

# A Model-Based Framework to Inform the Dose Selection and Study Design of Emicizumab for Pediatric Patients With Hemophilia A

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## Abstract

Emicizumab is a bispecific antibody mimicking the cofactor function of activated coagulation factor VIII to prevent bleeds in patients with hemophilia A. The dose selection for the first-in-child phase III study of emicizumab was addressed by pediatric pharmacokinetic prediction using an adult/adolescent population pharmacokinetic model developed in phase I-II studies. The model was modified to incorporate functions describing the age-dependent increase in body weight (BW) with or without clearance maturation to account for the differences in emicizumab pharmacokinetics between adults/adolescents and children. A minimal dose anticipated to achieve in children the same target efficacious exposure as for adults/adolescents was identified when considering BW and clearance maturation. It was the same BW-based dose as for adults/adolescents and was selected for the starting dose for the pediatric study. Whether considering clearance maturation or not in addition to BW led to uncertainty in the pediatric pharmacokinetic prediction and dose selection, which informed implementation of a dose-adapting scheme in the study design. Exposure matching to adults/adolescents was ultimately achieved in children with the starting dose, indicating that consideration of clearance maturation in addition to BW provided adequate pediatric pharmacokinetic predictions for emicizumab. This pharmacokinetic finding in conjunction with exposure-response information served as a basis for the efficacy demonstrated in children, avoiding a time-consuming process for exploring an optimal pediatric dose of emicizumab. This experience indicates that a model-based framework helped optimize the pediatric dose selection and study design, thereby streamlining the development process with extrapolation, of emicizumab for children.

## Keywords

adaptive design, dose selection, emicizumab, extrapolation, hemophilia A, monoclonal antibodies, pediatrics, pharmacokinetics and drug metabolism, pharmacometrics, rare diseases

Hemophilia A is an X-linked, inherited bleeding disorder that is caused by a deficiency of coagulation factor (F) VIII and occurs in  $\approx 1$  in 5000 male births.<sup>1</sup> The standard of care for hemophilia A includes episodic and prophylactic treatment of bleeds with FVIII product.<sup>2</sup> However, due to the short elimination half-life ( $\approx 8$ –19 hours), FVIII prophylaxis requires intravenous infusions several times per week.<sup>2–5</sup> This is burdensome, particularly in children in whom venous access can be difficult.<sup>6,7</sup> Moreover, development of anti-FVIII neutralizing alloantibodies (FVIII inhibitors) occurs in up to  $\approx 30\%$  of patients receiving FVIII product,<sup>2,8</sup> which renders FVIII treatment ineffective. Use of bypassing agents, such as activated prothrombin complex concentrate and recombinant activated FVII, is required unless immune tolerance induction against FVIII is achieved. However, the efficacy of bypassing agents is suboptimal and the treatment is more burdensome.

Emicizumab (HEMLIBRA; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan; and F. Hoffmann-La Roche Ltd., Basel, Switzerland) is a recombinant, humanized, bispecific monoclonal antibody (mAb) that bridges activated FIX and FX, thereby mimicking and

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replacing the cofactor function of missing activated FVIII in patients with hemophilia A.<sup>9,10</sup> Emicizumab can be injected subcutaneously with high bioavailability,<sup>11</sup> has a longer elimination half-life compared to existing treatments ( $\approx$ 4-5 weeks),<sup>11-13</sup> is highly efficacious in preventing bleeds regardless of the presence or absence of FVIII inhibitors,<sup>14-20</sup> and does not induce the development of FVIII inhibitors.<sup>18-20</sup> Taken together, these characteristics address several unmet needs in hemophilia A treatment. Owing to its weak binding affinities to the target antigens,<sup>10</sup> emicizumab exhibits linear pharmacokinetics without significant target-mediated drug disposition (TMDD).<sup>12,14,15</sup>

The phase III development program of emicizumab began with a study in adult/adolescent patients aged  $\geq$ 12 years with FVIII inhibitors (HAVEN 1), in which a subcutaneous loading dose of 3 mg/kg once weekly (QW) for the first 4 weeks followed by a subcutaneous maintenance dose of 1.5 mg/kg QW was tested.<sup>16</sup> Subsequently, a first-in-child study of emicizumab was conducted in pediatric patients aged <18 years (mainly <12 years) with FVIII inhibitors (HAVEN 2) initially to test QW dosing.<sup>17</sup> These 2 phase III studies provided substantial evidences of the efficacy and safety of emicizumab with the same body weight (BW)-based QW dosing regimen in adult/adolescent and pediatric patients with FVIII inhibitors, which supported the regulatory approval of the QW dosing regimen for this patient population of any age in many countries. Thereafter, less frequent but equivalent cumulative subcutaneous maintenance doses of 3 mg/kg every 2 weeks (Q2W) and 6 mg/kg every 4 weeks (Q4W) following the 4-week loading dose of 3 mg/kg QW were tested in adult/adolescent patients aged  $\geq$ 12 years without FVIII inhibitors (HAVEN 3)<sup>18</sup> and in those aged  $\geq$ 12 years with or without FVIII inhibitors (HAVEN 4),<sup>19</sup> respectively. These Q2W and Q4W dosing regimens were tested also in pediatric patients aged  $\geq$ 2 to <12 years with FVIII inhibitors (HAVEN 2)<sup>17</sup> and in those aged <12 years without FVIII inhibitors (HOHOEMI).<sup>20</sup> Consequently, all 3 dosing regimens were confirmed to have similar efficacy and safety profiles through the 5 phase III studies, and currently have been approved for all ages regardless of FVIII inhibitor status in many countries.

One of the key questions at the time of initial HAVEN 2 planning was how to select the QW dosing regimen to be tested in children aged <12 years in the study. In diseases in which the disease characteristics and treatment response are considered similar between adults and children, the development of new drugs for children can be guided by an extrapolation strategy. If a dosing regimen to achieve in children comparable exposure to adults (exposure matching) is identified, efficacy can be extrapolated to children from

adequately powered, randomized, controlled confirmatory studies in adults.<sup>21-26</sup> However, no single standard methodology of pediatric pharmacokinetic prediction from adult/adolescent data had been established for mAbs, which caused significant uncertainty in the dose selection of emicizumab for HAVEN 2. Meanwhile, conducting HAVEN 2 as a large-sized, multiple-cohort, dose-finding study was considered unfeasible, given the anticipated very limited number of children with FVIII inhibitors available for the study enrollment together with the strong demand for rapid access to new drugs in this patient population with high unmet medical needs.

A model-based framework was therefore employed to address these challenges in the first-in-child dose selection and study design of emicizumab. One of the objectives of this research is to describe how the pharmacokinetics of emicizumab in children was predicted a priori using an adult/adolescent population pharmacokinetic (PopPK) model, which was then compared a posteriori with the HAVEN 2 and HOHOEMI study data for validation. The other objective is to describe how the dose selection and study design for HAVEN 2 as well as the overall pediatric development ultimately were informed by the prior pediatric pharmacokinetic prediction. We present herein these contents in a time-series manner to detail the model-informed pediatric development of emicizumab.

## Methods

### Target Efficacious Exposure Selection for Children

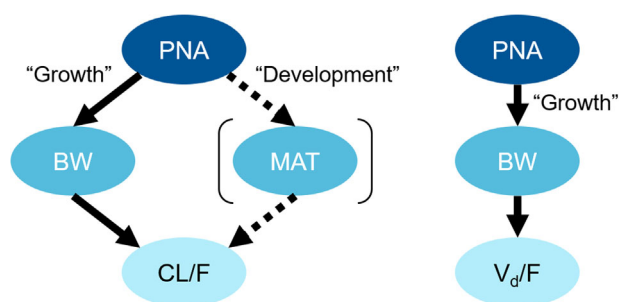
The disease characteristics of hemophilia A and the treatment response of emicizumab were considered similar between adults/adolescents and children. The pathogenic mechanism of hemophilia A is a genetic deficiency of FVIII, due to which bleeds can occur as the major symptom at any age. Most patients are diagnosed in early childhood, and preventing bleeds is the primary aim of the treatment throughout their life.<sup>2,27</sup> In addition, a mature coagulation system including the target antigens of emicizumab (ie, FIX and FX) becomes available from 6 months after birth onward. Although not fully matured on an individual factor basis before that, the activities of pro- and anti-coagulant factors are functionally balanced.<sup>28,29</sup> Therefore, no differences in the pharmacological effect of emicizumab were expected over a very wide range of patients' age.

Given the similar exposure-response relationship of emicizumab anticipated between adults/adolescents and children, as is the case with FVIII,<sup>30,31</sup> the initial HAVEN 2 dose selection aimed to achieve in children aged <12 years the same target efficacious exposure with the same BW-based QW dosing method as for adults/adolescents aged  $\geq$ 12 years in HAVEN 1. The

exposure-response relationship of emicizumab was quantitatively characterized by a repeated time-to-event model based on phase I-I/II study data from adult/adolescent patients, which suggested that plasma emicizumab concentrations of  $\geq 45 \mu\text{g/mL}$  should result in no bleeding events requiring episodic treatment with coagulation factor product to occur for 1 year in at least 50% of patients.<sup>32</sup> In adults/adolescents, the QW dosing regimen was selected to achieve this identified efficacious concentration as median trough level of plasma emicizumab concentration ( $C_{\text{trough}}$ ) at steady state ( $C_{\text{trough,ss}}$ ) for HAVEN 1 and HAVEN 3.<sup>32</sup> The same target efficacious exposure was therefore employed for the QW dose selection for children. Of note, in adults/adolescents, this efficacious concentration also provided the basis for selecting the Q2W and Q4W dosing regimens for HAVEN 3 and HAVEN 4, respectively.<sup>32</sup>

#### Model-Based Pediatric Pharmacokinetic Prediction

A linear 1-compartment with first-order absorption and elimination PopPK model of emicizumab that had been developed using phase I-I/II study data from healthy adults aged  $\geq 20$  years and adult/adolescent patients aged  $\geq 12$  years<sup>32</sup> was used for the pediatric pharmacokinetic prediction for emicizumab. Because BW is a well-known, age-related body size parameter accounting for the differences in pharmacokinetics between adults and children,<sup>33,34</sup> effects of BW had been incorporated into the model with fixed allometric exponents of 0.75 and 1 on BW for the apparent clearance (CL/F) and apparent volume of distribution ( $V_d/F$ ), respectively, without any significant effects of age identified.<sup>32</sup> However, the difference in body size across ages (growth) alone may not fully account for the age-dependent changes in pharmacokinetics, because the maturation of body functions (development) associated with drug disposition may progress over age, particularly in young children (up to 2 years after birth).<sup>33,34</sup> Although the significance of maturation in the pharmacokinetics of mAbs had not been well understood, there was a published case with palivizumab in which a possible maturation of mAb clearance was quantitatively characterized as a function of age, separately from the effect of BW by fixing the allometric exponent to 0.75 for the clearance.<sup>35</sup> In the course of model development of the adult/adolescent PopPK model of emicizumab, the allometric exponent for the CL/F was fixed to 0.75, a conventional value for clearance.<sup>36</sup> The clearance maturation function for palivizumab was developed on top of the same fixed allometric exponent of 0.75. This consistency of the exponent enabled combination of the clearance maturation function for palivizumab with the CL/F equation of emicizumab for the pediatric pharmacokinetic prediction. Therefore, to take into ac-



**Figure 1.** Schematic model of the assumed effects of age on the pharmacokinetics of emicizumab. Body weight (BW) with or without clearance maturation (MAT) were considered as the factors accounting for the age-dependent changes in emicizumab pharmacokinetics. Exact postnatal age (PNA) was used as a primary predictor of BW and clearance MAT to predict the apparent clearance (CL/F) and apparent volume of distribution ( $V_d/F$ ) of emicizumab in children.

count the uncertainty in the pediatric pharmacokinetic prediction for emicizumab, 2 hypothetical approaches were applied: one assumed that BW is the only age-related factor affecting emicizumab pharmacokinetics, and the other considered the age-dependent clearance maturation in addition to the BW-mediated effects of age (Figure 1).

The adult/adolescent PopPK model was modified to incorporate functions describing the age-dependent increase in BW and, when considered, clearance maturation to predict the CL/F and  $V_d/F$  in children. No age-related modifications were considered for the absorption half-life due to lack of available published information. Given the linear pharmacokinetics without significant TMDD for emicizumab, no age-dependent changes in TMDD were considered. The modified equations of CL/F and  $V_d/F$  were as follows:

$$\text{CL}/F_{i,t} = \theta_{\text{CL}/F} \times \left( \frac{\text{BW}_{i,t}}{70} \right)^{0.75} \times e^{\theta_{\text{PAT,CL}/F}} \times \left( 1 - \beta \times e^{-\text{PNA}_{i,t} \times \frac{\ln 2}{T_{\text{CL}}}} \right) \times e^{\eta_{\text{CL}/F,i}} \quad (1)$$

$$V_d/F_{i,t} = \theta_{V_d/F} \times \left( \frac{\text{BW}_{i,t}}{70} \right)^1 \times e^{\theta_{\text{PAT},V_d/F}} \times e^{\eta_{V_d/F,i}} \quad (2)$$

where  $\text{CL}/F_{i,t}$  and  $V_d/F_{i,t}$ , the CL/F and  $V_d/F$  at time  $t$  for patient  $i$ , respectively;  $\theta_{\text{CL}/F}$  and  $\theta_{V_d/F}$ , the typical CL/F and  $V_d/F$ , respectively (standardized for a healthy adult weighing 70 kg and not having anti-emicizumab antibodies with neutralizing potential);  $\text{BW}_{i,t}$ , the BW at time  $t$  for patient  $i$ ;  $\theta_{\text{PAT,CL}/F}$  and  $\theta_{\text{PAT},V_d/F}$ , the effects of patient on CL/F and  $V_d/F$ , respectively;  $\beta$ , the extent of immaturity of clearance at birth;  $\text{PNA}_{i,t}$ , the exact postnatal age (PNA) at time  $t$  for patient  $i$ ;  $T_{\text{CL}}$ , the maturation half-life of clearance;  $\eta_{\text{CL}/F,i}$  and  $\eta_{V_d/F,i}$ , the assigned interindividual variability of CL/F and

$V_d/F$  for patient  $i$ , respectively. All model parameter values were set as previously reported,<sup>32,35</sup> except for  $\beta$  being set to 0 when clearance maturation was not considered. Individual male BWs were derived as a function of PNA using a literature model.<sup>37</sup> PNA was used as a primary predictor of BW and clearance maturation, instead of originally used postmenstrual age (the sum of PNA and gestational age), assuming that gestational age was 40 weeks for all patients. These enabled adequate consideration of the age-mediated correlation between BW and clearance maturation in the simulations.

For the initial HAVEN 2 dose selection, prior predictions of  $C_{\text{trough,ss}}$  in children aged <12 years for potential QW maintenance doses needed to achieve the target efficacious exposure were derived as a function of PNA. Steady state was defined as 24 weeks after the start of emicizumab prophylaxis based on a previous observation in the absence of loading dose.<sup>15</sup> Growth and development in children while receiving emicizumab prophylaxis were taken into account to affect the  $CL/F$  and  $V_d/F$  in a real-time manner in the simulations. Additional descriptions are found in Methods S1 and S2. All simulations were performed using NONMEM version 7.2.0 (ICON Development Solutions, Ellicott City, Maryland).

#### Posterior Investigations Comparing Predicted Pediatric, Observed Pediatric, and Observed Adult/Adolescent Exposures

Data used for the posterior investigations were obtained in clinical studies that were conducted in accordance with relevant ethical standards as previously reported.<sup>16–20</sup>

A total of 405 patients (307 adults/adolescents aged  $\geq 12$  years and 98 children aged <12 years) received either of the 3 dosing regimens and had at least 1 postdose measurement of plasma emicizumab concentration in the 5 phase III studies. Three of the patients (1 adult and 2 children) who had anti-emicizumab antibodies with neutralizing potential<sup>38</sup> were excluded from the posterior investigations because their data interfered with the rigorous pharmacokinetic data comparisons. The data set for the posterior investigations therefore consisted of 402 patients (306 adults/adolescents and 96 children; Table 1). The observed  $C_{\text{trough}}$  until 24 weeks after the start of emicizumab prophylaxis, which is line with the definition of steady state applied in the simulations, together with the inpatient means of the observed  $C_{\text{trough}}$  after the first 24 weeks of treatment were used.  $C_{\text{trough}}$  for all 3 dosing regimens was confirmed to reach steady state by 24 weeks after the start of emicizumab prophylaxis in the individual studies.<sup>16–20</sup> Data after dose up-titration, dosing deviation, or treatment discontinuation were excluded.

Plasma emicizumab concentrations were measured by a previously described method.<sup>13</sup>

As a premise for the posterior investigations, correspondence between the literature model-predicted and actual observed relationships of PNA with BW at baseline in children was confirmed (Figure S1).

## Results

### Prior Pediatric Pharmacokinetic Prediction for QW Dose Selection

For the maintenance dose of 1.5 mg/kg that had been selected for adults/adolescents in HAVEN 1, when considering BW only, median  $C_{\text{trough,ss}}$  were predicted to be lower as age is younger, with a 45% lower value at 0 vs 12 years of baseline PNA. Consideration of clearance maturation in addition to BW resulted in 60% to 8% higher predicted median  $C_{\text{trough,ss}}$  over baseline PNAs of 0 to 12 years, correspondingly, than those derived considering BW only. When considering BW and clearance maturation, median  $C_{\text{trough,ss}}$  were predicted to be comparable over baseline PNAs of 1 to 12 years, achieving the target efficacious exposure as also anticipated in adults/adolescents,<sup>32</sup> with an 18% lower value at 0 vs 12 years of baseline PNA (Figure 2). These simulations suggested that, when considering BW only, the minimal maintenance doses needed for children to achieve the target efficacious exposure should be  $\geq 2.25$  and  $\geq 3$  mg/kg at  $\geq 1$  and <1 year of baseline PNA, respectively. When considering BW and clearance maturation, maintenance doses of  $\geq 1.5$  and  $\geq 2.25$  mg/kg were expected to sufficiently cover the target efficacious exposure at  $\geq 1$  and <1 year of baseline PNA, respectively (Figure 2).

### First-in-Child Dose Selection and Study Design

Anticipating these opposing age-related effects of BW and clearance maturation in the pharmacokinetics of emicizumab, there was a possibility that comparable exposure is achieved in adults/adolescents and children with a same BW-based dosing regimen. The maintenance dose of 1.5 mg/kg was therefore identified as the minimal dose likely to achieve the target efficacious exposure in children with QW dosing. Starting a first-in-child study with a lowest anticipated optimal dose was considered appropriate from a safety perspective, and testing a same dosing regimen as for an adult/adolescent study in a pediatric study could maximize the likelihood that an identical dosing regimen is ultimately approved for adults/adolescents and children. Consequently, the same BW-based dosing regimen as for HAVEN 1 was selected for the starting dosing regimen to be tested in HAVEN 2 (Figure 3).

Due to the potential need for a higher maintenance dose in children, the initial HAVEN 2 study design implemented the ability for 2 types of dose adaptation:



**Table 1.** Clinical Study Data Set for the Posterior Investigations

Pediatric patients aged <12 years					
Dosing regimen	QW <sup>a</sup>	Q2W <sup>b</sup>		Q4W <sup>c</sup>	
Study	HAVEN 2 <sup>17</sup>	HAVEN 2 <sup>17</sup>	HOHOEMI <sup>20</sup>	HAVEN 2 <sup>17</sup>	HOHOEMI <sup>20</sup>
ClinicalTrials.gov Identifier or JapicCTI-No.	NCT02795767	NCT02795767	JapicCTI-173710	NCT02795767	JapicCTI-173710
Data cutoff timing	30 April 2018	30 April 2018 or 24 weeks after first dose (whichever later)	18 July 2018	30 April 2018 or 24 weeks after first dose (whichever later)	18 July 2018
N	64	10	6	9	7
Emicizumab prophylaxis duration, week, median (range) <sup>d</sup>	57.7 (17.9–92.6)	24.0 (24.0–24.1)	39.9 (37.9–41.4)	24.0 (16.0–24.1)	34.1 (24.1–37.1)
Sex, male/female, no.	64/0		16/0		16/0
Age, year, median (range) <sup>e</sup>	6.63 (1.17–11.97)		8.57 (1.50–10.98)		7.19 (0.33–11.99)
BW, kg, median (range)	20.8 (9.5–63.0)		28.4 (10.9–51.5)		23.3 (6.6–54.8)
FVIII inhibitors, present/absent, no.	64/0		10/6		9/7
Prior prophylaxis, no/yes, no.	12/52		2/14		5/11
Adult/adolescent patients aged ≥12 years					
Dosing regimen	QW <sup>a</sup>	Q2W <sup>b</sup>		Q4W <sup>c</sup>	
Study	HAVEN 1 <sup>16</sup>	HAVEN 2 <sup>17</sup>	HAVEN 3 <sup>18</sup>	HAVEN 3 <sup>18</sup>	HAVEN 4 <sup>19</sup>
ClinicalTrials.gov Identifier or JapicCTI-No.	NCT02622321	NCT02795767	NCT02847637	NCT02847637	NCT03020160
Data cutoff timing	3 April 2018	30 April 2018	9 February 2018	9 February 2018	30 April 2018
N	111	3	99	52	41
Emicizumab prophylaxis duration, week, median (range) <sup>d</sup>	89.1 (7.1–120.3)	57.1 (53.0–91.7)	52.0 (17.3–70.3)	46.9 (7.3–71.3)	44.9 (28.0–48.9)
Sex, male/female, no.		213/0		52/0	41/0
Age, year, median (range) <sup>e</sup>		34 (12–77)		41 (16–65)	39 (14–68)
BW, kg, median (range)		74.8 (28.1–156.3)		74.1 (43.0–121.4)	74.7 (45.9–101.8)
FVIII inhibitors, present/absent, no.		114/99		0/52	5/36
Prior prophylaxis, no/yes, no.		102/111		52/0	11/30

BW, body weight; FVIII, factor VIII; N, number of patients included in the data set; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

<sup>a</sup> Patients received a subcutaneous loading dose of 3 mg/kg QW for first 4 weeks followed by a subcutaneous maintenance dose of 1.5 mg/kg QW.

<sup>b</sup> Patients received a subcutaneous loading dose of 3 mg/kg QW for first 4 weeks followed by a subcutaneous maintenance dose of 3 mg/kg Q2W.

<sup>c</sup> Patients received a subcutaneous loading dose of 3 mg/kg QW for first 4 weeks followed by a subcutaneous maintenance dose of 6 mg/kg Q4W.

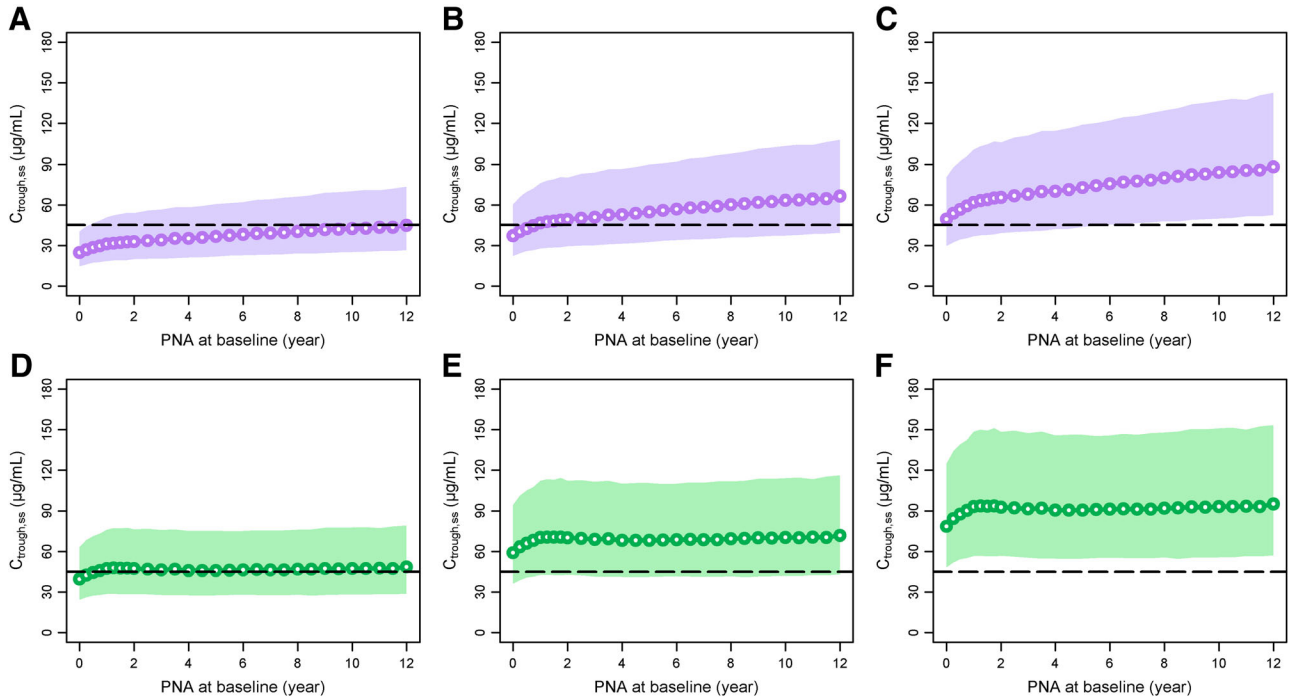
<sup>d</sup> Data after dose up-titration or treatment discontinuation were excluded.

<sup>e</sup> Time elapsed after birth (ie, exact postnatal age) is presented.

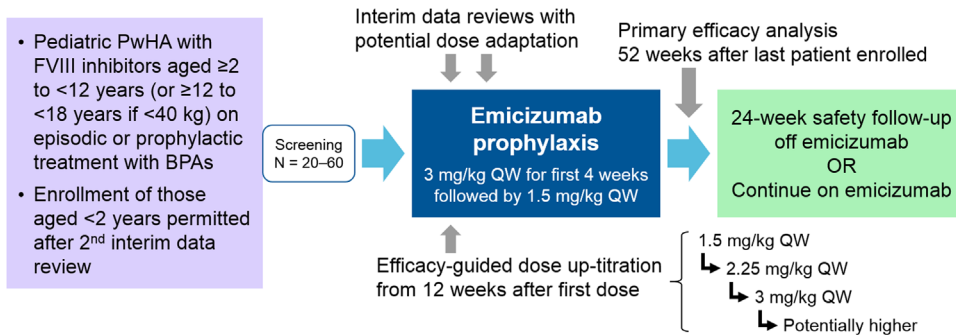
<sup>f</sup> The number of completed years (ie, standard age) is presented.

study-level dose adaptation guided by interim reviews of emerging data, and patient-level dose up-titration guided by individual efficacy. In addition, a staggered approach of patient enrollment by age was employed for HAVEN 2 to safely include young children (Figure 3). A Joint Monitoring Committee (JMC) was formed to conduct 2 interim reviews of the efficacy, safety, and pharmacokinetic data. The first review was planned to occur after first 3 to 5 children aged ≥2 to <12 years were treated with emicizumab for at least 12 weeks, at which time the JMC planned to evaluate the appropriateness of the starting maintenance dose of 1.5 mg/kg QW and to provide a recommendation on increasing the maintenance dose if necessary (Method S3). The second review was planned to occur after at least 10 children aged ≥2 to <12 years were treated for at least 12 weeks, at which time the JMC planned to provide

recommendations on opening the enrollment of children aged <2 years if appropriate and on additional adaptation of the maintenance dose if necessary. Adolescents aged ≥12 to <18 years weighing <40 kg were included from the start to allow access to clinical studies of emicizumab for this patient population who were excluded from HAVEN 1<sup>16</sup> (Figure 3). Maintenance doses of 2.25 and 3 mg/kg QW as well as a potential further higher dose of up to 6 mg/kg QW were selected for the efficacy-guided dose up-titration steps, which was based on the prior pediatric pharmacokinetic prediction in conjunction with a 2-fold safety margin established for enabling dose up-titration in adult/adolescent studies<sup>32</sup> (Figures 3, S2, and S3). The treatment period of at least 52 weeks until the primary analysis was selected as a meaningful duration for safety assessment in children.



**Figure 2.** Prior predicted relationships of exact postnatal age (PNA) at baseline with the trough level of plasma emicizumab concentration at steady state ( $C_{\text{trough,ss}}$ ) in children for once-weekly dosing. Given dosing regimens in combination of applied prediction approaches include a subcutaneous loading dose of 3 mg/kg once weekly for first 4 weeks followed by subcutaneous maintenance doses of (A) 1.5 mg/kg once weekly, (B) 2.25 mg/kg once weekly, and (C) 3 mg/kg once weekly considering body weight only in the prediction, and (D) 1.5 mg/kg once weekly, (E) 2.25 mg/kg once weekly, and (F) 3 mg/kg once weekly considering body weight and clearance maturation in the prediction. Assumed baseline PNAs in the prediction include every 0.25 years from 0 to 2 years and every 0.5 years from 2 to 12 years. Steady state was defined as 24 weeks after the start of emicizumab prophylaxis. Open circles and solid line represent the prior predicted median, shaded area represents the prior predicted 5th to 95th percentile range, and dashed line represents the target efficacious exposure at the time of phase III dose selection ( $\geq 45 \mu\text{g/mL}$ ).



**Figure 3.** Initial HAVEN 2 study design. The first interim data review was planned to evaluate the appropriateness of the starting maintenance dose of 1.5 mg/kg once weekly (QW) after first 3 to 5 children aged  $\geq 2$  to  $< 12$  years were treated with emicizumab for at least 12 weeks (Method S3). The second interim data review was planned to evaluate the appropriateness of opening the enrollment of children aged  $< 2$  years and the necessity of additional adaptation of the maintenance dose after at least 10 children aged  $\geq 2$  to  $< 12$  years were treated for at least 12 weeks. The efficacy-guided dose up-titration is detailed in Figure S2. After the appropriateness of the starting maintenance dose was confirmed, the intermediate dose up-titration step of 2.25 mg/kg QW was removed. Subsequently, 2 new cohorts were added to test less frequent maintenance doses of 3 mg/kg every 2 weeks and 6 mg/kg every 4 weeks instead of 1.5 mg/kg QW. BPA, bypassing agent; FVIII, factor VIII; PwHA, patients with hemophilia A.

**Pediatric Study and Development Consequences**

Owing to much faster patient enrollment than anticipated in HAVEN 2, the 2 planned interim data reviews were combined into 1 review. The JMC assessed all available data from the first 20 patients, of whom 10 children aged  $\geq 2$  to  $< 12$  years had been treated for at

least 12 weeks. With a similar pharmacokinetic profile to adults/adolescents as well as favorable efficacy and safety confirmed,<sup>39</sup> the JMC recommended keeping the maintenance dose and opening the enrollment of children aged  $< 2$  years with the same maintenance dose, concluding no need for study-level dose

adaptation. The efficacy-guided dose up-titration algorithm was accordingly updated to remove the intermediate dose step of 2.25 mg/kg QW. In addition, following the accumulation of the clinical experiences with the less frequent maintenance doses of 3 mg/kg Q2W and 6 mg/kg Q4W in adults/adolescents in HAVEN 3 and HAVEN 4, another pediatric study of HOHOEMI was planned to test the same BW-based Q2W and Q4W dosing regimens in children aged <12 years without FVIII inhibitors, and 2 new cohorts were added in HAVEN 2 to test these respective Q2W and Q4W dosing regimens in children aged  $\geq 2$  to <12 years with FVIII inhibitors. Efficacy-guided dose up-titration to 3 mg/kg QW was applied in HOHOEMI.

Posterior investigations using the  $C_{\text{trough}}$  data from the 5 phase III studies suggested that all 3 dosing regimens provided in children similar pharmacokinetic profiles with comparable exposures to adults/adolescents (Figure 4). Although the mean  $C_{\text{trough}}$  in children appeared slightly lower than those in adults/adolescents, the individual  $C_{\text{trough}}$  in children were all within the minimum-to-maximum ranges in adults/adolescents at every corresponding time point for all 3 dosing regimens, which indicated no obvious differences in emicizumab exposure between adults/adolescents and children. In addition, an exposure-response analysis based on phase I-III study data from adult/adolescent and pediatric patients revealed that an almost maximal effect of emicizumab for bleed prevention is achieved at approximately  $>30 \mu\text{g/mL}$ ,<sup>40</sup> which was largely covered during the maintenance period in children (Figure 4). These pharmacokinetic and exposure-response findings served as a basis for the efficacy consistently demonstrated in HAVEN 2 and HOHOEMI (Table S1). Dose up-titration due to suboptimal bleeding control occurred in only 2 of a total of 98 children enrolled in these pediatric studies. All 3 dosing regimens were safe and well tolerated in children.<sup>17,20</sup>

Taken together, these favorable pharmacokinetic, safety, and efficacy profiles confirmed the appropriateness of applying in children the same BW-based dosing regimens as for adults/adolescents and provided the basis for the regulatory approvals with extrapolation.

#### Posterior Validation of the Prior Pediatric Pharmacokinetic Prediction

The validity of the applied pediatric pharmacokinetic prediction approaches was assessed by comparing the prior predicted  $C_{\text{trough,ss}}$  for the QW dosing regimen, without any model update or parameter reestimation, with the corresponding actual observed  $C_{\text{trough,ss}}$  available from 61 children aged 1.22 to 11.97 years. The observed  $C_{\text{trough,ss}}$  were almost perfectly in line with the prior predictions derived considering BW and clearance maturation, while they tended to be underpredicted

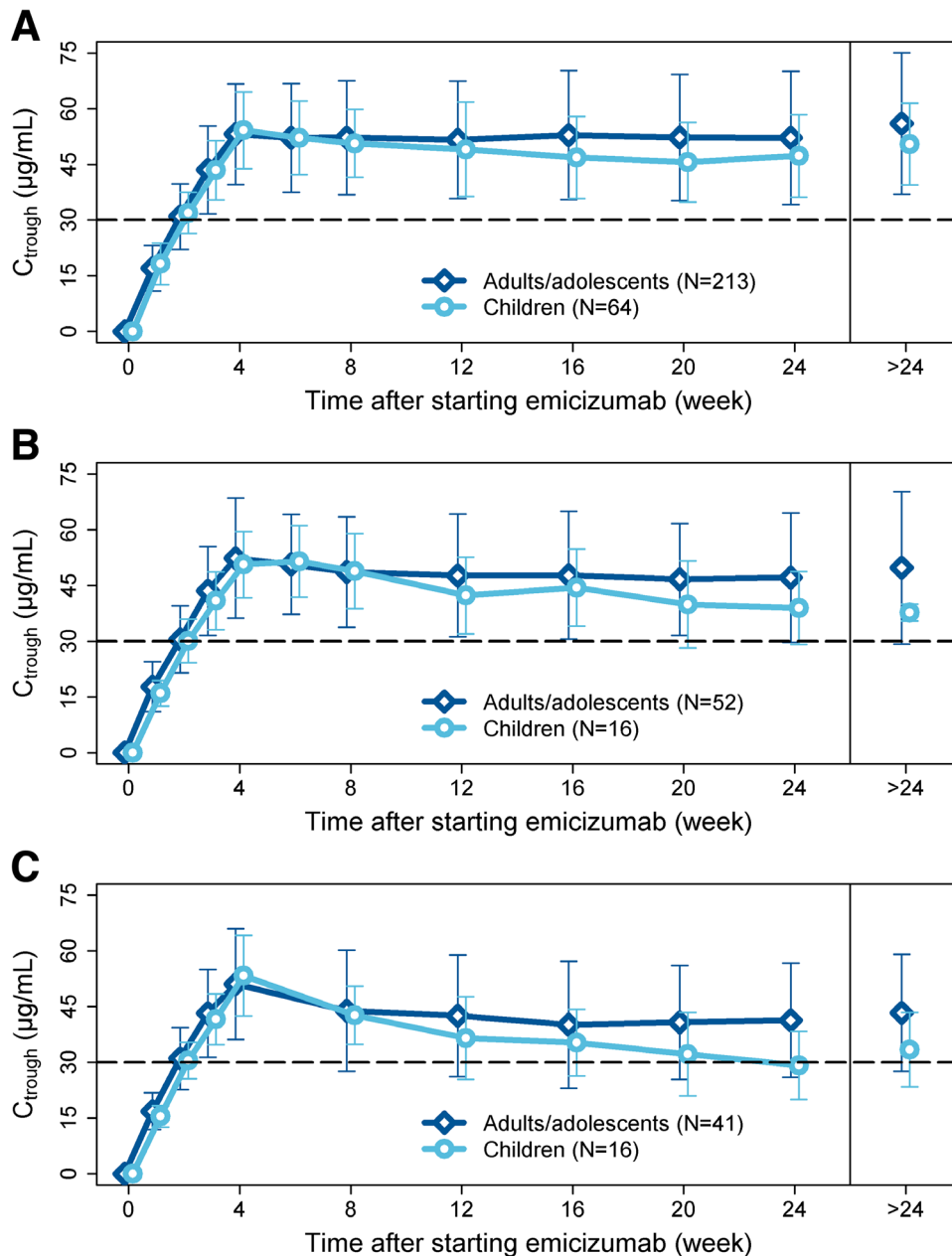
in children aged <6 years when considering BW only (Figure 5 and Table S2).

For further validating the prediction approach that considered BW and clearance maturation and was found adequate above, predictions of  $C_{\text{trough,ss}}$  for the Q2W and Q4W dosing regimens were additionally derived by the selected approach. These posterior predicted  $C_{\text{trough,ss}}$  were then compared with the corresponding actual observed  $C_{\text{trough,ss}}$  available from, for the respective dosing regimens, 16 children aged 1.50 to 10.98 years and 15 children aged 4 months to 11.99 years. Despite these smaller sample sizes, coverage of the observed  $C_{\text{trough,ss}}$  by the predictions was confirmed (Figure 6), which supported the initial validation by the larger data set for the QW dosing regimen.

## Discussion

The dose selection for the first-in-child phase III study of emicizumab in hemophilia A was guided by pediatric pharmacokinetic prediction using an adult/adolescent PopPK model. Multiple dose selection options were derived by taking into account the uncertainty on the prediction methodology (ie, whether considering clearance maturation or not in addition to BW), informing implementation of a dose-adapting scheme in the study design. Posterior investigations confirmed that comparable exposure was achieved in adults/adolescents and children with a same BW-based dosing regimen as predicted when considering BW and clearance maturation. The correspondence between the prior predicted and actual observed pharmacokinetic profiles in children with the starting dose (ie, the same BW-based dose as for adults/adolescents) streamlined the overall pediatric development process of emicizumab, avoiding a time-consuming process for exploring an optimal pediatric dose of emicizumab and increasing the confidence in the tested dosing regimens to be approved with extrapolation.

Several approaches of pediatric dose selection have been proposed for mAbs, with a general knowledge that young children with low BW are likely to exhibit lower exposure with BW-based dosing.<sup>41,42</sup> However, it is unknown whether this tendency is commonly applicable for every mAb. We employed a clearance maturation function developed for palivizumab,<sup>35</sup> on top of the well-established effects of BW, as a way to quantify a gap between hypothetical but possible scenarios (“uncertainty”) in the pediatric pharmacokinetic prediction for emicizumab. Although the clearance maturation function for palivizumab was developed in the absence of data from children/adolescents aged >2 to <18 years,<sup>35</sup> its use was considered reasonable to take into account the uncertainty in the pediatric pharmacokinetic prediction for emicizumab for several

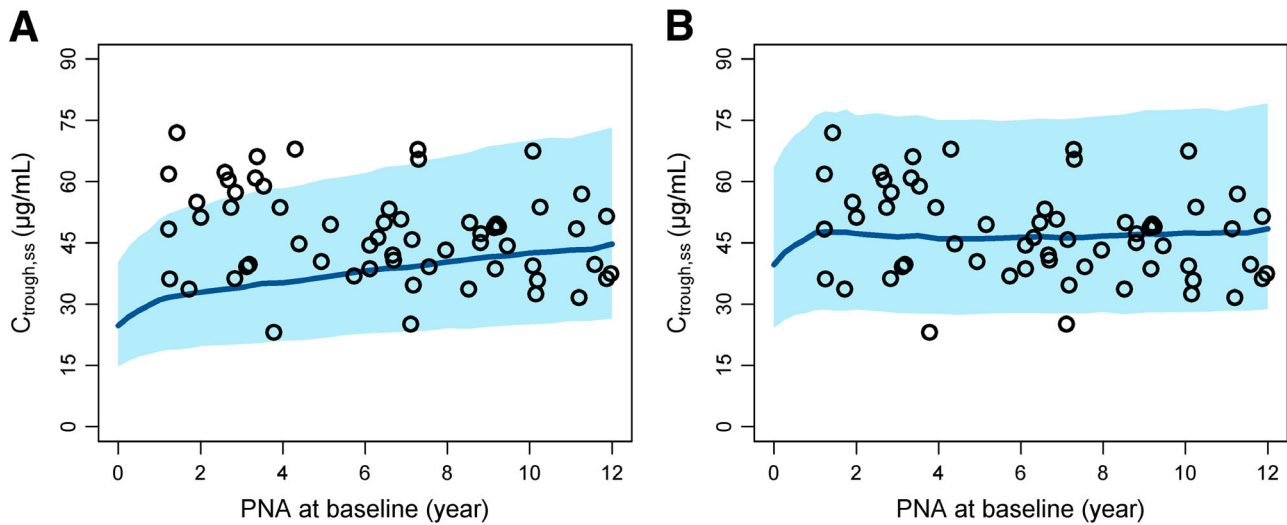


**Figure 4.** Comparisons of the observed time courses of the trough level of plasma emicizumab concentration ( $C_{\text{trough}}$ ) between adults/adolescents aged  $\geq 12$  years and children aged  $< 12$  years. Given dosing regimens include a subcutaneous loading dose of 3 mg/kg once weekly for first 4 weeks followed by subcutaneous maintenance doses of (A) 1.5 mg/kg once weekly, (B) 3 mg/kg every 2 weeks, and (C) 6 mg/kg every 4 weeks. Data are presented as mean (open diamonds for adults/adolescents and open circles for children)  $\pm$  standard deviation (vertical bars). Data plotted at “>24” represent the mean  $\pm$  standard deviation of the inpatient means of the observed  $C_{\text{trough}}$  after the first 24 weeks of treatment. Dashed line represents the updated efficacious exposure based on phase I-III study data ( $> 30 \mu\text{g/mL}$ ). N, number of patients included in the data set.

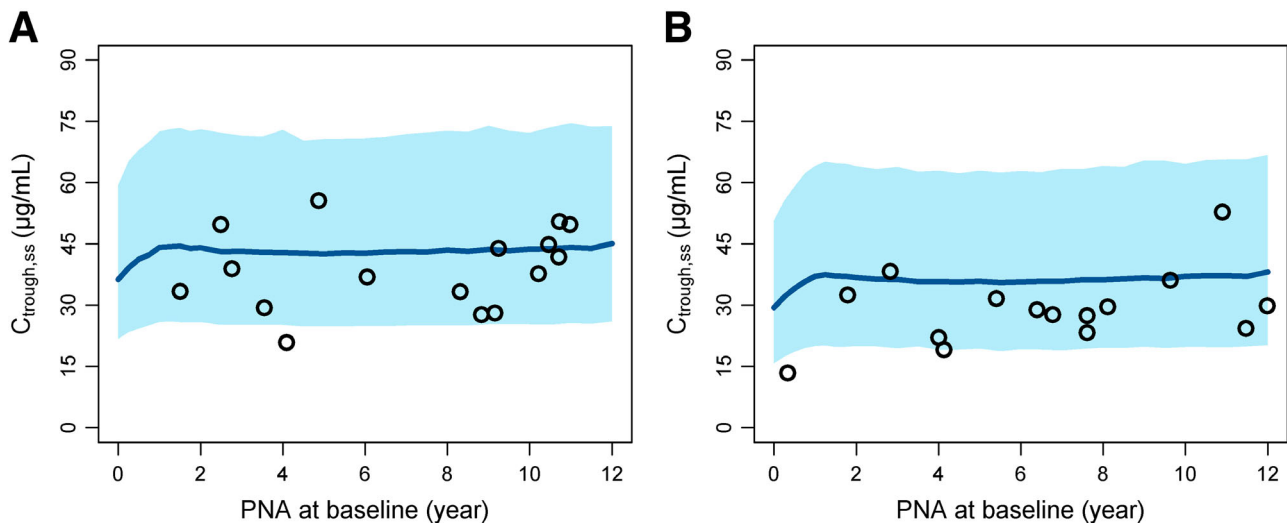
reasons. First, there can be in theory a maturation process for mAb clearance as well known for small-molecule drugs.<sup>33,34</sup> The clearance maturation function for palivizumab was the only available published information for our use. Second, the clearance maturation function is a precise (continuous rather than discrete) description of the effect of age. This can be an advantage over other possible approaches such as

the age-dependent exponent (ADE) approach which considers age less precisely (ie, using age categories).<sup>43</sup> Finally, if the clearance maturation is truly effective, the allometric exponent will apparently decrease from a value  $> 0.75$  at 0 years of age to 0.75 asymptotically as age increases, with the impact of clearance maturation being absorbed into the allometric exponent due to the correlation between age and BW. This expected trend is





**Figure 5.** Comparisons of the prior predicted and actual observed relationships of exact postnatal age (PNA) at baseline with the trough level of plasma emicizumab concentration at steady state ( $C_{\text{trough,ss}}$ ) in children for once-weekly dosing. Given dosing regimens in combination of applied prediction approaches include a subcutaneous loading dose of 3 mg/kg once weekly for first 4 weeks followed by a subcutaneous maintenance dose of 1.5 mg/kg once weekly (A) considering body weight only and (B) considering body weight and clearance maturation in the prediction. Assumed baseline PNAs in the prediction include every 0.25 years from 0 to 2 years and every 0.5 years from 2 to 12 years. Steady state was defined as 24 weeks after the start of emicizumab prophylaxis. Same actual observations from 61 children are presented in both panels. Open circles represent the actual observations, solid line represents the prior predicted median, and shaded area represents the prior predicted 5th to 95th percentile range.



**Figure 6.** Comparisons of the posterior predicted and actual observed relationships of exact postnatal age (PNA) at baseline with the trough level of plasma emicizumab concentration at steady state ( $C_{\text{trough,ss}}$ ) in children for every-2-week and every-4-week dosing. Given dosing regimens in combination of applied prediction approaches include a subcutaneous loading dose of 3 mg/kg once weekly for first 4 weeks followed by subcutaneous maintenance doses of (A) 3 mg/kg every 2 weeks and (B) 6 mg/kg every 4 weeks considering body weight and clearance maturation in the prediction. Assumed baseline PNAs in the prediction include every 0.25 years from 0 to 2 years and every 0.5 years from 2 to 12 years. Steady state was defined as 24 weeks after the start of emicizumab prophylaxis. Actual observations from 16 and 15 children are presented in panels A and B, respectively. Open circles represent the actual observations, solid line represents the posterior predicted median, and shaded area represents the posterior predicted 5th to 95th percentile range.

consistent with the ADE approach.<sup>43</sup> In the posterior investigations, ultimately, consideration of clearance maturation in addition to BW demonstrated a superior predictive performance of the pharmacokinetics of emicizumab in children aged <6 years compared to

consideration of BW only. Because the number of children aged <6 years included in the investigation was 24 (39.3% of 61), which would not be too small to derive a conclusion, and because the validity of the applied pediatric pharmacokinetic prediction approach which

used the prior information of the clearance maturation function for palivizumab was confirmed by actual observations, our finding may have some generalizability to other mAbs. The linear pharmacokinetics without significant TMDD for emicizumab, as is the case with palivizumab, may have enabled reproduction of the initial finding of the possible clearance maturation for mAbs from palivizumab. However, because the clearance maturation function for palivizumab is an empirical description of body functions that has not been adequately supported by ontogeny or mechanistic information, further investigations are needed to elucidate the underlying ontogeny and mechanism to support the consideration of clearance maturation in the pediatric pharmacokinetic prediction for mAbs. The possible mechanisms may include decreased endothelial cellular concentration of neonatal Fc receptor (FcRn) and/or increased plasma concentration of endogenous immunoglobulin G which competes with mAbs in FcRn binding, possibly resulting in reduced FcRn-mediated recycling and promoted endosomal degradation of mAbs, in adults compared to children.<sup>44,45</sup> In addition, because the significance of maturation in the pharmacokinetics of mAbs is controversial, other approaches not considering clearance maturation such as the ADE approach may be considered for the pediatric pharmacokinetic prediction for mAbs. Use of a mechanistic model (eg, physiologically based pharmacokinetic model) could also be an option.

When developing a pharmacokinetic model relevant to children, whether modeling the clearance maturation separately from the effect of BW by fixing the allometric exponent (like the palivizumab case<sup>35</sup>) or modeling the effect of BW only absorbing the impact of clearance maturation into an allometric exponent (like the ADE approach<sup>43</sup>) will depend on what data are available for the modeling and what the modeling objective is. If the objective is to descriptively explore factors affecting pharmacokinetics based on data from adults/adolescents and children, modeling the effect of BW without clearance maturation may be sufficient. In contrast, if the objective is to develop a model enabling prospective pediatric pharmacokinetic prediction based on data from adults/adolescents only, both approaches can be options provided that reasonable model parameters enabling extrapolation use of the model are available.

The posterior investigations revealed that emicizumab exposure provided by BW-based dosing was comparable over a very wide range of age across adults/adolescents and children. With the negligible peak-trough fluctuation at steady state for the QW dosing regimen,<sup>13</sup> the comparable  $C_{\text{trough,ss}}$  over age indicate an apparently proportional relationship of BW with the CL/F of emicizumab. This interpretation is in

line with the estimated apparent exponent on BW for the CL/F of emicizumab by a PopPK analysis based on phase I-III study data from adult/adolescent and pediatric patients (0.911)<sup>13</sup> and a theoretical apparent exponent derived in a simulation study that applied a similar pediatric pharmacokinetic prediction approach to this research (0.94).<sup>46</sup> These findings support the appropriateness of applying the BW-based dosing method regardless of age for emicizumab.

Through the clinical development program of emicizumab, only 1 child aged <1 year (4 months) was enrolled in a phase III study (HOHOEMI). With the Q4W dosing regimen, this patient exhibited a lower  $C_{\text{trough,ss}}$  than those in the others aged  $\geq 1$  years (Figure 6). However, because the exposure remained within the observed variability in adults/adolescents, this observation was considered too limited to conclude that such a young patient population should exhibit a clinically relevant lower exposure as a consequence of potential effects of age. Importantly, this patient experienced no bleeding events, suggesting meaningful efficacy despite the observed lower exposure. Application of different dosing regimens was therefore deemed not warranted even for the patient population aged <1 year.

After phase III study data became available, the efficacious exposure was updated from  $\geq 45 \mu\text{g/mL}$ , which was identified in 18 patients from phase I-I/II studies,<sup>32</sup> to  $>30 \mu\text{g/mL}$ , which was identified in a total of 445 patients from phase I-I/II and III studies.<sup>40</sup> These initial and updated efficacious exposures were considered appropriate at the time of phase III dose selection and after phase III study data became available, respectively, meaning that the update of the efficacious exposure was driven by the increase of the available data, without affecting the validity in the efficacy of the QW, Q2W, and Q4W dosing regimens.

Recent research showed that 42% of drugs failed in demonstrating their efficacy in children,<sup>47</sup> and another investigation reported that lack of efficacy accounted for 86% of the reasons for pediatric study failures.<sup>48</sup> Dosing has been identified as a potential contributing factor to pediatric study failures due to lack of efficacy, with 2 major issues identified: lack of dose-finding nature considered in the study design, and inadequately targeted exposure matching under a different disease condition from adults.<sup>48</sup> However, in children, particularly for rare diseases, conducting a large-sized, multiple-cohort, dose-finding study is generally unfeasible. Application of innovative methodologies should help enable rational and rapid identification of an optimal pediatric dose.<sup>49-52</sup> The initial HAVEN 2 study design was a model-informed adaptive design that addressed several challenges for identifying an optimal pediatric dose within a single

study. Prior identification of the minimal dose likely to achieve exposure matching, together with implementation of the dose-adapting scheme resulting from the uncertainty quantified by whether considering clearance maturation or not in addition to BW, were enabled by the knowledge-integrative, model-based pediatric pharmacokinetic prediction. Consideration of efficacy in the dose-adapting scheme aimed to mitigate the risk of study failure in case of different exposure-response relationship of emicizumab in children from adults/adolescents. Application of patient-level dose up-titration limited the duration with suboptimal bleeding control, generating more dose-exposure-response information. Although the need for study-level dose adaptation was ultimately not indicated in the study, thereby failing to demonstrate the benefit of this aspect of the model-informed dose selection, our approach may serve as a model for future pediatric dose selection and study design to streamline the development process of new drugs for children.

Because this research is based on a single-drug experience with emicizumab, it may limit the generalizability of the findings. Nonetheless, this case study based on the relatively large pediatric data set provides useful information for streamlining future clinical investigations in children.

## Conclusions

A model-based approach guided the dose selection for the first-in-child phase III study of emicizumab in hemophilia A, with implementation of a dose-adapting scheme proposed for the study design. Exposure matching to adults/adolescents was achieved in children with the starting dose (ie, the same BW-based dose as for adults/adolescents) which was selected considering BW and clearance maturation in the prior pediatric pharmacokinetic prediction, indicating that consideration of clearance maturation in addition to BW was adequate for emicizumab. Successful prior identification of the dose to achieve exposure matching enabled rational and rapid identification of an optimal pediatric dose of emicizumab. This experience indicates that a model-based framework helped optimize the pediatric dose selection and study design, thereby streamlining the development process with extrapolation, of emicizumab for children.

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## Conflicts of Interest

K.Y. is an employee of Chugai Pharmaceutical Co., Ltd. C.S., C.D., and C.P. are employees of F. Hoffmann-La Roche AG. T.C. and G.G.L. were employees of Genentech, Inc. at the time of the research and are currently employees of Spark Therapeutics, Inc. S.N. was an employee of Chugai Pharmaceutical Co., Ltd. at the time of the research. C.S., T.C., C.P., and G.G.L. hold stock in F. Hoffmann-La Roche Ltd. S.N. holds stock in Chugai Pharmaceutical Co., Ltd. K.Y., C.S., and S.N. are inventors of patents related to anti-activated FIX/FX bispecific antibodies.

## Author Contributions

K.Y. wrote the manuscript. K.Y., C.S., T.C., C.D., S.N., and G.G.L. designed the research and acquired the data. K.Y. and C.P. analyzed the data. All authors interpreted the data.

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## Data-Sharing Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform ([www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com)). For further details on Chugai's Data Sharing Policy and how to request access to related clinical study documents, see [www.chugai-pharm.co.jp/english/profile/rd/ctds\\_request.html](http://www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html).

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Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.