Population pharmacokinetic/pharmacodynamic analysis of garadacimab in patients with hereditary angioedema

P010

Fiona Glassman,[1] Ankur Sharma,[1] Shen Cheng,[2] Curtis Johnston,[2] Bernardo De Miguel Lillo,[3] John-Philip Lawo,[4] Iris Jacobs,[1] Daniel Polhamus,[2] Partha Nandy[1]

[1]CSL Behring, King of Prussia, PA, USA; [2]Metrum Research Group, Tariffville, CT, USA; [3]CSL Behring S.A., Barcelona, Spain; [4]CSL Behring Innovation GmbH, Marburg, Germany.

Conclusions

- Garadacimab pharmacokinetics (PK)/pharmacodynamics (PD) were characterized by a population PK/PD model using pooled data from five clinical studies in healthy adults (aged >17 years) or patients (aged ≥12 years) with hereditary angioedema (HAE)
- PK/PD simulations supported administration of a 400 mg loading dose (two 200 mg injections) followed by 200 mg once monthly (q1m) dose in patients aged ≥12 years, with no need for dose adjustments in population subgroups
- Age, race, use of concomitant or on-demand therapy or HAE, renal function, and immunogenicity did not impact garadacimab PK

BACKGROUND

HAE[1–3]

- Causes recurrent, unpredictable, debilitating, and potentially life-threatening attacks
- HAE attacks are mediated by the uncontrolled production of bradykinin arising from dysregulation of the kallikrein-kinin pathway

Garadacimab[4–6]

- First-in-class, fully human, monoclonal antibody targeting activated factor XII (FXIIa), the principal initiator of the kallikrein–kinin pathway[4]
- Garadacimab has high affinity, potency, and specificity, and is shown to decrease bradykinin production *in vitro*[4]
- In the pivotal Phase 3 (VANGUARD) study, garadacimab 200 mg q1m reduced monthly attack rate vs placebo (87% reduction; P<0.0001), with favorable safety and tolerability profiles[5]

Garadacimab PK/PD[6–7]

- Pivotal Phase 3 (VANGUARD) PK analysis showed that garadacimab concentrations reached a steady state after loading dose and were consistent across the treatment period[6]
- PK and PD correlation in randomized placebo-controlled Phase 1 and 2 studies indicate that FXIIa-mediated kallikrein activity is a biomarker of the pharmacological effect of garadacimab[6,7]

OBJECTIVES

- Evaluate the PK/PD relationship between garadacimab concentration and FXIIa-mediated kallikrein activity
- Evaluate the impact of intrinsic and extrinsic factors in population subgroups to assess the need for dose adjustments

CLINICAL STUDIES, POPULATIONS, AND DOSING REGIMENS

- A population PK model of garadacimab and a population PK/PD model for FXIIa-mediated kallikrein activity were developed using PK/PD observations from five clinical studies

PK/PD data pooled from five clinical studies

Healthy adults (aged >17 years)

- Phase 1 randomized, placebo-controlled, single-ascending dose study (n=48)[7]: 0.1–10 mg/kg IV or 1–10 mg/kg SC[7]
- Phase 1 ethnobridging, single-ascending dose study (n=37)[8,9*]: 3 or 10 mg/kg IV or 200 or 600 mg SC[9]

Adult patients with HAE (aged >17 years)

- Phase 2 study (n=44)[6,10]: IV loading dose† and 75, 200, or 600 mg SC q1m

Adult and adolescent patients with HAE (aged ≥12 years)

- Pivotal Phase 3 study (n=64)[5]: 400 mg SC loading dose‡ 200 mg SC q1m
- Phase 3 OLE (n=161)[11]: 400 mg SC loading dose‡ 200 mg SC q1m

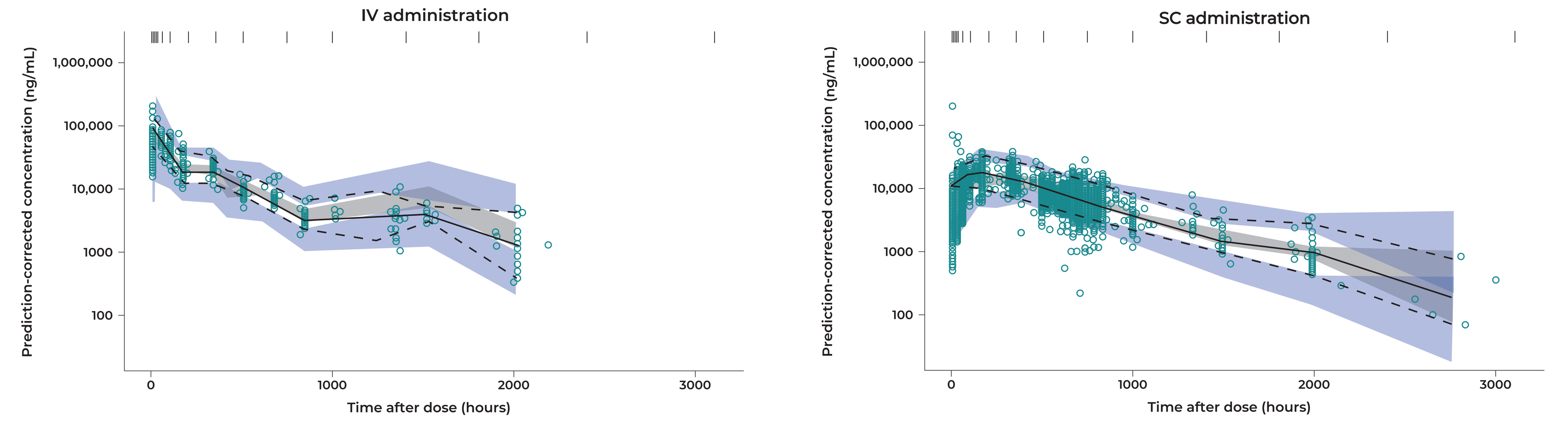
N=262 unique participants with evaluable concentrations of garadacimab

*Caucasian healthy adults were body-weight matched (±15%) 1:1 with Japanese healthy adults; †IV loading doses of placebo or garadacimab 40, 100, or 300 mg followed by placebo or garadacimab 75, 200, or 600 mg SC, respectively; ‡Two 200 mg SC injections.
HAE, hereditary angioedema; IV, intravenous; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; q1m, once monthly; SC, subcutaneous.

RESULTS: POPULATION PK MODEL

Garadacimab PK was well described by a two-compartmental model with first-order absorption and elimination

PK model: Prediction-corrected VPCs over time after dose, stratified by route of administration



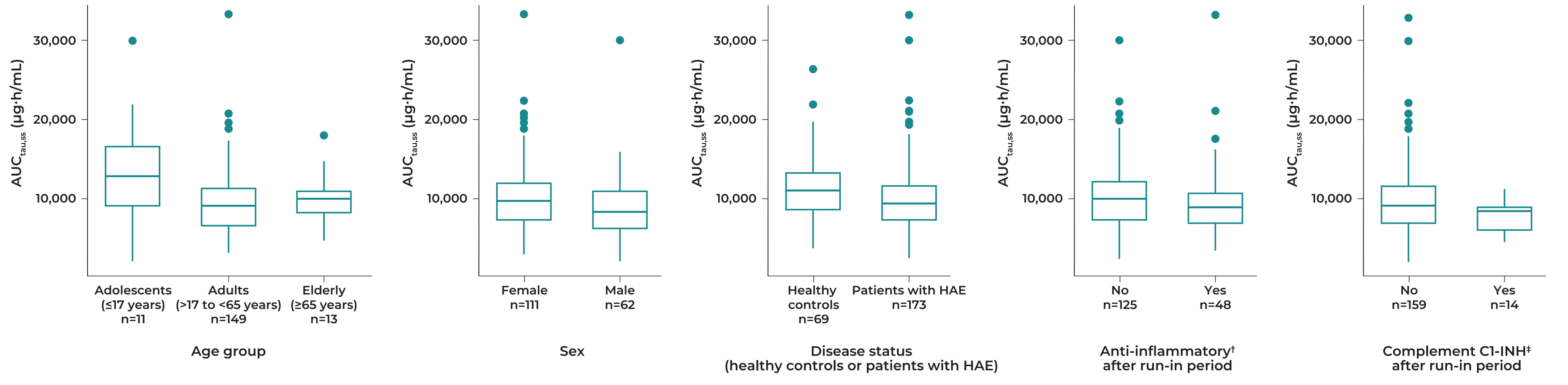
Black lines represent the median (solid), and 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 95% CIs of the corresponding percentiles (i.e. 5th, 50th, and 95th). The points represent observed garadacimab concentrations.
CI, confidence interval; IV, intravenous; PK, pharmacokinetics; SC, subcutaneous; VPC, visual predictive check.

- Model diagnostics: PK model consistent with observed data with no noticeable systematic bias

Covariate analysis

Age, sex, disease status, and use of concomitant or on-demand therapy did not impact garadacimab PK, supporting no need for dose adjustment

Representative box plots* of simulated PK exposure metrics vs covariates of all healthy adults and patients with HAE using EBEs



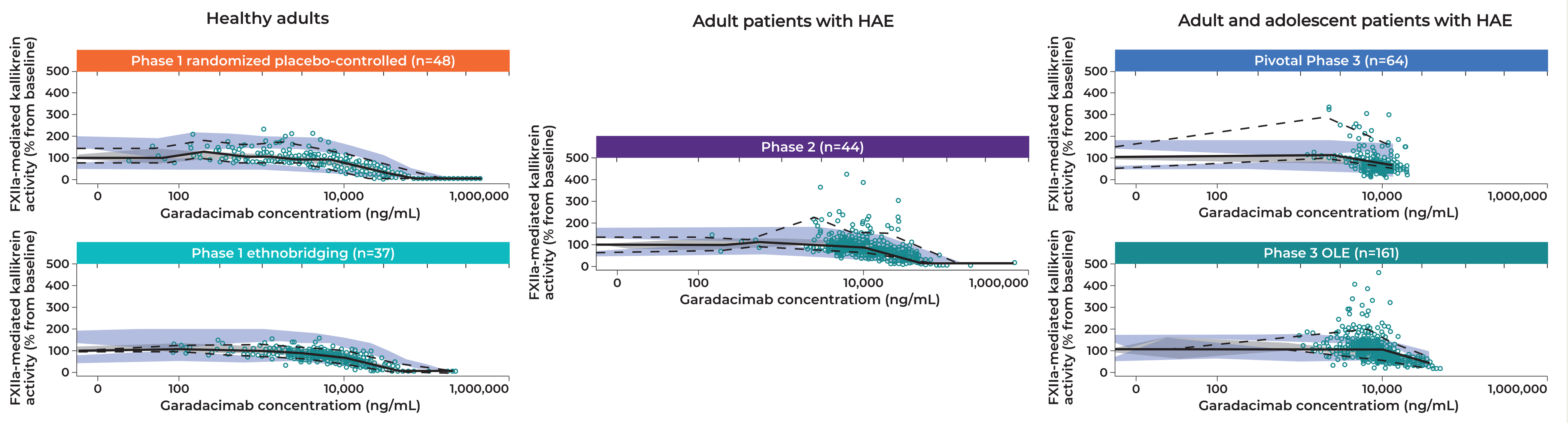
Median values are represented by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to 1.5 x IQR.
*Comparable box plots obtained for other covariates: race, ethnicity, and renal or liver function; †Other concomitant therapies: analgesics, antibacterials, and antihistamines; ‡Other concomitant on-demand therapies: conestat alfa, icatibant acetate, and any other on-demand therapies. $AUC_{tau,ss}$, area under the concentration-time curve during the dosing interval at steady state; C1-INH, C1-esterase inhibitor; EBE, empirical Bayes estimate; HAE, hereditary angioedema; IQR, interquartile range; PK, pharmacokinetics.

- Body weight was shown to be an important covariate with effect on clearance and volume of distribution, but was identified as a non-clinically relevant covariate
  - Exposure-response analysis showed no differences in monthly HAE attack rate across different body weights
- Race, ethnicity, and renal/liver function were identified as non-clinically relevant covariates
- Variability of clearance and volumes of distributions did not impact garadacimab efficacy, supporting the 200 mg q1m dosing with no need for dose adjustment

RESULTS: POPULATION PK/PD MODEL

Inhibition of FXIIa-mediated kallikrein activity was described with a direct-effect, sigmoidal maximum effect model

PD model: VPCs of FXIIa-mediated kallikrein activity vs garadacimab concentration, stratified by study in healthy adults or patients with HAE



Black lines represent the median (solid), and 5th and 95th percentiles (dashed) of the observed data. Blue and grey shaded regions represent the 95% CIs of the corresponding percentiles (i.e. 5th, 50th, and 95th).
Circles represent observed FXIIa-mediated kallikrein activity.
CI, confidence interval; FXIIa, activated factor XII; OLE, open-label extension; PD, pharmacodynamics; VPC, visual predictive check.

- Model diagnostics: PK/PD model was consistent with observed data, with no noticeable systematic bias
- Baseline FXIIa-mediated kallikrein activity was unlikely to show a clinically meaningful effect on a half-maximal effective concentration of garadacimab

Dose justification simulations

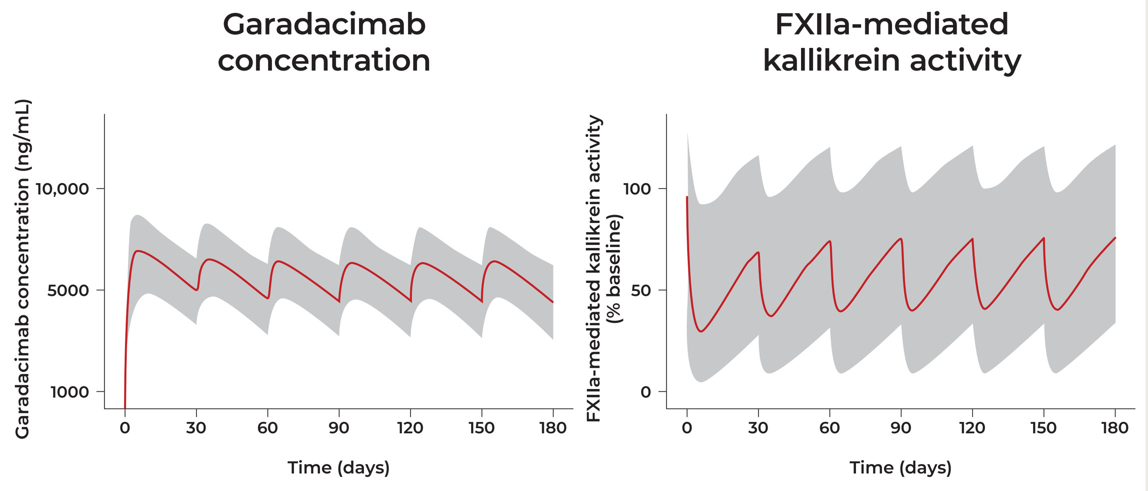
Simulated PK/PD parameters support a dosing regimen of 400 mg SC loading dose (two 200 mg injections) followed by 200 mg q1m, with no need for dose adjustment

Model-predicted, steady-state PK parameters in patients with HAE from the pivotal Phase 3 (VANGUARD) study

PK parameter Mean (SD)	Garadacimab 200 mg q1m (n=39)
CL/F (L/h)	0.0217 (0.00793)
V/F (L)	7.42 (4.20)
$AUC_{tau,ss}$ (µg·h/mL)	10,300 (3380)
$C_{max,ss}$ (µg/mL)	21.2 (6.58)
$C_{min,ss}$ (µg/mL)	9.30 (3.73)
t_{max} (h or **days**)	139 (16.7) or **5.8**
$t_{1/2}$ (h or **days**)	445 (97.4) or **18.5**

$AUC_{tau,ss}$, area under the concentration–time curve for a dosing interval at steady state; CL/F, apparent clearance after subcutaneous dosing; C_{max}, maximum concentration; $C_{max,ss}$, maximum concentration in the dosing interval at steady state; $C_{min,ss}$, minimum concentration in the dosing interval at steady state; HAE, hereditary angioedema; q1m, once monthly; SC, subcutaneous; SD, standard deviation; $t_{1/2}$, elimination half-life; t_{max}, time of the maximum concentration in the dosing interval; V/F, apparent central volume of distribution after SC dosing.

PK/PD simulations (N=20,000) vs over time in adolescent and adult patients with HAE (aged ≥12 years)



Dosing regimen: 400 mg SC loading dose and 200 mg SC q1m doses. Red lines represent the simulated median. Grey shaded areas represent areas between the simulated 5th and 95th percentiles.
FXIIa, activated factor XII; HAE, hereditary angioedema; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous, q1m, once monthly.

- Steady-state PK exposures and PD response were reached after the first garadacimab administration as a 400 mg SC loading dose (two 200 mg injections)

Scan 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. Cao H et al. *J Allergy Clin Immunol* 2018;142:1355–1358; 5. Craig TJ et al. *Lancet* 2023;401:1079–1090; 6. Craig TJ et al. *Lancet* 2022;399:945–955; 7. McKenzie A et al. *Clin Transl Sci* 2022;15:626–637; 8. ClinicalTrials.gov. NCT04580654. Available at: https://clinicaltrials.gov/study/NCT04580654 (accessed February 2024); 9. Glassman F et al. J *All and Clin Immunol* 2023;151:AB1449; 10. ClinicalTrials.gov. NCT03712228. Available at: https://clinicaltrials.gov/study/NCT03712228 (accessed February 2024); 11. ClinicalTrials.gov. NCT04739059. Available at: https://clinicaltrials.gov/study/NCT04739059 (accessed February 2024).

Disclosures

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