2 (1.2) 2 (1.2)
Mean (SD) BMI, kg/m²	28.1 (6.2)
HAE-C1-INH type, n (%) Type I Type II HAE-nC1-INH†	 145 (90.1) 14 (8.7) 2 (1.2)
Number of HAE attacks per month during run-in,‡ mean (SD)	3.6 (2.4)
Median (range) exposure in OLE, months	9.5 (3.0–16.7)

*Includes Other and Multiple; †Two patients with FXII-HAE, analyzed separately for safety data (primary endpoint); ‡All patients had their baseline attack rate measured during a run-in period; for rollover patients, the run-in period was at the beginning of the first study the patient was enrolled in.

Median garadacimab exposure in the OLE was 9.5 months (N=161; n=92 rollover; n=69 garadacimab naïve (Table 1)

- Garadacimab exposure in the pivotal Phase 3 study was 6 months (n=36)
- For garadacimab-treated rollover patients from the pivotal Phase 3 study, median exposure across both studies was 13.5 months

Table 2. Garadacimab demonstrated a favorable safety profile in the OLE, similar to the Phase 3 study

AEs	Pivotal Phase 3 trial[1] (N=64) Median exposure 6 months		OLE (N=159)* Median exposure 9.5 months
	Placebo (n=25)	Garadacimab (n=39)	
Patients with ≥1 TEAE, n (%)	15 (60)	25 (64)	119 (75)
Related to treatment†	3 (12)	4 (10)	19 (12)
TEAEs leading to study discontinuation, n (%)	0	0	1 (1)‡
AESIs per protocol[1§] , n (%)	0	0	0
SAEs, n (%)	0	1 (3)¶	3 (2)#

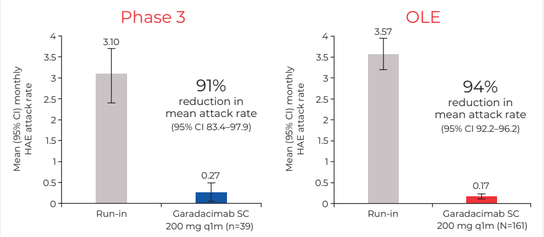
*The two patients with HAE-nC1-INH were not included in this analysis; of the two patients, one (50%) experienced one TEAE: a mild case of COVID-19 deemed unrelated to garadacimab treatment; †As identified by investigator; ‡One garadacimab-related ISR leading to study discontinuation; §AESIs in this study were thromboembolic events, bleeding events and severe hypersensitivity, including anaphylaxis; ¶One severe, serious AE (laryngeal attack) was deemed unrelated to garadacimab treatment; # No garadacimab-related SAE was reported in the OLE.

The most frequently reported TEAEs (≥3% of subjects) by preferred terms were COVID-19 (31.1%), nasopharyngitis (9.3%), injection-site erythema (6.8%), headache (5.6%), upper respiratory tract infection (5.0%), and toothache (3.1%)

Time-normalized number of attacks

- In the OLE, once-monthly garadacimab reduced the mean monthly attack rate vs run-in period by 94% (**Figure 2**)

Figure 2. Once-monthly garadacimab showed a significant and clinically meaningful reduction in the number of HAE attacks per month vs run-in

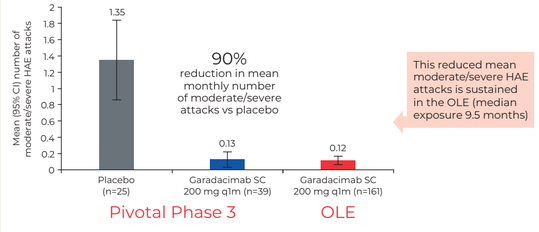


- Median (interquartile range) monthly attack rate in the OLE was **0.0** (0.17) **vs 2.85** (2.45) during run-in
- In the OLE, **98% of patients had a ≥50% reduction in attack rate** vs run-in (**Figure 4**)

Sustained efficacy

- For patients previously treated with garadacimab in the pivotal Phase 3 study, continued treatment sustained the mean monthly attack rate at 0.2 or below

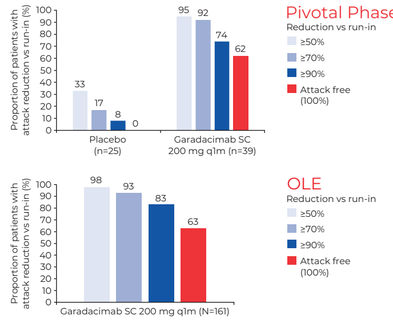
Figure 3. Once-monthly garadacimab reduced moderate/severe HAE attack rate in pivotal Phase 3 study compared with placebo and is sustained in OLE



Attack-free patients

- In the pivotal Phase 3 study, no patients who received placebo were attack free, whereas 62% of patients who received garadacimab were attack free (**Figure 4**)
- **57%** of patients who rolled over to the OLE were attack free and **95%** of attack free garadacimab-treated patients in the pivotal Phase 3 study remained attack free in the OLE (median exposure 13.2 months)
- **63% of patients were attack free in the OLE** (median exposure of 9.5 months)

Figure 4. Attack-free garadacimab-treated patients in the pivotal Phase 3 study and OLE



References

1. Craig T et al. *Lancet* 2023; 401(10382):1079–1090;
2. Craig T et al. *Lancet* 2022; 399(10328):945–955.

Disclosures

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ADA, antidrug antibody; AE, adverse event; AE-QoL, Angioedema Quality of Life Questionnaire; AESI, adverse event of special interest; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; FXII, factor XII; HAE, hereditary angioedema; HAE-C1-INH, HAE with C1 inhibitor deficiency; HAE-nC1-INH, HAE with normal C1-esterase inhibitor; IGART, Investigator's Global Assessment of Response to Therapy; ISR, injection-site reaction; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; q1m, once-monthly; QoL, quality of life; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; 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.