Pharmacometric Analysis Supports Early Onset of Protection With Garadacimab Against Hereditary Angioedema Attacks

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CONCLUSIONS

- **Pharmacokinetic (PK) data and exposure–response (ER) predictions demonstrated that garadacimab reaches steady-state exposures after the subcutaneous (SC) loading dose (2 × 200 mg SC injections) at first administration**
- **Garadacimab maintains steady-state exposures over subsequent once-monthly (q1m) dosing intervals**
- **The loading dose maximizes the likelihood of reaching target therapeutic thresholds, resulting in an early onset of protection against hereditary angioedema (HAE) attacks as early as Week 1 after first administration**

BACKGROUND

- HAE causes recurrent, unpredictable, debilitating, potentially life-threatening attacks of angioedema[1,2]
- Activated factor XII (FXIIa) is the principal initiator of the kallikrein–kinin system, which results in the production of bradykinin, a key mediator of HAE attacks[1-3]
- In Phase 2 and pivotal Phase 3 studies, garadacimab (first-in-class, fully human, anti-FXIIa antibody) demonstrated durable protection against HAE attacks with a favorable safety profile[4,5]
- In a *post hoc* analysis from the pivotal Phase 3 (VANGUARD) study, garadacimab 200 mg SC q1m reduced the mean monthly HAE attack rate as early as Week 1 after the first administration versus placebo[6]

0.11 **Mean HAE attack rate at Week 1** with garadacimab vs 1.81 with placebo[6]

96% **Reduction in mean HAE attack rate from run-in at Week 1** with garadacimab vs 26.1% with placebo[6]

- PK analysis in a subset of garadacimab-naïve patients (n=15) from the Phase 3 OLE study demonstrated that garadacimab exposure exceeded target therapeutic threshold from Week 1 after first administration[7]

OBJECTIVES OF THE PHARMACOMETRIC ANALYSES

- To assess the relationship between the PK of garadacimab 200 mg SC q1m dosing regimen and HAE attack rate
- To characterize the PK of garadacimab after the first administration as an SC loading dose (2 × 200 mg SC injections) and the impact of the loading dose on exposure

METHODS: PK AND ER MODEL

Characterization of the observed PK of garadacimab after the SC loading dose

- Analyses based on data from the Phase 3 open-label extension (OLE) study, including a representative group of patients (n=15) with available samples taken pre-dose and at Day 7, 14, 21, and 30

Population ER model

- A repeated-time-to-event ER model relating longitudinal garadacimab concentration with HAE attack rate was built with data across three clinical studies: Phase 2, pivotal Phase 3, and Phase 3 OLE
- Simulations (n=1000) were used to infer efficacy (predicted HAE attack rate, relative risk of HAE attacks) of the garadacimab dosing regimen: SC loading dose (2 × 200 mg SC injections) followed by 200 mg q1m

Population ER model: Pooled dataset from three clinical studies using data from 177 unique patients who received garadacimab or placebo

Adults with HAE (aged ≥18 years)

Phase 2 study (N=44)[4]

IV loading dose† and 75, 200, or 600 mg SC q1m

Adults and adolescents with HAE (aged ≥12 years)

Pivotal Phase 3 study (N=64)[5]

2 × 200 mg SC injections (SC loading dose) and 200 mg SC q1m

Phase 3 OLE study (N=161)[8]*

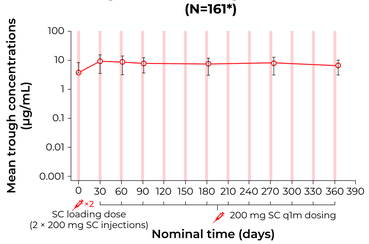
2 × 200 mg SC injections (SC loading dose) and 200 mg SC q1m

*Data cut-off February 13, 2023; †IV loading doses of placebo or garadacimab 40, 100, or 300 mg, followed by placebo or garadacimab 75, 200, or 600 mg SC, respectively.
ER, exposure–response; HAE, hereditary angioedema; IV, intravenous; OLE, open-label extension; q1m, once monthly; SC, subcutaneous.

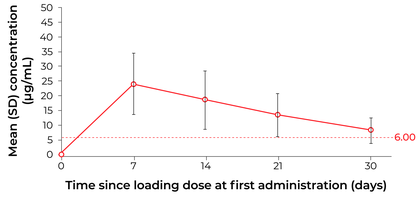
RESULTS

1. PK profile after the SC loading dose from the Phase 3 OLE study: Garadacimab reached steady-state exposures after the SC loading dose and remained at steady state between subsequent q1m dosing intervals

Mean garadacimab trough concentrations (N=161*)



Mean (SD) garadacimab concentration after the SC loading dose (n=15, garadacimab-naïve)[7]

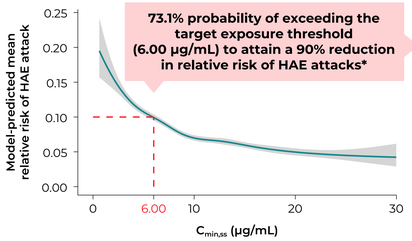


Observed PK parameter after the SC loading dose (n=15, garadacimab-naïve)	
C_{max} (µg/mL): Mean (SD); Median (min, max)	24.51 (10.95); 24.00 (8.17, 44.10)
t_{max} (h): Median (min, max)	167.75 (118.63, 335.17)
$AUC_{0\text{-}30}$ (h·µg/mL): Mean (SD); Median (min, max)	10,684.52 (5064.08); 9311.26 (3953.38, 21,706.02)

*PK analysis set comprised all patients in the safety analysis set with ≥1 measurable concentration of garadacimab. The red bars indicate when the administrations of the loading dose and the q1m injections take place.
$AUC_{0\text{-}30}$, area under the concentration time curve from Day 0 to 30; C_{max}, maximum concentration; max, maximum; min, minimum; OLE, open-label extension; PK, pharmacokinetic; q1m, once monthly; SC, subcutaneous; SD, standard deviation; t_{max}, time to maximum concentration.

2. ER predictions demonstrated increasing efficacy with increasing exposure. Garadacimab exposures exceeded target therapeutic thresholds after the first administration as an SC loading dose

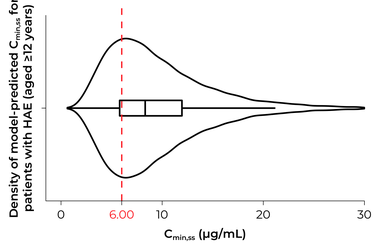
Relative risk of HAE attack by $C_{min,ss}$ with garadacimab 200 mg q1m dosing regimen



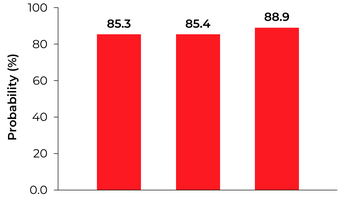
PK exposure thresholds at steady state

Exposure metric	Therapeutic threshold	Probability of exceeding threshold* (%)
$C_{min,ss}$	6.00 µg/mL	73.1
$C_{max,ss}$	14.5 µg/mL	75.4
$AUC_{tau,ss}$	7640 h·µg/mL	73.7

High probabilities of exceeding target therapeutic thresholds to attain 90% reduction in relative risk of HAE attacks



Probability of exceeding target exposure thresholds after the SC loading dose by PK parameter

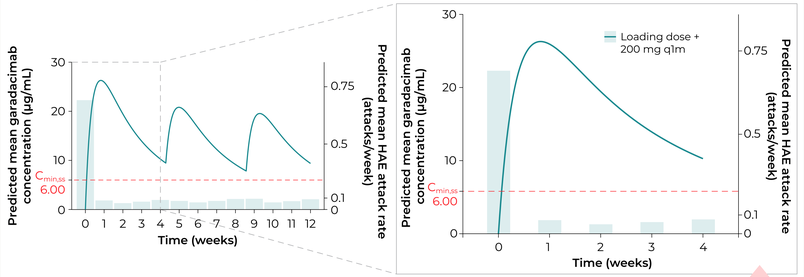


Population ER predictions demonstrated exposures above target therapeutic thresholds after the SC loading dose: 85.3% of patients predicted to attain a 90% reduction in relative risk of HAE attacks

Top panels: model-predicted mean relative risk of HAE attack is shown as the teal line with an approximate 95% CI in grey. Bottom panels: density of predicted $C_{min,ss}$ or $C_{max,ss}$ in which the boxplot indicates the 25th, 50th, and 75th percentiles with whiskers extending to 1.5 × IQR. The dashed red line indicates the exposure threshold corresponding to a ≥90% reduction in relative risk of HAE attack.
*With a 200 mg q1m steady-state dose.
$AUC_{tau,ss}$, area under the concentration–time curve after the loading dose; $AUC_{tau,ssCI}$, area under the concentration–time curve at steady state; CI, confidence interval; $C_{max,1}$, maximum concentration after the loading dose; $C_{max,ssCI}$, maximum concentration at steady state; $C_{min,1}$, minimum concentration after the loading dose; $C_{min,ssCI}$, minimum concentration at steady state; ER, exposure–response; HAE, hereditary angioedema; IQR, interquartile range; PK, pharmacokinetic; q1m, once monthly; SC, subcutaneous.

3. Model-predicted garadacimab concentrations remained above the target therapeutic threshold at steady state

ER-predicted garadacimab concentration and HAE attack rate over time



ER-predicted HAE attack rates declined after the first administration of garadacimab as an SC loading dose (2 × 200 mg SC injections) and remained consistently low

Teal lines and bars represent predicted mean garadacimab concentrations and predicted mean HAE attack rates, respectively. The red dashed lines represent the target therapeutic $C_{min,ss}$.
$C_{min,ss}$, minimum concentration at steady state; ER, exposure–response; HAE, hereditary angioedema; q1m, once monthly; SC, subcutaneous.

References

1. Busse PJ et al. *J Allergy Clin Immunol Pract* 2021;9:132–150; 2. Maurer M et al. *Allergy* 2022;77:1961–1990; 3. Davis AE, 3rd. *Transfus Apher Sci* 2003;29:195–203; 4. Craig TJ et al. *Lancet Haematol* 2024;1:e436–e447; 5. Craig TJ et al. *Lancet* 2023;401:1079–1090; 6. Staubach P et al. *Clinic Exp Allergy* 2024;doi.org/10.1111/cea.14568; 7. Magerl M et al. Abstract 548. Presented at the European Academy of Allergy and Clinical Immunology Congress, May 31–June 3, 2024, Valencia, Spain; 8. Anderson J et al. *Ann Allergy Asthma Immunol* 2023;131:S5.

Disclosures

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