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Population Pharmacokinetics and Exposure-Response Analyses to Guide Dosing of Icatibant in Pediatric Patients With Hereditary Angioedema

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Abstract

Elevated bradykinin levels are responsible for the development of clinical symptoms in patients with hereditary angioedema (HAE). Icatibant is a bradykinin type 2 receptor antagonist indicated for the acute treatment of HAE attacks. A population modeling and simulation approach was used to examine sources of variability impacting icatibant pharmacokinetics (PK) and provide guidance on icatibant dosing in pediatric patients with HAE. An exposure-response analysis was performed for the time to onset of symptom relief (TOSR). Data from 141 adults (133 healthy, 8 with HAE) who received subcutaneous icatibant 30 mg and 31 pediatric patients with HAE who received 0.4 mg/kg (capped at 30 mg) were included in the analysis. Icatibant PK was described by a 2-compartment model with linear elimination. Complete absorption of icatibant was expected within 1 hour of dosing. The apparent clearance and central volume of distribution were 15.4 L/h and 20.4 L, respectively. Icatibant PK was mainly dependent on body weight. The mean TOSR was very short (1.38 hours). A flat exposure-response was observed, confirming that the relationship plateaued at the level of exposure observed in pediatric patients. Simulations confirmed that weight band–based dosing regimens (10 mg [12-25 kg], 15 mg [26-40 kg], 20 mg [41-50 kg], 25 mg [51-65 kg], and 30 mg [>65 kg]) resulted in exposure similar to the 0.4-mg/kg dose. This analysis showed that icatibant undergoes rapid absorption, reaches levels required for therapeutic response, and promptly relieves HAE symptoms. A weight band–based dosing regimen is appropriate in pediatric patients with HAE.

Keywords

icatibant, hereditary angioedema, population pharmacokinetics, exposure-response, weight band–based dosing

Hereditary angioedema (HAE) is a rare autosomal-dominant disorder characterized clinically by unpredictable, recurrent, and potentially life-threatening attacks of edema affecting the skin and mucous membranes.[1] The prevalence of HAE is estimated to be ≈1:50 000.[2] It results from deficient or dysfunctional C1 inhibitor, which leads to elevated levels of the vasodilation signaling peptide bradykinin and subsequently increased vascular permeability and contraction of visceral smooth muscle.

Patients with HAE are advised to always have acute treatment on hand in case of an attack.[2] Icatibant is a synthetic decapeptide that is approved for the treatment of attacks of angioedema in adult patients with HAE[3]; it inhibits the bradykinin B2 receptor with high specificity and potency, and its long biological half-life is sufficient to allow systemic administration by subcutaneous injection.[4,5] In adults, a single subcutaneous injection of 30 mg icatibant results in achievement of maximum plasma concentrations within 1 hour of administration[6] and produces a rapid and durable response for relief of symptoms of HAE attacks irrespective of edema location.[7,8] Repeated use of icatibant over time for the treatment of multiple HAE attacks in adults produces a consistent response for each attack, with no diminution of efficacy.[9]

Recently, a phase 3 multicenter, open-label, nonrandomized single-arm study demonstrated the efficacy and safety of icatibant as an acute treatment in children and adolescents with HAE.[10] Here we describe a

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population pharmacokinetic (popPK) analysis of icatibant in adult and pediatric patients with HAE and in healthy adults, which includes an evaluation of the impact of intrinsic and extrinsic factors on icatibant PK to better understand sources of variability following subcutaneous icatibant administration. We also assessed the exposure-response relationship of the time to onset of symptom relief (TOSR) in pediatric patients and performed simulations to guide a weight band–based dosing regimen, which is advantageous in its lower treatment burden compared with body weight–based dosing regimens, particularly in young populations.

Methods

Clinical Studies

The popPK analysis was performed using data collected from 6 clinical studies (Table S1). All studies were approved by ethics review boards and were conducted in accordance with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable local regulatory requirements and laws. All study subjects or their legal representatives provided written informed consent or assent before any study-specific activity was performed.

The analysis included data from healthy adults (studies HGT-FIR-061, HGT-FIR-065, JE049-1102, and JE049-1103) in phase 1 clinical studies designed to assess: (1) the safety and PK of icatibant following single and multiple ascending doses, (2) the bioavailability of icatibant relative to the site of subcutaneous injection (thigh, abdomen, or arm), and (3) the potential effect of icatibant on the QT interval. A phase 2 proof-of-concept study was performed to investigate the efficacy and safety of icatibant in adult patients with HAE (JE049-2101).[11] In addition, a phase 3 open-label, nonrandomized, single-arm study was performed to evaluate the PK, tolerability, and safety of a single subcutaneous dose of icatibant (0.4 mg/kg) in pediatric patients with HAE (HGT-FIR-086).[10] The study enrolled patients aged 2 to 17 years, including 10 prepubertal children (Tanner stage I) and 21 pubertal/postpubertal adolescents (Tanner stage II-V). The primary efficacy end point was TOSR, defined as the earliest time after treatment when $\geq$20% improvement of the composite symptom score (see Method S1 and Method S2) was achieved without the worsening of any single component score. Measurements of HAE symptom scores were reported by the investigator before and after icatibant treatment. Blood samples for PK measurements were collected predose and 0.25, 0.5, 2, 4, and 6 hours after dosing. In adolescent patients, blood samples were also collected 0.75 and 1 hour after dosing. Plasma icatibant concentrations were measured using a validated liquid chromatography with tandem mass spectrometry method as described previously.[6]

PopPK Analysis of Icatibant

Various compartment models were developed to optimally assess the concentration-time profiles of icatibant in the full population. The impact of covariates such as body weight and age were then analyzed to evaluate the PK of icatibant in pediatric patients with HAE. The popPK models for icatibant consisted of the following: (1) a description of the relationships between plasma concentration and time; (2) a variance component characterizing between-subject variability in model parameters; and (3) residual unexplained variability, which was modeled using additive, proportional, or additive and proportional models. The popPK model had the following form:

$$Cp_{ij} = C\left(D_i,\ t_j, \theta_i\right) \cdot \left(1 + \varepsilon_{p,ij}\right) + \varepsilon_{a,ij}$$

$$\theta_i = \left(\theta_{i1}, \ldots, \theta_{ip}\right)$$

where Cp_{ij} is the concentration at the jth collection time t_j for subject i, D_i is the dosing history for subject i, θ_i is the vector of p PK parameters for subject i, and $\varepsilon_{p,ij}$ and $\varepsilon_{a,ij}$ are the proportional and additive random residual error terms, respectively, associated with jth concentration for subject i. The ε_p and ε_a are normally distributed, with mean 0 and variances of ${\sigma_p}^2$ and ${\sigma_a}^2$, respectively. Between-subject variability was modeled using exponential random-effects models with the form:

$$\theta_{in} = \left(\theta_{TV,n} e^{(\eta_{in})}\right)$$

$$\left(\eta_{1,\ \ldots,}\eta_p\right) = MVN\left(0,\ \Omega\right)$$

where θ_{in} is the value of the ith PK parameter of the nth individual, $\theta_{TV,n}$ is the typical value of the nth PK parameter in the population, and η_{in} is the random interindividual deviation from the typical value $\theta_{TV,n}$ for subject i. Interindividual random effects (η_1,…, η_p), also known as ETAs, are multivariate normally distributed effects with mean 0 and estimated variance ${\omega_n}^2$ included in the variance-covariance OMEGA matrix. Residual variability was described by the following model with additive and proportional components:

$$y_{ij} = \hat{y}_{ij} \cdot \left(1 + \varepsilon_{1ij}\right) + \varepsilon_{2ij}$$

where y_{ij} and $\hat{y}_{ij}$ represent the jth observed and predicted concentration, respectively, for the ith individual; and ε_{1ij} and ε_{2ij} are the proportional and additive random residual effects, respectively. Each ε is normally

distributed with mean 0 and variance σ^2. An allometric component accounting for the effect of weight on apparent total clearance (Cl/F) and central volume of distribution (V_c/F) was included in the base PK model with estimated exponents. Model evaluation was based on standard model diagnostics and goodness-of-fit criteria (eg, log-likelihood difference) and conducted by examining pertinent graphical representations of goodness of fit (eg, fitted and observed concentrations vs time, weighted residuals vs time).[12]

In the first step of the covariate analysis, covariates (weight, age, sex, race, occurrence of an HAE attack within 12 hours of dosing) were screened using visual inspection, and the most relevant covariates were formally evaluated within the icatibant popPK model using a full model approach.[13] A multivariate approach using the full model was used to assess the statistical effect of covariates. Continuous covariates were included in the model using the following power functions:

$$\theta_i = \theta_{\text{Typical}} \cdot \left(\frac{Cov_i}{Cov_{reference\ value}} \right)^{\theta_{\text{eff}}}$$

where θ_i is the population value for subjects with covariate equal to Cov_i, $\theta_{Typical}$ is the typical value of the PK parameter for subjects having the covariate equal to the reference value ($Cov_{reference\ value}$), and θ_{eff} is the effect value of the covariate on parameter θ. Categorical covariates with numerical values from 1 to n were tested in the model using the following exponent function:

$$\theta_i = \theta_{\text{Typical}} \cdot \exp\left(\theta_{\text{effi}} \cdot [Cov = i]\right)$$

where $\theta_{Typical}$ is the population value of PK parameters for subjects in the category of reference and exp(θ_{effi}) is the multiplicative effect of category i on parameter θ. Full model parameter estimates and 95% confidence intervals (CIs) were obtained via nonparametric bootstrapping with ≈1000 replicates. A nonsignificant covariate was removed from the model if the 95%CI of the covariate included the null hypothesis, which was defined as 0 for a continuous covariate and 1 for a categorical covariate.

The performance of the final popPK model of icatibant was evaluated using several methods including diagnostic plots and visual predictive checks (VPCs).[14] Prediction-corrected VPCs were performed to allow visual comparison between distributions of simulated icatibant concentrations derived with the final models and those observed in the original data set. In prediction-corrected VPCs, both the observed and the model-predicted values were normalized to population-predicted values at each point after dosing. On the basis of the estimates of the final model, concentration-time profiles of icatibant concentrations were simulated using 1000 replicates. For each time, nonparametric 95%CIs of the 2.5th, 50th, and 97.5th percentiles of predicted-corrected concentrations were computed and compared with the 2.5th, 50th, and 97.5th percentiles of observed-corrected concentrations. These percentiles were plotted versus time after icatibant dosing to visually assess concordance between the model-based simulated data and the observed data.

Concentration-time profiles of icatibant were simulated using the final popPK model and the actual dosing history in the study. The following exposure parameters were derived: area under the curve up to 6 hours ($AUC_{0\text{-}6}$), maximum concentration (C_{max}), time to maximum concentration (t_{max}), half-life associated with the distribution phase ($t_{1/2[\alpha]}$), and terminal elimination half-life ($t_{1/2[\beta]}$). In addition, the model-predicted concentrations at TOSR (C_{TOSR}) and area under the curve up to TOSR ($AUC_{0\text{-}TOSR}$) were derived. AUC parameters were estimated with simulated rich concentration-time profiles using the trapezoidal rule. PK and exposure parameters were summarized with descriptive statistics.

Exploratory Exposure-Response Analysis. Exploratory analyses were performed to assess the relationship between TOSR and exposure parameters of icatibant ($AUC_{0\text{-}6}$, $AUC_{0\text{-}TOSR}$, C_{max}, and C_{TOSR}) in pediatric patients. Kaplan-Meier curves stratified by tertiles of exposure were derived. Kaplan-Meier figures were also derived according to age group and sex.

Simulations to Support Dosing in Pediatric Patients According to Weight Bands. Monte Carlo simulations were performed for weight-based dosing (0.4 mg/kg) and weight band–based dosing (10 mg for 12-25 kg, 15 mg for 26-40 kg, 20 mg for 41-50 kg, 25 mg for 51-65 kg, and 30 mg for >65 kg). A total of 6000 virtual pediatric patients were simulated using a generalized additive modeling approach for location, scale, and shape on age normative data for male and female patients; the data were based on growth charts in the 6- to 11-year and 12- to 17-year age groups,[15,16] as pediatric patients with HAE are expected to have similar bodyweight distributions relative to healthy pediatric subjects. Individual $AUC_{0\text{-}6}$ and C_{max} values were derived according to both weight-based (0.4 mg/kg) and weight band–based dosing.

Software

PopPK modeling was performed using a nonlinear mixed-effects modeling approach with NONMEM 7.3 and PsN 4.2.0. Data-set preparation, exploration, and visualization of the data were performed using R v3.5.1. The results of the VPC were analyzed by R v3.5.1.

Table 1. Demographic Characteristics of the Pharmacokinetic Analysis Population

Characteristic	n = 172
Age, y	
Mean (%CV)	26.6 (38.9)
Median (range)	25.0 (3.42-54.0)
Body weight, kg	
Mean (%CV)	69.2 (22.0)
Median (range)	69.5 (12.3-102)
Age group, y, n (%)	
2-11	12 (7.0)
12-17	19 (11.0)
18-65	141 (82.0)
Sex, n (%)	
Male	101 (58.7)
Female	71 (41.3)
Race, n (%)	
Black or African American	36 (20.9)
White	132 (76.7)
Other	4 (2.3)
Population, n (%)	
Healthy subjects	133 (77.3)
Adult patients with HAE	8 (4.7)
Pediatric patients with HAE	31 (18.0)
HAE attack status in pediatric patients,[a] n (%)	
No HAE attack	10 (32.3)
HAE attack	21 (67.7)

CV, coefficient of variation; HAE, hereditary angioedema.
[a] n = 31. Attack occurred within 12 hours of icatibant dosing.

Results

Subject Demographics and Baseline Characteristics

Baseline characteristics of subjects included in the popPK analysis are summarized in Table 1. The population consisted of a total of 172 subjects, including 31 pediatric and 141 adult subjects. Median (range) age and body weight were 25.0 years (3.42-54.0 years) and 69.5 kg (12.3-102 kg), respectively. A total of 133 healthy adults (77.3%), 8 adult patients with HAE (4.7%), and 31 pediatric patients with HAE (18.0%) were included in the popPK analysis. Icatibant was administered in 10 pediatric patients who received icatibant in the absence of an HAE attack (32.3%) and in 21 pediatric patients who received icatibant for the treatment of an attack (67.7%). Baseline characteristics of subjects in each study are presented in Table S2.

PopPK Modeling of Icatibant

Individual observed concentration-time profiles of icatibant for each study are presented in Figure 1. Overall, peak concentrations of icatibant following subcutaneous dosing of 0.4 mg/kg were slightly lower in pediatric patients relative to adults. A total of 2172 concentrations were included in the popPK analysis data set (Table S3). The base popPK model included 2 compartments with a first-order rate constant of absorption and lag time (t_{lag}) and the effect of body weight on Cl/F and V_c/F. PK parameter estimates of icatibant derived with the base model were robustly estimated, with relative standard error < 10% and acceptable shrinkage (Table S4). The observed and predicted concentrations were close to the identity line, indicating adequate goodness of fit (Figure S1).

Relationships between random effects (ETA) of PK parameters and covariates were explored graphically to assess sources of variability (Figures S2-S7). After taking body weight into account, a residual effect of age on Cl/F was observed. Weak trends were observed between the ETA values of Cl/F and sex and between Cl/F and the occurrence of an HAE attack. A residual trend was observed between the ETA of V_c/F and sex and between V_c/F and the occurrence of an HAE attack. The full popPK model of icatibant included the effect of age, sex, and HAE attack on Cl/F and the effect of race, sex, and HAE attack on V_c/F. The model was evaluated with a bootstrap resampling strategy (Table S5). The effect of HAE attack on V_c/F was not significant and was therefore removed from the final model. The following covariates were statistically significant and were retained in the final popPK model: body weight on all clearance and volume parameters (as per the base model); age, sex, and HAE attack on Cl/F; and sex and race on V_c/F.

Goodness of fit for the final popPK model is presented in Figure 2. Individual predicted and observed concentrations of icatibant were symmetrically distributed around the line of identity, and population-predicted concentrations were adequately characterized. Conditional weighted residuals (CWRESs) of icatibant were homogeneously distributed around 0 as depicted by the locally weighted scatterplot smoothing (LOESS) trend line between CWRES and population-predicted concentrations. The LOESS was very close to 0, suggesting no relevant bias in the predictions of high and low concentrations of icatibant. The appropriateness of the final popPK model was evaluated using prediction-corrected VPCs on plasma concentration-time profiles of icatibant. VPC plots stratified by age group are presented in Figure S8. The observed 5th percentile, median, and 95th percentile of icatibant concentrations were consistent with their corresponding model-predicted values in pediatric and adult subjects.

PopPK parameter estimates of icatibant derived with the final model are presented in Table 2. Systemic absorption of icatibant in the systemic circulation was very rapid (k_a = 3.27 h^{-1}, corresponding to an absorption half-life [$t_{1/2(a)}$] of ~12.7 minutes). Thus, complete absorption would be expected within ≈1 hour of dosing. The Cl/F of icatibant was 15.4 L/h. The Cl/F of icatibant in a typical 40-kg child (aged 2-11 years) and in a 60-kg adolescent (aged 12-17 years) is expected

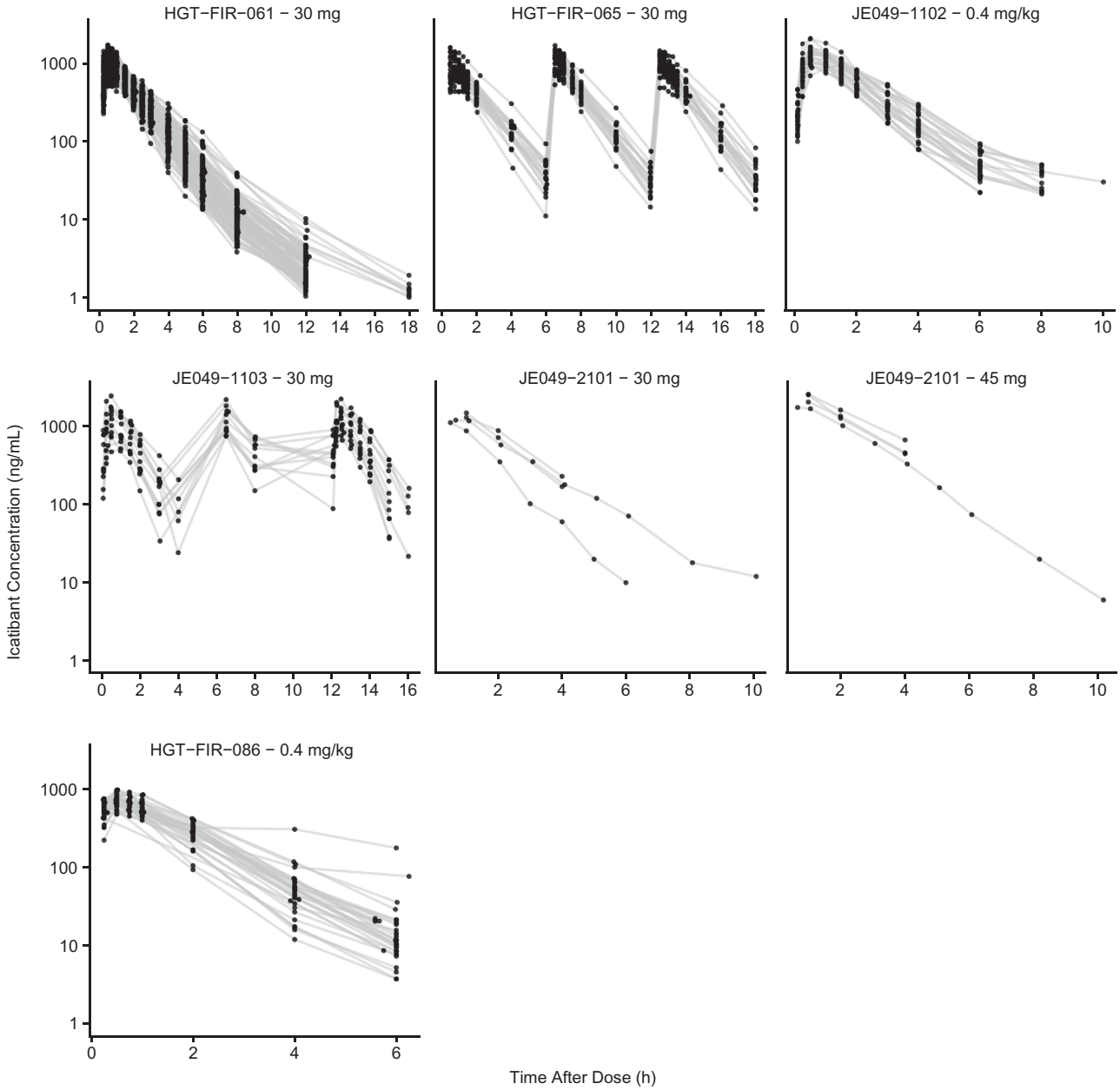

Figure 1. Individual observed concentration-time profiles of icatibant in pediatric and adult subjects by study and by dose. The concentrations are not dose-normalized. The following studies were conducted in healthy adults: HGT-FIR-061 (n = 76; single dose of 30 mg icatibant), HGT-FIR-065 (n = 25; 3 doses of 30 mg icatibant administered every 6 hours), JE049-1102 (n = 24; single ascending doses of 0.05, 0.2, and 0.4 mg/kg icatibant), and JE049-1103 (n = 12; 3 doses of 30 mg icatibant on day 1, single doses on days 8 and 15). Study JE049-2101 (n = 8; single doses of 30 and 45 mg icatibant) was conducted in adult patients with hereditary angioedema (HAE). Study HGT-FIR-086 (n = 31; single dose of 0.4 mg/kg [≤30 mg] icatibant) was conducted in pediatric patients with HAE.

to be 25% and 7% lower, respectively, than in a 70-kg adult. A linear model was used to characterize the effect of age on Cl/F (after taking body weight into account); the slope for the observed residual effect of age was −0.0107; the shallowness of the slope suggests that age had a very minor impact on Cl/F. For example, clearance estimates in subjects aged 10 and 45 years are expected to be 16% faster and 20% slower, respectively, relative to a subject aged 25 years. The interplay of body weight and age on Cl/F and the effect relative to a 70-kg adult are presented in Figure S9. The effect of body weight was captured in the model using an exponential function, and the effect of age was captured in the model using a linear function. The combined effect of weight- and age-matched information on observed Cl/F was also analyzed. Age had a minor effect on Cl/F

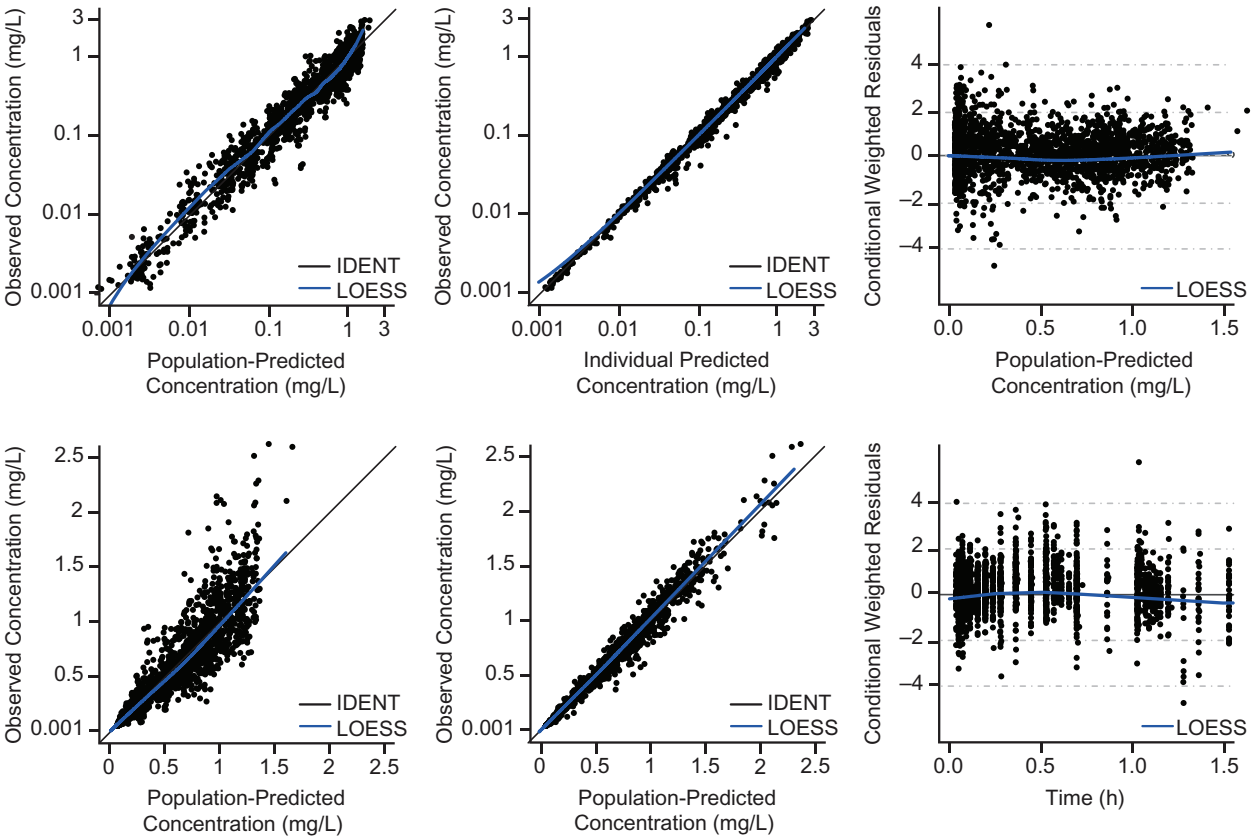

Figure 2. Goodness of fit of the final icatibant population pharmacokinetic model. The upper panel shows the observed concentrations versus the population-predicted concentrations (left) and the individual-predicted concentrations using a log scale. The lower panel shows the same using a linear scale. The dashed gray line in the right-hand panels represents conditional weighted residuals +4 and −4. IDENT, line of identity; LOESS, locally weighted scatterplot smoothing.

after taking body weight into account. An increase in Cl/F was observed in pediatric patients, followed by a plateau in younger adults (aged 18-30 years), and then a decline in Cl/F in adults aged >30 years.

The typical Cl/F of icatibant was about 12% lower in females than in males and was 9% lower in pediatric patients who experienced an acute attack during the study; thus, the effects of sex and HAE attacks on the Cl/F of icatibant were not deemed clinically relevant. The typical V_c/F and V_p/F of icatibant were 20.4 and 1.75 L, respectively, and were dependent on weight and race. The typical V_c/F of icatibant in nonwhite subjects was 11% higher than that observed in white subjects; the difference was not considered clinically relevant. The distribution and terminal elimination half-lives of icatibant for a typical 70-kg adult were 0.89 and 3.2 hours, respectively. PK and exposure parameters of icatibant by age and dose are presented in Table 3. Pediatric patients with HAE treated with the 0.4 mg/kg (≤30 mg) regimen presented mean $AUC_{0\text{-}6}$ and C_{max} parameters that were about 50% and 42% lower, respectively, than those observed in adult patients with HAE treated with a 30-mg dose.

Exploratory Exposure-Response Relationship. The mean TOSR was very short (1.38 hours), and all patients displayed resolution of symptoms within 4 hours (Table S6). The probability of no symptom relief as a function of icatibant $AUC_{0\text{-}6}$ and C_{max} are presented in Figure 3. The median TOSR associated with the first, second, and third tertiles of $AUC_{0\text{-}6}$ and C_{max} were all very close to 1.00 hour, suggesting a very rapid effect for all exposures of icatibant. A flat exposure-response relationship was also observed for $AUC_{0\text{-}TOSR}$, whereas a shallow relationship for C_{TOSR} was observed, whereby the first, second, and third tertiles were associated with a median time to 50% probability of TOSR of 2.00, 1.03, and 1.00 hours, respectively (Figures S10 and S11). No apparent differences in TOSR were observed according to sex or age (Figures S12 and S13).

Simulations to Support Weight Band–Based Dosing in Pediatric Patients With HAE. The distribution of simulated $AUC_{0\text{-}6}$ and C_{max} values versus age for the weight-based regimen (0.4 mg/kg) and a 5 weight band–based regimen (10 mg for 12-25 kg, 15 mg for 26-40 kg, 20 mg for 41-50 kg, 25 mg for 51-65 kg, and 30 mg for >65 kg)

Table 2. Typical Pharmacokinetic Parameters of Icatibant Following Subcutaneous Administration: Final Population Pharmacokinetic Model

Parameter	Typical Value	% RSE	Between-Subject Variability, % (%RSE)	Shrinkage (%)
k_a, h^{-1}	3.27	3.50	35.3 (19.6)	19.1
t_{lag}, h	0.0426	10.6	55.6 (33.6)	34.2
Cl/F, L/h	15.4	2.50	22.7 (12.6)	2.0
	× (weight/70)$^{0.516}$	12.7		
	× 1 + (−0.0107 × [age − 25])	10.3		
	× 0.882 if female	29.2		
	× 0.911 if HAE attack	50.2		
V_c/F, L	20.4	3.10	26.9 (12.9)	5.8
	× (weight/70)$^{0.671}$	9.7		
	× 0.855 if female	26.8		
	× 1.11 if nonwhite	26.2		
Cl_p/F, L/h	0.398	9.40	107.8 (22.3)	19.2
	× (weight/70)$^{0.516}$	12.7		
V_p/F, L	1.75	5.50	53.9 (33.0)	23.5
	× (weight/70)$^{0.671}$	9.7		
Proportional error, %	13.0		NA	NA

Cl/F, apparent total clearance; Cl_p/F, apparent intercompartmental clearance; HAE, hereditary angioedema; k_a, absorption rate constant; NA, not applicable; RSE, relative standard error; t_{lag}, lag time; V_c/F, apparent volume of distribution; V_p/F, apparent peripheral volume of distribution.

Table 3. Icatibant Pharmacokinetic Parameters by Age and Dose

Population	Dose	n	Mean (%CV), Median [Range] C_{max} (ng/mL)	Mean (%CV), Median [Range] AUC_{0-6} (ng·h/mL)
Pediatric patients with HAE				
2-5 years	0.4 mg/kg	2	692 (18.1), 692 [604-780]	900 (24.6), 900 [744-1056]
6-11 years	0.4 mg/kg	10	746 (18.7), 751 [547-962]	1345 (15.5), 1275 [1077-1753]
12-17 years	0.4 mg/kg	19	739 (13.4), 747 [516-916]	1416 (23.3), 1383 [916-2160]
2-17 years	0.4 mg/kg	31	738 (15.1), 747 [516-962]	1360 (22.8), 1288 [744-2160]
Healthy subjects	0.4 mg/kg	24	1240 (25.1), 1258 [836-2120]	2669 (20.9), 2704 [1720-3829]
	30 mg	109	974 (30.1), 915 [524-2115]	2038 (23.8), 1941 [1126-3311]
Adult patients with HAE	30 mg	4	1279 (16.7), 1254 [1056-1551]	2725 (25.3), 2975 [1734-3216]
	45 mg	4	2136 (16.3), 2222 [1680-2421]	5473 (18.6), 5565 [4155-6608]

AUC_{0-6}, area under the concentration-time curve from 0 to 6 hours; C_{max}, maximum concentration; CV, coefficient of variation; HAE, hereditary angioedema.

are presented in Figure 4. Descriptive statistics of AUC_{0-6} and C_{max} for the 5 weight band–based regimen are presented in Table S7. For the 12- to 25-kg group, the median AUC_{0-6} derived with the weight band–based regimen (10 mg) was 39% higher than that derived with the weight-based regimen. Within all other weight groups, the median AUC_{0-6} and C_{max} derived with the weight band–based regimen were within 20% of those derived with the weight-based regimen. Similar results were observed for C_{max} across body-weight groups.

Discussion

Using pooled data from healthy adults, adults with HAE, and pediatric patients with HAE, a popPK profile of icatibant was obtained and used to identify variables impacting icatibant PK characteristics. Study HGT-FIR-086 in pediatric patients showed that subcutaneously administered icatibant undergoes rapid absorption and promptly relieves HAE symptoms.[10] The functions used to describe the effect of body weight and age were important for optimal characterization of the observed Cl/F values across a wide range of ages. A steep increase in Cl/F was observed in pediatric patients, followed by a plateau in younger adults (aged 18-30 years) and then a decline in adults aged >30 years.

Body weight was found to be the most significant covariate explaining the variability in Cl/F; pediatric patients with HAE who received 0.4 mg/kg icatibant (up to 30 mg) presented AUC_{0-6} and C_{max} values that were lower than those observed in adult patients with HAE who received a 30-mg dose, which is the approved dose in adults. As a bradykinin receptor antagonist, icatibant has a modified peptide structure and is poorly distributed into adipose tissue. Its PK properties may be similar to other biologics and thus subject to body weight. Age had a minor effect on Cl/F after taking body weight into account. Icatibant is extensively metabolized by proteolytic enzymes into 2 inactive

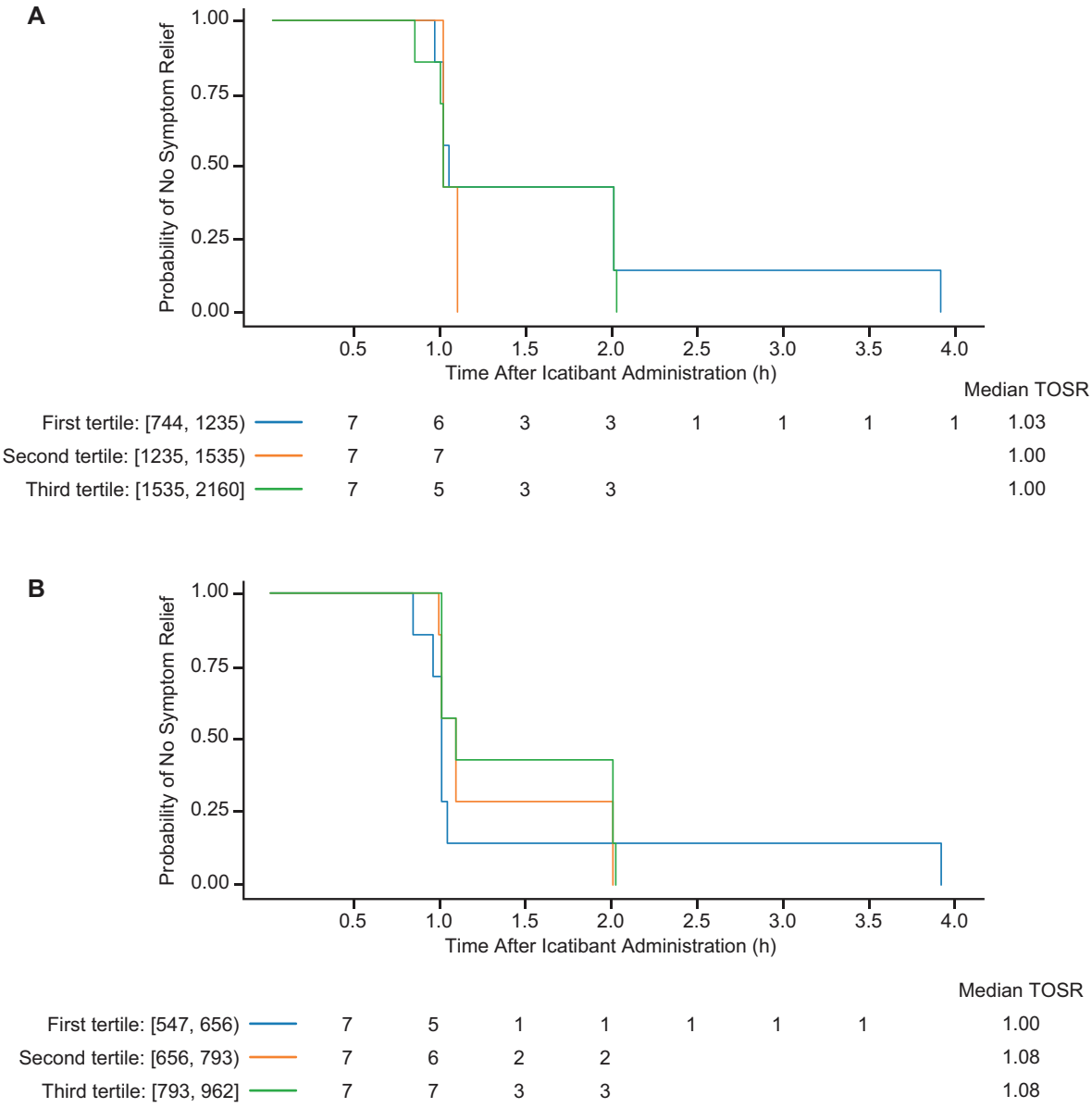

Figure 3. Probability of no symptom relief as a function of area under the concentration-time curve from 0 to 6 hours ($AUC_{0\text{-}6}$; A) and maximum concentration (C_{max}; B) in pediatric patients with hereditary angioedema (HAE). $AUC_{0\text{-}6}$ (ng·h/mL) and C_{max} (ng/mL) values are presented for each tertile with the respective number of patients who did not have symptom relief. At 4 hours all patients had symptom relief; thus, the probability is 0%. TOSR, time to onset of symptom relief.

metabolites with only <10% of the parent drug excreted unchanged in human urine.[17] The 2 metabolites are formed by cleavage of icatibant and are present in human plasma following subcutaneous dosing with molar ratios similar to those of the parent.[6,10] Age-dependent expression of proteolytic enzymes involved in icatibant metabolism may affect the extent of metabolism and subsequently exposure.

Despite the impact of body weight, results from an exposure-response analysis showed that lower exposure in pediatric patients did not affect the response to icatibant treatment, as all patients displayed resolution of symptoms within 4 hours of treatment with icatibant. In addition, simulations performed to guide a 5 weight band–based regimen in pediatric patients showed that $AUC_{0\text{-}6}$ and C_{max} values are expected to be consistent with those observed for the weight-based dosing regimen in this population. Although the 10-mg dose administered to patients in the 12- to 25-kg weight band resulted in slightly higher icatibant exposure relative to a 0.4-mg/kg dose, $AUC_{0\text{-}6}$ was lower than in adult patients with HAE (1731 vs 3216 ng·h/mL) following extrapolation principles between pediatrics and adults. Furthermore, weight band–based dosing

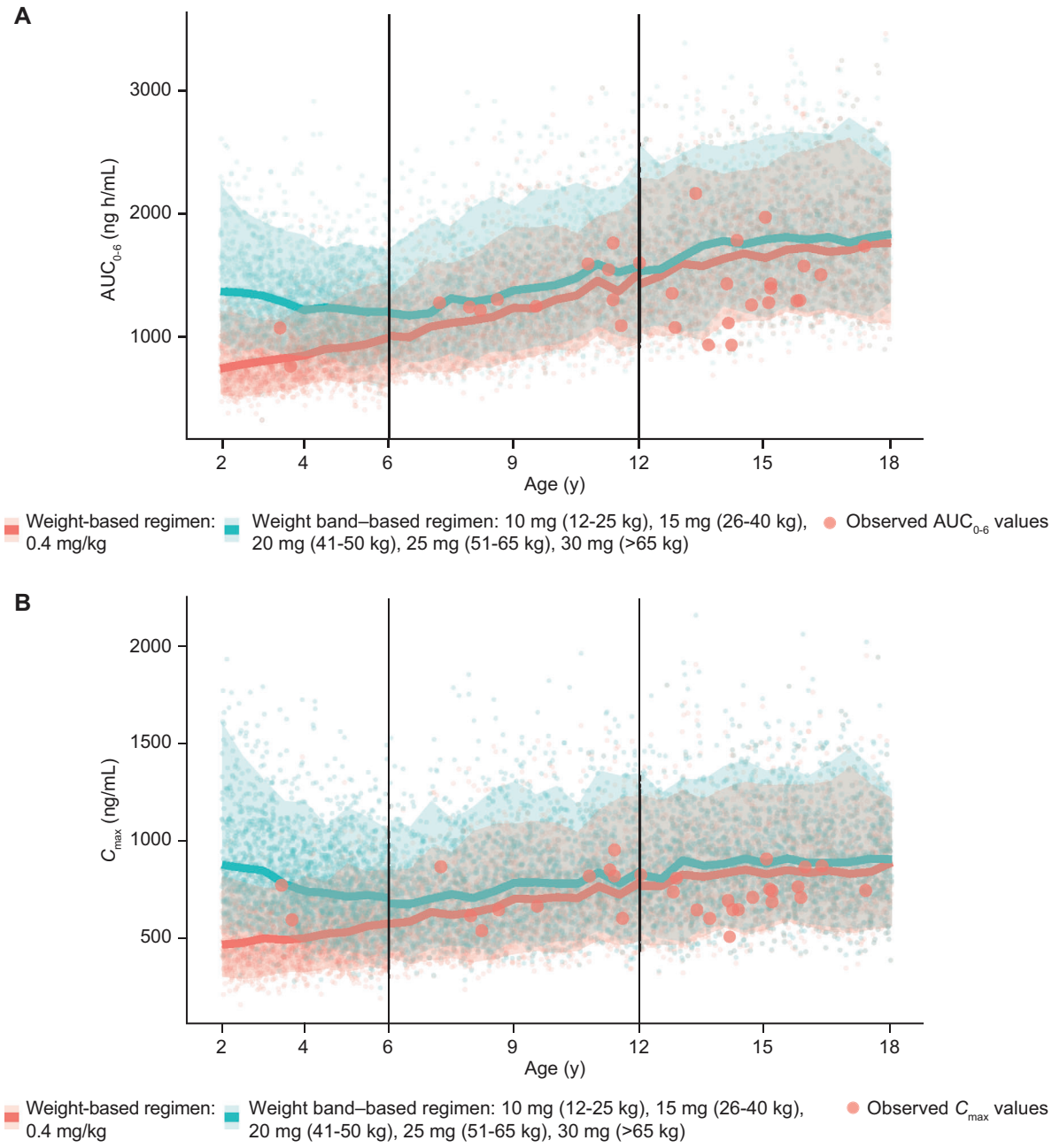

Figure 4. Simulated icatibant area under the concentration-time curve from 0 to 6 hours (AUC_{0-6}; A) and maximum concentration (C_{max}; B) versus age (weight-based and weight band–based regimens). Individual simulated AUC_{0-6} and C_{max} values are shown. Shaded areas indicate the 5th and 95th percentiles.

was deemed acceptable on the basis of the safety profile of icatibant,[18] and the 5 weight band–based regimen was recently approved in Europe.[19] Weight band–based dosing, which involves the use of prefilled syringes for each weight band, is expected to facilitate ease of use in pediatric patients compared with the weight-based dosing regimen. Overall, the proposed 5 weight band–based dosing regimen is expected to result in rapid resolution of HAE symptoms similar to that observed for the 0.4-mg/kg regimen evaluated in the HGT-FIR-086 clinical study in pediatric patients.

Rich PK samples were collected from 21 pediatric patients with HAE who received icatibant within 12 hours following the onset of an HAE attack. Although this supported popPK and exposure-response analyses of icatibant in its intended indication, an assessment of the potential impact of the time of HAE attack onset on PK and exposure-response relationships could not be made. Nevertheless, the mean TOSR in

pediatric patients experiencing an HAE attack was very short (1.38 hours), and all patients displayed resolution of symptoms within 4 hours of icatibant treatment.

Conclusions

In summary, icatibant undergoes rapid absorption after subcutaneous administration, and symptom resolution occurred within 4 hours of dosing in all pediatric patients with HAE. The results of this analysis suggest that body weight has a significant impact on the PK of icatibant. Although not directly evaluated in clinical studies, the proposed 5 weight band–based dosing regimen is expected to result in comparable icatibant exposure and efficacy across pediatric patients with HAE.

Conflicts of Interest

Y. Wang is an employee of Takeda Pharmaceutical Company Limited and holds stocks/options in Takeda. C. Jomphe and J.F. Marier are employees of Certara, which was contracted by Shire (a Takeda Company) to perform data analyses. P. Martin was an employee of Takeda Pharmaceutical Company Limited when these studies and analyses were conducted.

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Data-Sharing Statement

Takeda provides access to the deidentified individual patient data (IPD) for eligible studies to aid qualified researchers in addressing legitimate scientific objectives. Access to this IPD will be provided following approval of a data-sharing request and under the terms of a data-sharing agreement.

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