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Population Pharmacokinetic/Pharmacodynamic and Exposure–Response Modeling of Garadacimab in Healthy Volunteers and Patients With Hereditary Angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disease that manifests as recurrent, unpredictable, and potentially life-threatening attacks of angioedema. Garadacimab is a first-in-class, fully human, monoclonal antibody targeting activated factor XII (FXIIa) that is under clinical development for the long-term prophylaxis of HAE attacks. We developed population pharmacokinetic (PK)/pharmacodynamic (PD)/exposure–response (ER) models using pooled data across clinical studies to quantify the relationship between garadacimab concentration and the relative risk of HAE attacks and to support the rationale for 200 mg once-monthly dosing. The PK of garadacimab was adequately characterized by a two-compartment model with first-order absorption and elimination. The PD, as analyzed by FXIIa-mediated kallikrein activity, was adequately characterized by a direct inhibitory response model. PK/PD parameters were generally consistent across multiple covariates. ER analysis based on a repeated-time-to-event model showed that administration of garadacimab 200 mg subcutaneously (SC) once monthly results in 75% of patients reaching the target therapeutic threshold (90% reduction in relative risk of attack vs. run-in). Use of a loading dose (two 200 mg SC injections) as the first administration achieved steady-state PK exposures and PD response, with 85% of patients having exposures surpassing the therapeutic threshold. The models support the use of garadacimab 200 mg SC once-monthly dosing in patients aged ≥ 12 years, with no need for dose adjustments, and indicate that, due to the achievement of garadacimab steady-state exposures after the first administration, the use of a loading dose may facilitate the early onset of protection against HAE attacks, as observed in clinical studies.

1 | Introduction

Hereditary angioedema (HAE) is a rare genetic disease that manifests as recurrent, unpredictable, and potentially life-threatening attacks of angioedema [1, 2]. Angioedema attacks most commonly affect the skin, gastrointestinal tract, and upper respiratory tract [1, 2]. HAE can be broadly classified as either HAE due to C1 inhibitor (C1INH) deficiency

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Summary

- What is the current knowledge on the topic?
  - Hereditary angioedema (HAE) is a rare genetic disease manifesting as recurrent, unpredictable, and potentially life-threatening attacks of angioedema.
  - Garadacimab is a first-in-class, fully human, monoclonal antibody targeting factor XIIa currently under evaluation for the long-term prophylaxis (LTP) of HAE attacks.
- What question did this study address?
  - What is the relationship between garadacimab concentration and the relative risk of HAE attacks, and how does this support the dosing rationale for garadacimab as LTP of HAE?
- What does this study add to our knowledge?
  - Population pharmacokinetic/pharmacodynamic models support the use of garadacimab 200 mg SC once-monthly dosing in patients aged ≥ 12 years, with no need for dose adjustments.
  - The use of a loading dose facilitates the achievement of garadacimab steady-state exposures after the first administration and onset of efficacy as early as week 1.
- How might this change clinical pharmacology or translational science?
  - Garadacimab is a promising LTP treatment for HAE that may provide early onset of protection using an SC loading dose followed by a fixed SC once-monthly dosing regimen.

or dysfunction (HAE-C1INH) or HAE due to normal C1INH (HAE-nC1INH) [1–3]. The estimated global prevalence of HAE-C1INH is between 1 in 50,000 and 1 in 100,000, although the true prevalence might be higher because HAE is often misdiagnosed [4–6].

Activated factor XII (FXIIa) is the key initiator of the kallikrein–kinin system, which results in the production of plasma kallikrein and bradykinin [7, 8]. C1INH is the main regulator of the kallikrein–kinin system through the inhibition of FXIIa and plasma kallikrein [8]. Deficiency (HAE-C1INH-Type1) or dysfunction (HAE-C1INH-Type2) of C1INH leads to unregulated activation of these proteases, leading to excess production of bradykinin, which increases vascular permeability, resulting in fluid accumulation in the subcutaneous and submucosal tissues [1, 2, 7]. Because FXIIa is the key initiator of this process, it is an attractive target for HAE therapies [8–10].

Garadacimab is a first-in-class, fully human, immunoglobulin G4 monoclonal antibody targeting FXIIa that is under evaluation for the long-term prophylaxis of HAE attacks in an ongoing phase III open-label extension (OLE) study in adults and adolescents and in an open-label study in pediatric patients aged ≥ 2 years [11–17]. The first-in-human phase I study of garadacimab showed that inhibition of FXII-mediated kallikrein activity and garadacimab plasma concentrations increased in a dose-dependent manner; notably, single-dose intravenous (IV) garadacimab was well tolerated at doses up to 10 mg/kg [11]. In a recently completed phase I ethnobridging study, garadacimab was shown to have comparable pharmacokinetics (PK) and safety profiles in healthy Japanese and White volunteers, together with a good tolerability profile [18].

Safety and efficacy outcomes were carefully considered when selecting the optimal dosing strategy. In a phase II randomized, placebo-controlled study, subcutaneous (SC) administration of garadacimab 75, 200, or 600 mg once monthly (28 ± 2 days) significantly reduced the HAE attack rate compared with placebo (all doses: $p \leq 0.0003$) and demonstrated a favorable safety profile at all dose levels [12]. PK and pharmacodynamic (PD) correlation indicated that FXIIa-mediated kallikrein activity can be used as a biomarker of the pharmacologic effect of garadacimab [12]. *Post hoc* PK/PD analyses also showed that increasing concentrations of garadacimab decreased the relative risk of an HAE attack [12]. Showing the best benefit–risk profile, the 200 mg SC once monthly (30 ± 4 days) dose was selected for further evaluation in the 6-month pivotal phase III (VANGUARD) study and the ongoing phase III open-label extension ([OLE] NCT04739059) studies, during which garadacimab 200 mg SC once monthly demonstrated early and durable efficacy (significant reduction of HAE attack rate vs. placebo in the pivotal phase III study [primary endpoint]; $p < 0.0001$) and a favorable safety profile suitable for long-term prophylaxis (LTP) [13, 17, 19]. PK analysis from the pivotal phase III study indicated that garadacimab concentrations achieved steady-state exposures after the loading dose and remained consistent over the duration of the once monthly administration intervals [13].

Population approaches in drug development are a valuable strategy that provides to provide information regarding PK and PD variability and dose–concentration–effect relationships for registration purposes [20]. Similarly, the use of exposure–response (ER) models can support optimization of dosing regimens and provide confirmatory evidence for efficacy [21]. For this reason, we developed population PK (PopPK), population PK/PD (PopPK/PD), and ER models using pooled data from phase I, II, and III studies to quantify the relationship between the concentration of garadacimab and the relative risk of HAE attacks and to further support the 200 mg SC dosing rationale of garadacimab LTP for HAE, in addition to long-term safety outcomes.

2 | Materials and Methods

2.1 | Clinical Studies and Populations

A PopPK model of garadacimab and a PopPK/PD model for FXIIa-mediated kallikrein activity were developed using data pooled from five studies: two phase I studies in healthy volunteers (ACTRN 12616001438448 and NCT04580654) [11, 22], one phase II study in patients with HAE-C1INH or HAE-nC1INH (including the randomized, placebo-controlled and open-label periods; NCT03712228) [12, 14], and two phase III studies in patients with HAE-C1INH (pivotal phase III [VANGUARD] NCT04656418 and phase III OLE NCT04739059) [13, 15, 17]. Details of these studies, including

the treatment arms, number of participants, dosages, and routes of administration, are summarized in Table S1. For the PopPK model, participants (healthy volunteers or patients with HAE) who received at least one dose of garadacimab prior to one evaluable garadacimab PK sample were included in the analysis. In the PopPK/PD model, participants who received at least one dose of garadacimab or placebo as well as at least one evaluable FXIIa-mediated kallikrein activity measurement were included in the analysis.

An ER model for garadacimab and HAE attacks was developed by combining data from the phase II study and the two phase III studies (pivotal [VANGUARD] and OLE) to build a modeling dataset (Table S1) [12, 13, 15]. The ER analysis population included all patients with HAE (all subtypes) who were either randomized to placebo or included in the PK analysis population (i.e., those who received at least one dose of garadacimab).

2.2 | Testing Methodologies

Blood samples were collected at prespecified time points/dates in each study for the preparation of plasma for analysis (Table S1). For patients receiving garadacimab, the analysis variable for the PopPK model was garadacimab plasma concentration; this was measured using a validated clinical enzyme-linked immunosorbent assay as previously described [11]. The PD analysis variable was FXIIa-mediated kallikrein activity percent of baseline (POB), measured using a chromogenic substrate (S-2302, Chromogenix, Bedford, MA, USA) with an in-house enzymatic assay method, as previously described [11, 12].

2.3 | Data Treatment and Missing Observations

Observations below the limit of quantification in the PK/PD data were excluded from the analyses. Covariates with more than 30% missing values were excluded from the PK/PD and ER analyses. Regression-based imputation methods were used for covariates with 10%–30% missing values. One patient from the pivotal phase III (VANGUARD) study was excluded from the final ER model analysis and model inference because of overlapping comorbidities that may have contributed to the occurrence of attacks or whose symptoms may have been mistaken for symptoms of HAE attacks.

2.4 | Development of PopPK and PopPK/PD Models

The base structural PopPK model was a two-compartment model following IV and SC dosing, with first-order absorption and first-order elimination. The base PopPK/PD model described the inhibition of FXIIa-mediated kallikrein activity by garadacimab with a direct sigmoidal maximum effect (E_{max}) model. Interindividual variability (IIV) was incorporated, assuming a log-normal distribution on clearance (CL) and central volume of distribution (V2) in the PopPK model and on concentration that causes half-maximal effect (EC_{50}), baseline effect (E_0), and Hill coefficient (γ) in the PopPK/PD model. A full block IIV matrix was estimated to appropriately assess the correlation among IIV terms. Typical fixed-allometric scaling was used to incorporate body weight into the base PopPK model.

The final PopPK and PopPK/PD models expanded the base model to include covariate effects. Table S2 shows the explored covariates: primary covariates included baseline age, weight, sex, and ethnicity as well as population (healthy volunteer vs. patient with HAE), HAE subtype, garadacimab formulation, and liver and hepatic function parameters. Additional covariates of interest such as anti-drug antibodies (ADAs) and medication-related covariates were also explored. A full-covariate modeling approach emphasizing parameter estimation was implemented, and the full model was constructed to minimize correlation or collinearity in predictors, as per the global model approach described by Burnham and Anderson [23–25]. Population parameters were estimated, and remaining trends were assessed by graphical inspection of all covariate effects against various residual diagnostics (e.g., Bayes estimates of individual random effects or normalized prediction distribution errors). For the PopPK model, the impact of covariates on drug exposures was evaluated by plotting the model-predicted CL, V2, and concentration–time curve for a dosing interval at steady state ($AUC_{tau,ss}$) vs. categorical and continuous covariates. The magnitudes of covariate effects relative to a reference subject were evaluated via model predictions of CL and $AUC_{tau,ss}$, where the reference subject was a non-Asian healthy subject with a baseline weight of 70 kg, baseline serum creatinine of 0.75 mg/dL, baseline alanine aminotransferase of 25 U/L, and baseline bilirubin of 8 μmol/L. Point estimates of a single covariate effect in the model were visualized by means of forest plots for parameters of interest by varying single covariates individually while keeping all other conditions constant (*ceteris paribus*). Forest plots guided the model predictions to make inferences about covariate effects for PK parameters, such as CL and $AUC_{tau,ss}$, or the PD parameter EC_{50}. Individual CL, V2, and $AUC_{tau,ss}$ were predicted using empirical Bayes estimates (EBEs) from the model, assuming administration of garadacimab 200 mg SC once-monthly dosing. In the PopPK/PD model, the magnitudes of covariate effects were evaluated via model predictions of EC_{50} normalized to a reference subject with a baseline FXIIa-mediated kallikrein activity of 0.134 POB (reference range: 80%–125%).

The performance of the final models was evaluated by goodness-of-fit plots and longitudinal visual predictive checks (VPCs) based on 1000 Monte Carlo simulation replicates of the analysis dataset. Further details of the PopPK and PopPK/PD models and the model codes are provided in Methods S1.

2.5 | Development of the ER Model

In the ER base model, the hazard for HAE attacks consisted of three components: a baseline hazard describing the attack risk during the run-in period, a placebo effect, and an effect of garadacimab using a maximum inhibition (I_{max}) structure to reduce the baseline hazard of HAE attack. The effect of garadacimab was modeled through continuous-time garadacimab concentration using parameters from the PopPK final model. Covariate effects on the HAE attack hazard were modeled using

a modified full-covariate modeling framework. Each covariate was assessed on both the baseline and the garadacimab effect components of the HAE attack hazard. Time-invariant covariates explored for the ER model included baseline age and body weight, sex, ethnicity, HAE subtype, baseline attack rate, and types of long-term prophylaxis and on-demand treatments used in prior studies (Table S2).

For the ER model, the primary analysis variable was the repeated time-to-event HAE attack. Because the patients had multiple attacks over the duration of the studies, the modeling strategy was framed as a repeated time-to-event (RTTE) analysis.

After fitting the full-covariate model, a model reduction step was performed. IIV was considered for the RTTE model through the parameters in the baseline hazard, the placebo effect, and the effect of garadacimab. Further details of the ER model and the model code are provided in Methods S2.

The adequacy of the final model and parameter estimates were investigated using plots of the EBEs against covariate values and VPCs. Simulations from the final HAE attack model were used to describe the effects of covariates and to generate model-based predictions of HAE attack rates.

2.6 | Software

Data manipulation, visualization, and model predictions for the PopPK/PD model were conducted using R version 4.1.1 or

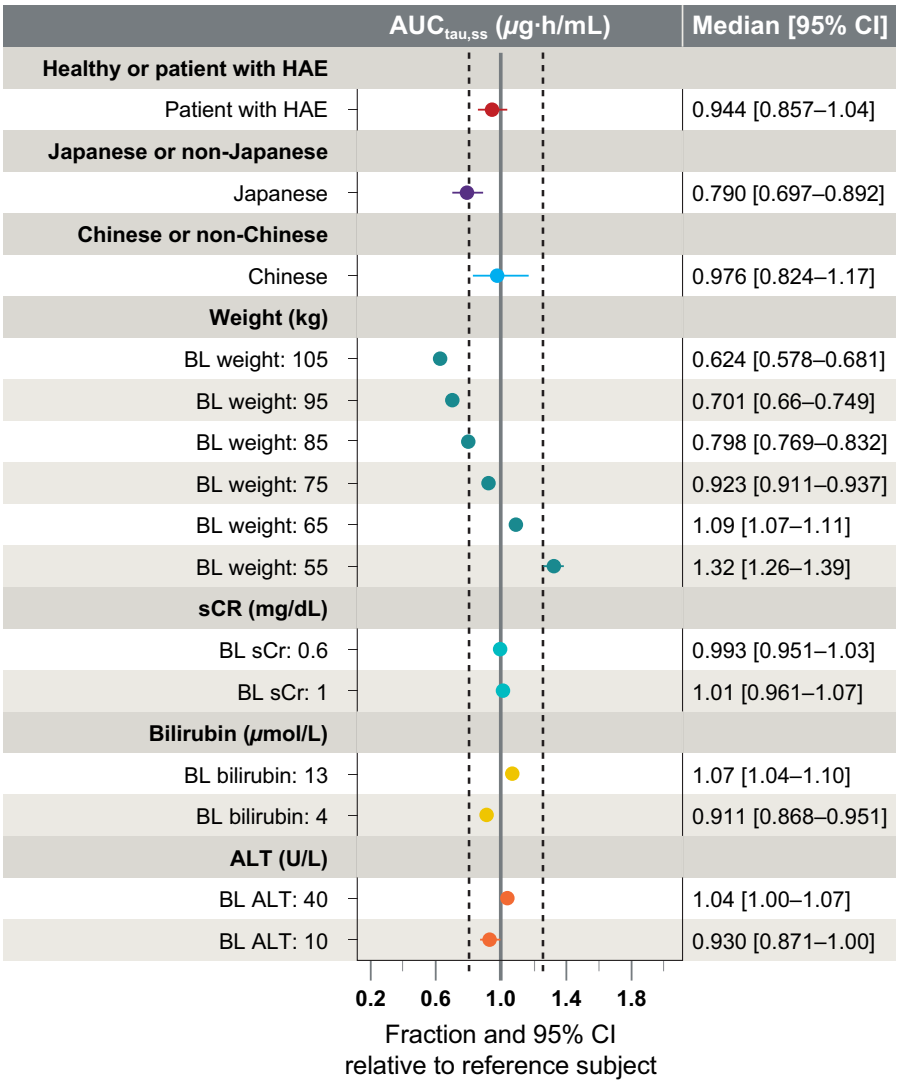

FIGURE 1 | PopPK final model: Univariate forest plot showing covariate effects on garadacimab AUC$_{tau,ss}$ relative to a reference subject. The covariates in the model were visualized by varying single covariates individually while keeping all other conditions constant (*ceteris paribus*). Results are presented relative to a reference subject, i.e., a non-Japanese, non-Chinese, healthy volunteer with BL weight of 70 kg, BL sCR 0.75 mg/dL, BL ALT 25 U/L, and BL bilirubin 8 μmol/L. The circles represent the median and the solid horizontal lines represent the 95% confidence intervals. The reference range of 80%–125% within the two dashed lines was analogous to the region of practical equivalence. For continuous covariates, the upper and lower values used in the predictions were determined based on the 10th and 90th percentiles in the observed dataset. AUC$_{tau,ss}$, area under the concentration–time curve for a dosing interval at steady state; ALT, alanine aminotransferase; BL, baseline; CI, confidence interval; HAE, hereditary angioedema; sCR, serum creatinine.

higher. Analyses for repeated-measures endpoints were conducted via non-linear mixed effects modeling using NONMEM version 7.5 (ICON PLC, Ireland) using the algorithm of first-order conditional estimation with η–ε interaction. For the ER model, data manipulation, visualization, and model predictions were conducted using R version 4.1.3. Analyses for HAE attacks were conducted via non-linear mixed effects modeling using NONMEM version 7.5 (ICON PLC, Ireland).

3 | Results

3.1 | Patient Demographics

The PK analysis dataset for the model development included 242 unique participants (healthy volunteers or patients with HAE) who received garadacimab. Baseline continuous covariates were comparable across studies, and baseline categorical covariates per study are summarized in Table S3. Patient ages ranged from 12 to 73 years (median 41 years), weight ranged from 43.3 to 153 kg (median 79.2 kg), and the number of HAE attacks per week in the run-in period ranged from 0.13 to 3.11 (median 0.61). The studies had comparable ratios of male and female participants, except for the phase I study (ACTRN 12616001438448), which included only healthy male volunteers per protocol [11]. The analysis dataset used for FXIIa-mediated kallikrein activity model estimation in the PopPK/PD model included 242 unique participants who received garadacimab and 20 unique participants who received placebo. For the ER model, the full analysis dataset included 177 unique patients with HAE who received either placebo or garadacimab treatment.

3.2 | PopPK Analysis

In the base model, the dose-normalized garadacimab concentration over time validated the use of a linear PopPK model to characterize garadacimab PK (Figure S1). The observed data were adequately characterized by the final PopPK model, as shown by prediction-corrected VPC over time after dose (Figure S2). Tables S4 and S5 show the PK fixed effects and random effects parameters in the base and final models.

In the covariate analysis, Chinese ethnicity, baseline serum creatinine, baseline bilirubin, and baseline alanine aminotransferase had no clinically meaningful effect on CL or $AUC_{tau,ss}$ (see Figure 1 for $AUC_{tau,ss}$). Although the point estimate for Japanese ethnicity was marginally outside the reference range for both parameters, further analysis using EBE simulations indicated no difference between Japanese and non-Japanese patients with HAE. This suggests that Japanese ethnicity was not a clinically meaningful covariate. In the final model estimates, body weight had the largest effect on CL and $AUC_{tau,ss}$; participants with lower body weights had lower CL estimates and higher $AUC_{tau,ss}$, and participants with higher body weights had higher CL estimates and, thus, lower $AUC_{tau,ss}$.

Descriptive PK metrics at the steady state for the 39 PK-evaluable patients with HAE in the pivotal phase III (VANGUARD) study were summarized using the final model EBEs (Table 1). Expanding the sampling data to include all patients with HAE from the phase II and phase III studies ($n = 173$) showed similar PK metrics (Table 1).

TABLE 1 | Model-predicted PK parameters of garadacimab at steady state in patients with HAE who were treated with garadacimab (loading dose of two 200 mg SC injections followed by 200 mg once monthly).

	Patients with HAE	
PK parameters, mean (SD)	**Pivotal phase III (VANGUARD) [13] ($n = 39$)**	**Phase II, pivotal phase III (VANGUARD), and phase III OLE [12–15, 17] ($n = 173$)**
CL/F (L/h)	0.0217 (0.00793)	0.0243 (0.0122)
V2/F (L)	7.42 (4.20)	8.36 (5.55)
$AUC_{tau,ss}$ (μg·h/mL)	10,300 (3380)	9920 (4470)
$C_{max,ss}$ (μg/mL)	21.2 (6.58)	20.5 (9.66)
$C_{min,ss}$ (μg/mL)	9.30 (3.73)	8.94 (4.64)
t_{max} (h)	139 (16.7)[a]	140 (18.3)
$t_{1/2}$ (h)	445 (97.4)[b]	442 (120)

Note: [a]5.8 days; [b]8.5 days.

Abbreviations: $AUC_{tau,ss}$, area under the concentration–time curve for a dosing interval at steady state; CL/F, apparent clearance after SC dosing; $C_{max,ss}$, maximum concentration in the dosing interval at steady state; $C_{min,ss}$, minimum concentration in the dosing interval at steady state; F, absolute bioavailability; HAE, hereditary angioedema; OLE, open-label extension; PK, pharmacokinetics; SC, subcutaneous; SD, standard deviation; $t_{1/2}$, elimination half-life; t_{max}, time of the maximum concentration in the dosing interval; V2/F, apparent central volume of distribution after dosing.

3.3 | Considerations Across Populations

The model-predicted CL, V2, and $AUC_{tau,ss}$ were generally similar in patients with HAE and healthy volunteers. In patients with HAE, body weight was associated with increased garadacimab CL and V2 and decreased $AUC_{tau,ss}$. Otherwise, in patients with HAE, model-predicted CL, V2, and $AUC_{tau,ss}$ were generally comparable across all the explored covariates. Figure S3 shows the effects of age group, sex, ethnicity, HAE subtype, disease status, clinical study, and ADA status on model-predicted $AUC_{tau,ss}$ using EBE simulations of the final PopPK model. In addition, the impact of renal function (estimated glomerular filtration rate) and baseline aspartate aminotransferase was assessed on PK exposure metrics, including CL, V2, and $AUC_{tau,ss}$, and the effects were generally comparable across these two covariates in patients with HAE (see Figure S3 for $AUC_{tau,ss}$).

Post-baseline use of concomitant medications was explored using the EBE simulations of the PopPK model and found that the use of analgesics, anti-inflammatories, antirheumatics, antihistamines, and antibacterials did not appear to affect the PK of garadacimab (Figure S4). Furthermore, garadacimab PK parameters did not appear to be affected by the concomitant administration of medications that interfere with hemostasis; separate analyses using the EBE simulations were conducted for medications with any direct impact on hemostasis (such

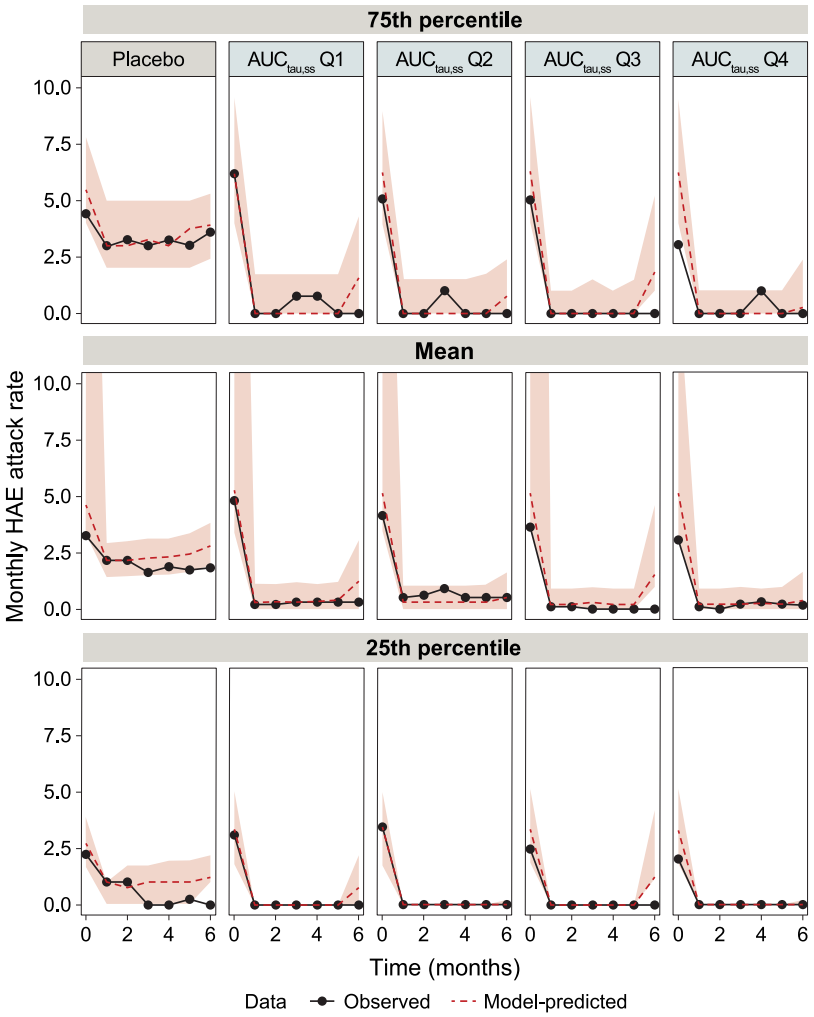

FIGURE 2 | Monthly HAE attack rate vs. time in the pivotal phase III (VANGUARD) study, stratified by quartiles of garadacimab $AUC_{tau,ss}$ at 3 months. Lines represent the mean, 25th or 75th percentiles of the observed (solid) and predicted (dashed) data. The shaded region represents 95% confidence intervals. $AUC_{tau,ss}$, area under the concentration–time curve for a dosing interval at steady state; HAE, hereditary angioedema; Q, quartile.

as factor Xa inhibitors, anticoagulants, and heparins) and for medications with any indirect impact on hemostasis (such as aspirin and non-steroidal anti-inflammatories) (Figure S5). No systemic bias was noted in the conditional weighted residuals or normalized prediction distribution errors vs. these medications.

3.4 | PopPK/PD Analysis

In the final PopPK/PD model, baseline FXIIa-mediated kallikrein activity was incorporated as a covariate on EC_{50} and E_0. The final model provided a reasonable description of the FXIIa-mediated kallikrein activity POB, as judged by visual inspection of model diagnostic plots. The EC_{50} model predictions normalized to the reference subject showed that the point estimates and 95% confidence intervals (CIs) were almost fully contained within the reference range, indicating that baseline FXIIa-mediated kallikrein activity was unlikely to have a clinically meaningful effect on the EC_{50} (Figure S6). Tables S6 and S7 show the PD fixed and random effects parameter estimates for the base and final models.

The VPC of FXIIa-mediated kallikrein activity vs. garadacimab concentration indicated general alignment between model-predicted and observed FXIIa-mediated kallikrein activity percent change at the 5th, 50th, and 95th percentiles across the garadacimab concentration range in this analysis (Figure S7).

3.5 | ER Analysis

The ER base model provided a reasonable description of the data, as judged by visual inspection of VPCs, and all parameters were well estimated with adequate precision. The final ER model accounted for IIV on baseline hazard and on concentration achieving EC_{50} and had a fixed Hill coefficient of 1, a fixed I_{max} value of 1, and a full variance–covariance matrix (Ω) (Table S8). Sampling importance-resampling-based CIs identified baseline body weight as the only covariate that contained the null effect for both ER parameters; as it was correlated with exposure, it was removed as a predictor. Examination of the random effects of the final model showed minimal association with baseline covariates (Table S9). VPCs of the ER relationship showed good alignment across studies and exposure.

Figure 2 shows the monthly HAE attack rate vs. time for the pivotal phase III (VANGUARD) study, stratified by quartiles of $AUC_{tau,ss}$ at 3 months. Overall, the VPCs of the ER relationship and for different covariate stratifications were not suggestive of model deficiencies.

When comparing model-predicted HAE attacks, hereditary angioedema with normal C1 inhibitor and factor XII mutation (HAE-FXII) and hereditary angioedema with normal C1 inhibitor and plasminogen mutation (HAE-PLG) subtypes had slightly lower model-predicted efficacy compared with HAE-C1INH-Type1/2 but with wide prediction intervals. The higher degree of uncertainty associated with predictions of HAE-FXII/HAE-PLG subtypes, as reflected in the prediction intervals, was likely due to the limited number of patients (and thus data) with HAE-FXII/HAE-PLG contributing to the model. Figure 3 shows conditional model predictions of the monthly attack rate at 3 months with fixed covariate levels, and Table S10 shows the reference levels for the covariates at different percentiles.

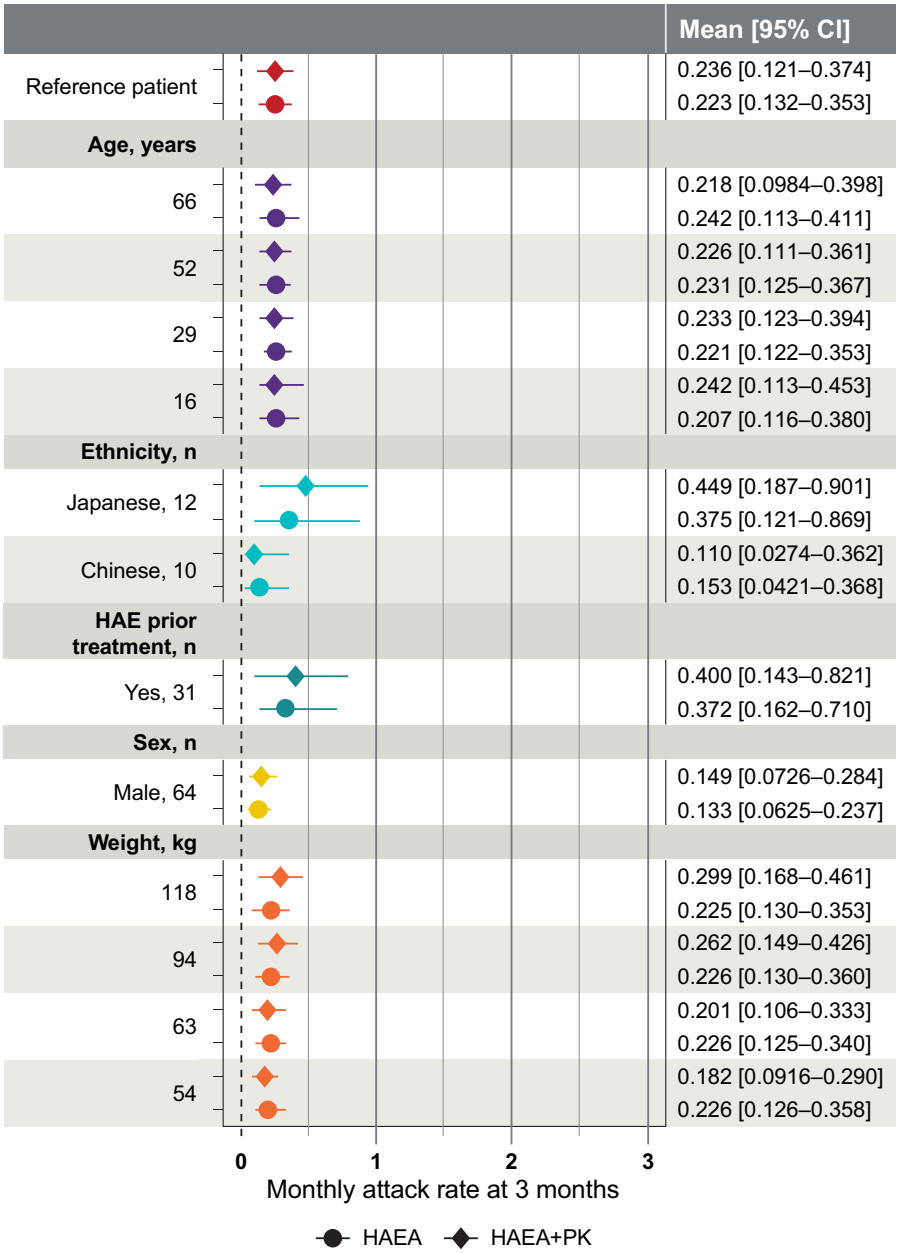

FIGURE 3 | Forest plots: Conditional predictions of monthly attack rates at 3 months with fixed covariate levels. Points and lines indicate the mean and 95% prediction interval, respectively, for the mean monthly attack rate. Results are presented relative to a reference subject (41 years of age, body weight of 79 kg, baseline monthly attack rate of 2.9, female sex, non-Chinese and non-Japanese ethnicity, HAE-C1INH-Type1/2, had not received any prior treatment). Covariates are fixed at the indicated levels in either HAEA, in which case PK assumes the reference subject, or in both the HAEA and PopPK model. PK is simulated at steady state with a loading dose of two 200 mg SC injections followed by 200 mg SC once monthly. Continuous covariate levels (age and weight) correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of the covariate in the analysis population. CI, confidence interval; HAE, hereditary angioedema; HAEA, HAE attack model alone; HAE-C1INH-Type1/2, hereditary angioedema with deficiency or dysfunction of C1 inhibitor; PK, pharmacokinetics; Pop, population; SC, subcutaneous; SD, standard deviation.

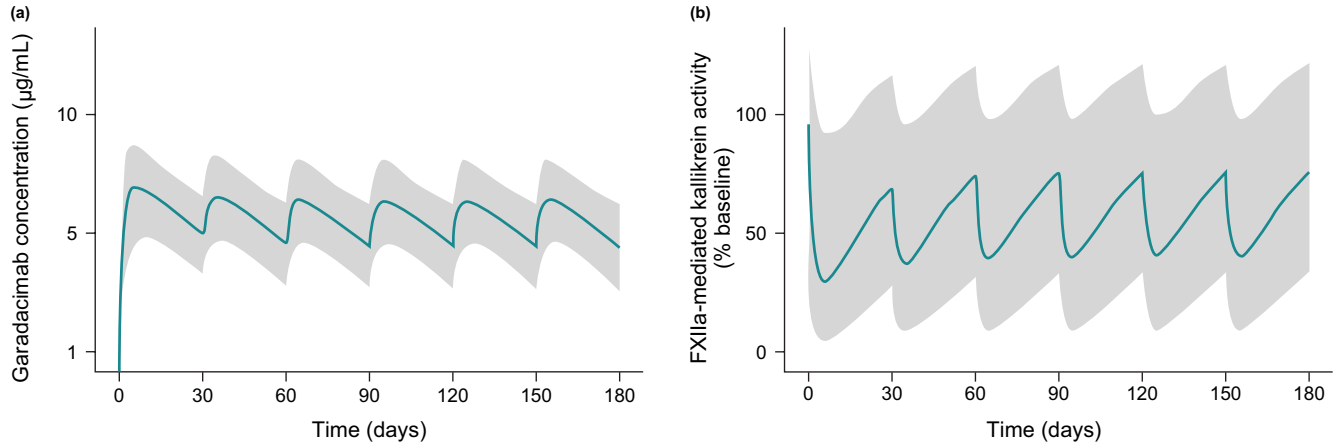

FIGURE 4 | PK/PD predictions: Model-predicted (a) garadacimab concentration and (b) FXIIa-mediated kallikrein activity, vs. time in patients aged ≥12 years. Dosing regimen: Loading dose of two 200 mg SC injections followed by 200 mg SC once monthly. $N = 20{,}000$. The solid lines represent the predicted median, and the shaded areas represent the predicted 5th and 95th percentiles. PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous.

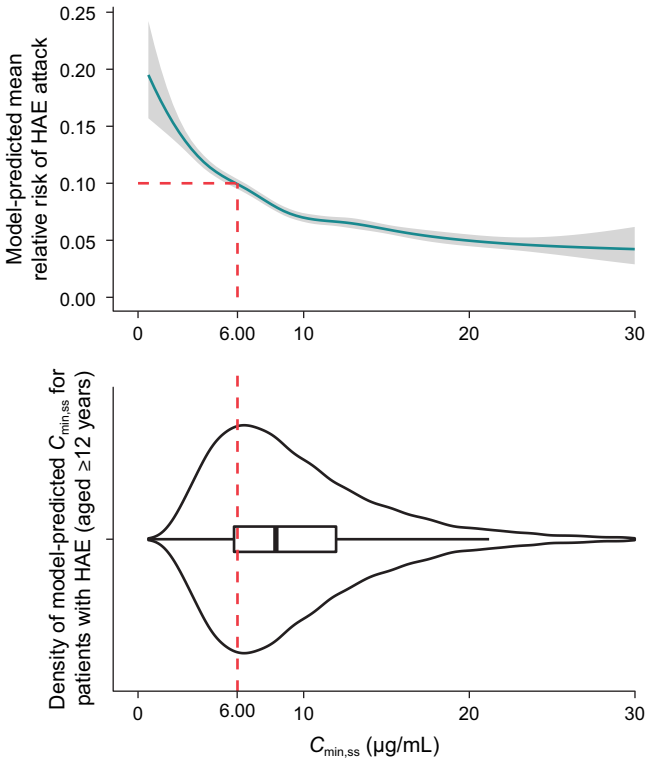

FIGURE 5 | Population predictions: Relative risk of HAE attack in the adolescent and adult populations by $C_{min,ss}$. The top graph shows the predicted mean relative risk of an HAE attack, shown as a solid line with an approximate 95% CI in the shaded areas. The bottom graph shows the density of predicted $C_{min,ss}$ in which the boxplot indicates the 25th, 50th, and 75th percentiles, with whiskers extending to 1.5×IQR. The dashed line indicates the exposure threshold corresponding to a ≥90% reduction in the relative risk of HAE attacks. CI, confidence interval; $C_{min,ss}$, minimum concentration in the dosing interval at steady state; HAE, hereditary angioedema; IQR, interquartile range.

3.6 | Dose Justification

The garadacimab clinical dosing regimen, including a loading dose of two 200 mg SC injections as the first administration followed by 200 mg SC once monthly, was evaluated in adolescent and adult patients with HAE by simulating longitudinal PK and PD profiles. For adolescent patients (aged 12–17 years), covariates were sampled from the National Health and Examination Survey database, whereas for adult patients (aged >17 years), covariates were sampled from the analysis dataset. For each age group, 10,000 samples were simulated without parameter uncertainty with IIV.

PopPK/PD analyses demonstrated the achievement of model-predicted steady-state PK exposures and PD responses after the first administration of garadacimab as a loading dose of two 200 mg SC injections (Figure 4). In the ER model, population predictions were performed to assess model-predicted ER characteristics across several exposure metrics ($AUC_{tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$) for patients receiving the loading dose as the first administration followed by 200 mg SC once monthly. Increasing efficacy was demonstrated with increasing exposure, regardless of the selected exposure metric, population, or efficacy metric. Figure 5 and Figure S8 show the relative risk of HAE attack by $C_{min,ss}$, $AUC_{tau,ss}$, and $C_{max,ss}$. The threshold to attain a 90% reduction in relative risk corresponded to a $C_{min,ss}$ of 6.00 µg/mL, an $AUC_{tau,ss}$ of 7640 µg·h/mL, and a $C_{max,ss}$ of 14.5 µg/mL, and the probability of exceeding those thresholds with a 200 mg once-monthly steady-state dose was 0.731, 0.737, and 0.754 for $C_{min,ss}$, $AUC_{tau,ss}$, and $C_{max,ss}$, respectively. Figure 6 shows the model-predicted mean garadacimab concentrations over time and the model-predicted mean HAE attack rate over time.

Exploratory ER predictions demonstrated that with the dosing regimen of two 200 mg SC injections as a loading dose followed by 200 mg SC once monthly, a majority of patients are predicted to remain above the therapeutic threshold during the dosing interval, with 75% of patients predicted to achieve a ≥90% reduction in attack rate compared with baseline (Table S11). Simulations also indicated that the probability of exceeding the therapeutic threshold was reached after the first garadacimab administration as a loading dose, with approximately 85% of patients having exposures surpassing the target therapeutic threshold (Table S12).

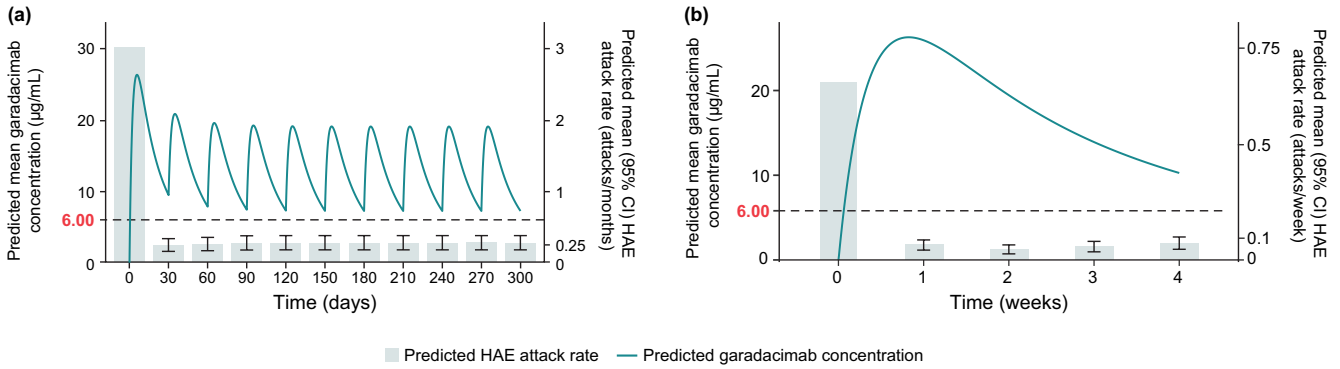

FIGURE 6 | Model-predicted garadacimab plasma concentrations vs. model-predicted HAE attack rate over (a) 300 days (~42 weeks) and (b) 4 weeks. The solid lines represent the predicted mean garadacimab concentration after the administration of the loading dose (two 200 mg SC injections) followed by 200 mg once monthly; bars represent predicted mean HAE weekly attack rates with associated 95% CIs. The dashed line shows the therapeutic threshold for $C_{min,ss}$ at a garadacimab concentration of 6.00 µg/mL. CI, confidence interval; HAE, hereditary angioedema; SC, subcutaneous.

4 | Discussion

Our analyses showed that garadacimab PK was adequately characterized by a two-compartment PopPK model with first-order absorption and elimination. Although *post hoc* model predictions indicated that increases in body weight were associated with increased CL and V2 and decreased $AUC_{tau,ss}$, in the ER analysis, there was no difference in monthly attack rate across a range of body weights. Therefore, this difference is not considered to be clinically relevant, and no dose adjustments are recommended. Furthermore, CL, V2, and $AUC_{tau,ss}$ were generally similar across all other covariates of interest, including healthy volunteers vs. patients with HAE, ADA status, ethnicity, and hepatic and renal function parameters, indicating that no dose adjustments of garadacimab are needed in these populations. The kidneys and liver are generally not significantly involved in the metabolism of monoclonal antibodies because of their large molecular size [26, 27], supporting our finding that hepatic and renal function variations did not affect the PK of garadacimab. We performed population analyses exploring the use of garadacimab with concomitant medications based on screened usage of these medicines prior to or during garadacimab treatment and after treatment cessation. In our analysis, the use of concomitant medications of common use (e.g., analgesics and antihistamines) and prescription medications (e.g., antirheumatics and antibacterials), including those that interfere with hemostasis (e.g., aspirin and factor Xa inhibitors) did not affect garadacimab PK. These results align with the general observation of fewer drug–drug interactions occurring with monoclonal antibodies than with small-molecule drugs, thanks to different catabolism routes and enhanced therapeutic efficacy through targeted therapy [26, 27].

For garadacimab PD, FXIIa-mediated kallikrein activity POB observations were adequately characterized by a direct inhibitory response model. Evaluation of covariate effects explored by means of univariate predictions showed that the effect of baseline FXIIa-mediated kallikrein activity on EC_{50} was generally not clinically meaningful; in fact, estimated changes in EC_{50} across baseline FXIIa-mediated kallikrein activity levels were contained within 80%–125% of the reference subject. This suggests that there is no need for adjustment of the clinical dose for varying baseline FXIIa-mediated kallikrein activity.

A time-varying Poisson process model with a maximum inhibition ER relationship described garadacimab patient response to monthly attacks well. Model population predictions indicate that the 200 mg SC once-monthly dosing regimen results in the majority of patients reaching exposures in the target therapeutic threshold and suggest no need for additional dose adjustment. Furthermore, exploratory analysis demonstrated that the loading dose of two 200 mg SC injections of garadacimab allows the rapid achievement of steady-state PK exposures and PD response following the first administration of garadacimab, thereby contributing to the early onset of efficacy in reducing HAE attacks observed in clinical studies. Given that HAE is a chronic disease, with randomly occurring and potentially life-threatening attacks, early onset of protection against HAE attacks is desirable for patients [19]. Therefore, use of a loading dose to maximize the likelihood of reaching the target therapeutic threshold could be an important tool to increase the number of patients meeting international guideline treatment goals of total control of the disease and "normalization" of patients' lives [2].

Strengths of our analysis include the quantitative evaluation and characterization of the PK of garadacimab, the evaluation of the need for dose adjustments across a broad range of covariates and the quantification of the relationship between PK and the risk of HAE attack across patient populations. As for limitations, the limited number of patients (and thus data) with HAE-FXII/HAE-PLG enrolled in the garadacimab clinical program may have contributed to the slightly higher uncertainty of the model-predicted efficacy in these HAE subtypes.

In conclusion, garadacimab PK/PD was adequately characterized in this model, and population PK/PD predictions support the use of garadacimab 200 mg SC once-monthly dosing in patients aged ≥ 12 years with no need for dose adjustments in population subgroups. The models suggest that the administration of a loading dose of garadacimab (two 200 mg SC injections) may support the early onset of protection against HAE attacks observed in clinical studies, due to the rapid achievement of garadacimab steady-state exposures after the first administration.

Author Contributions

All authors wrote the manuscript. R.G., S.C., F.G., A.S., B.D.M.-L., M.W., C.J., J.F., D.P., and P.N. designed and performed the research. R.G., S.C., F.G., A.S., B.D.M.-L., M.W., C.J., J.-P.L., I.P., J.F., D.P., and P.N. analyzed the data and contributed to data interpretation.

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Conflicts of Interest

R.G., M.W., C.J., and D.P. are full-time employees of Metrum Research Group and were paid consultants for this work. S.C. and J.F. were full-time employees of Metrum Research Group at the time the study was conducted and were paid consultants for this work. F.G. was a full-time employee of CSL Behring at the time the study was conducted and a shareholder of CSL Limited. A.S., B.D.M.-L., and P.N. are full-time employees of CSL Behring LLC and shareholders of CSL Limited. J.-P.L. and I.P. are full-time employees of CSL Innovation GmbH and shareholders of CSL Limited. As an associate editor for *CPT: Pharmacometrics & Systems Pharmacology*, Jonathan French was not involved in the review or decision process for this paper.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.