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Original Research Article

A Pharmacometric Approach to Substitute for Conventional Dose-Finding Study in Rare Diseases: Example of Phase 3 Dose Selection for Emicizumab in Hemophilia A

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Supplementary Methods

PK and PD sampling time points in the clinical studies

In healthy volunteers, PK samples were collected before and 8 hours, 1, 2, 3, 4, 5, 6, 7, 10 days, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 weeks after a single SC administration of emicizumab. The last PK sampling time points were 4, 4, 16, 20, and 24 weeks after administration for the given doses of 0.001, 0.01, 0.1, 0.3, and 1 mg/kg, respectively. In patients, PK samples were collected before and 8 hours, 1, 2, 3, 4, 5, 6, and 7 days after the first SC administration of emicizumab, and subsequently at trough at 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, and 16 weeks after the start of emicizumab treatment, and thereafter at trough every 4 weeks. PD samples were collected before and 2, 4, and 7 days after the first SC administration of emicizumab, and subsequently at trough at 2, 4, 6, 8, 10, 12, 14, and 16 weeks after the start of emicizumab treatment, and thereafter at trough every 4 weeks. Additional PK and PD samples were collected during a post-emicizumab follow-up, after restarting emicizumab treatment, and after up-titrating the dose.

Validation of the developed PopPK and RTTE models

The validity of the developed PopPK and RTTE models was confirmed using data which became available since the data cutoff for Phase 3 dose selection (November 2014) until February 2016 [19]. VPCs on the time courses of plasma emicizumab concentration (prediction-corrected) and cumulative bleeding count were made to compare the subsequently available observations and the model-based simulations without parameter re-estimation.

Hazard functions for each prophylaxis pattern

Baseline bleeding hazard (Eq. 7) was applied to the prior 6 months for 8 patients without prior prophylaxis with coagulation factor treatment:

$$h_{i,t} = \lambda_i \qquad (7)$$

Baseline bleeding hazard with the prophylactic effect of coagulation factor treatment (FVIII or a bypassing agent) (Eq. 8) was applied to the prior 6 months for 10 patients with prior prophylaxis with coagulation factor treatment:

$$h_{i,t} = \lambda_i \times \left(1 - \frac{\theta_{PLX}}{1+\theta_{PLX}}\right) \qquad (8)$$

Baseline bleeding hazard with the prophylactic effect of emicizumab (Eq. 9) was applied to the emicizumab treatment period for all the 18 patients and to a post-emicizumab follow-up for 3 patients without or before receiving prophylaxis with coagulation factor treatment:

$$h_{i,t} = \lambda_i \times \left(1 - \frac{\frac{C_{emi,i,t}}{EC_{50,i}}}{1+\frac{C_{emi,i,t}}{EC_{50,i}}}\right) \qquad (9)$$

Baseline bleeding hazard with the combined prophylactic effect of emicizumab plus FVIII (Eq. 10) was applied to a post-emicizumab follow-up for 1 patient during receiving prophylaxis with FVIII:

$$h_{i,t} = \lambda_i \times \left(1 - \frac{\frac{C_{emi,i,t}}{EC_{50,i}} + \theta_{PLX}}{1+\frac{C_{emi,i,t}}{EC_{50,i}} + \theta_{PLX}}\right) \qquad (10)$$

There were no actual observations to support modeling of the combined prophylactic effect of emicizumab plus a bypassing agent in the dataset. Eq. 3 is therefore not applicable to this prophylaxis pattern.

Illustration of the exposure-response relationship

In the simulations using the developed RTTE model, 10,000-patient populations were generated for each plasma emicizumab concentration of every 2 μg/mL from 0 to 20 μg/mL, every 5 μg/mL from 20 to 100 μg/mL, and every 10 μg/mL from 100 to 200 μg/mL. Repeated onset of bleeding events over time were simulated individually at each plasma emicizumab concentration in the absence of

PK profile fluctuations with a minimum time unit of observation of one day. Individual annual bleeding rates were derived by counting the number of bleeding events simulated to occur during 52 weeks, and then summarized to derive the statistics and the proportions of patients with zero ABR.

Derivation of the PK and efficacy simulations at the selected Phase 3 dosing regimens

In the simulations using the developed PopPK and RTTE models, 10,000-patient populations with a log-normally distributed baseline BW were generated for each dosing regimen of a repeated SC loading dose of 3 mg/kg QW for first 4 weeks followed by SC maintenance doses of 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W. The mean and standard deviation of the log-transformed BW were assumed to be 4.27 and 0.283, respectively. These assumptions were intended to lead the median and 2.5^{th}- to 97.5^{th}-percentile range of the simulated BW to 71.6 kg and 41.1 to 125 kg, respectively, which mimics the BW distribution of the adult and adolescent patients without FVIII inhibitors in a global Phase 3 study of a recombinant FVIII Fc fusion protein [37]. Individual plasma emicizumab concentrations were simulated at time points of every 24 hours for each dosing regimen, and then summarized to derive the statistics. Individual annual bleeding rates were also simulated and summarized for each dosing regimen.

Supplementary Figures

Fig. S1 Individual time courses of activated partial thromboplastin time (aPTT, **a** *solid lines*) or activated factor XI-triggered thrombin generation (TG, **b** *solid lines*) with bleeding onset (*open circles*) during emicizumab treatment. Data during a post-emicizumab follow-up are not plotted

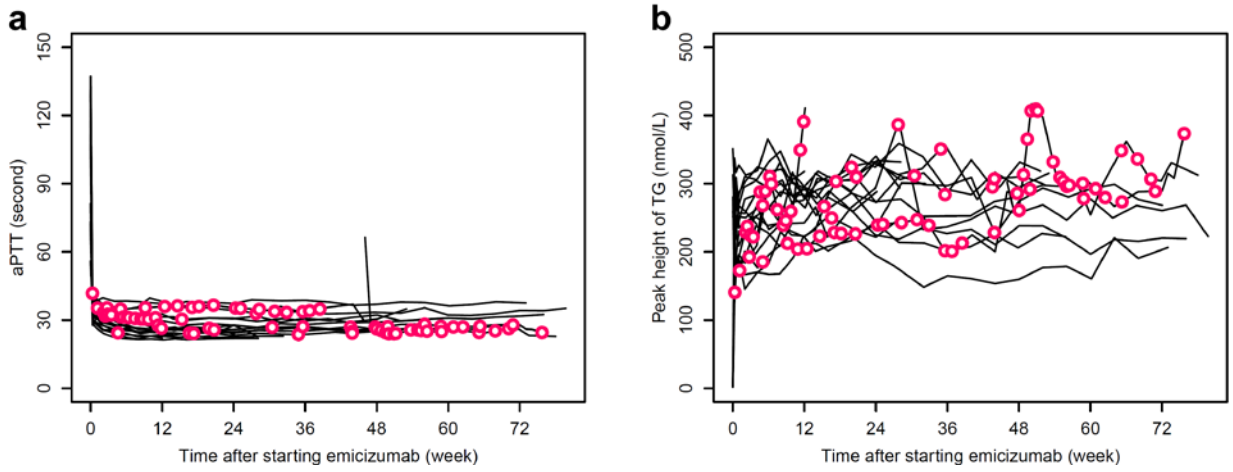


Fig. S2 Prediction-corrected visual predictive check plots with stratification by study for the developed population pharmacokinetic model. Data from the healthy volunteer study (**a**) and the patient study (**b**) are presented. *Red solid line* observed median, *red dashed lines* observed 5th (*lower*) and 95th (*upper*) percentiles, *shaded areas* simulated 95% confidence intervals of 5th percentile (*blue bottom*), median (*red middle*), and 95th percentile (*blue top*)

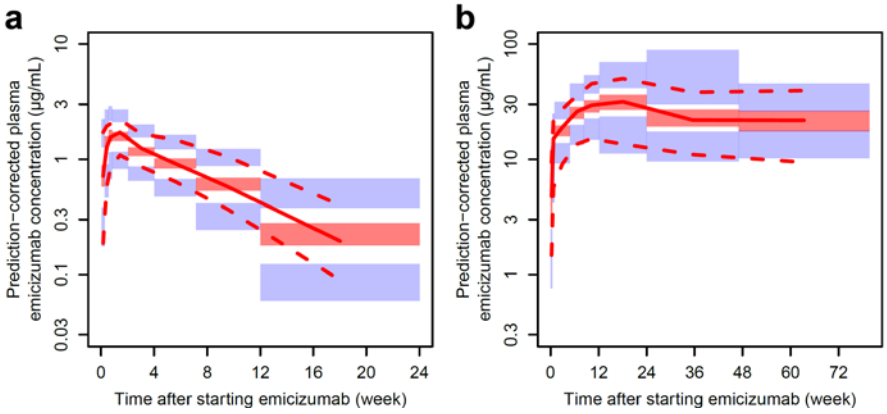


Fig. S3 Goodness-of-fit plots for the developed population pharmacokinetic model. **a**, **b** *black open circles* observations of plasma emicizumab concentration, *black solid line* line of identity, *red solid line* loess smoothing line, **c**, **d** *black open circles* conditional weighted residuals of plasma emicizumab concentration, *black solid line* line of zero, *red solid line* loess smoothing line

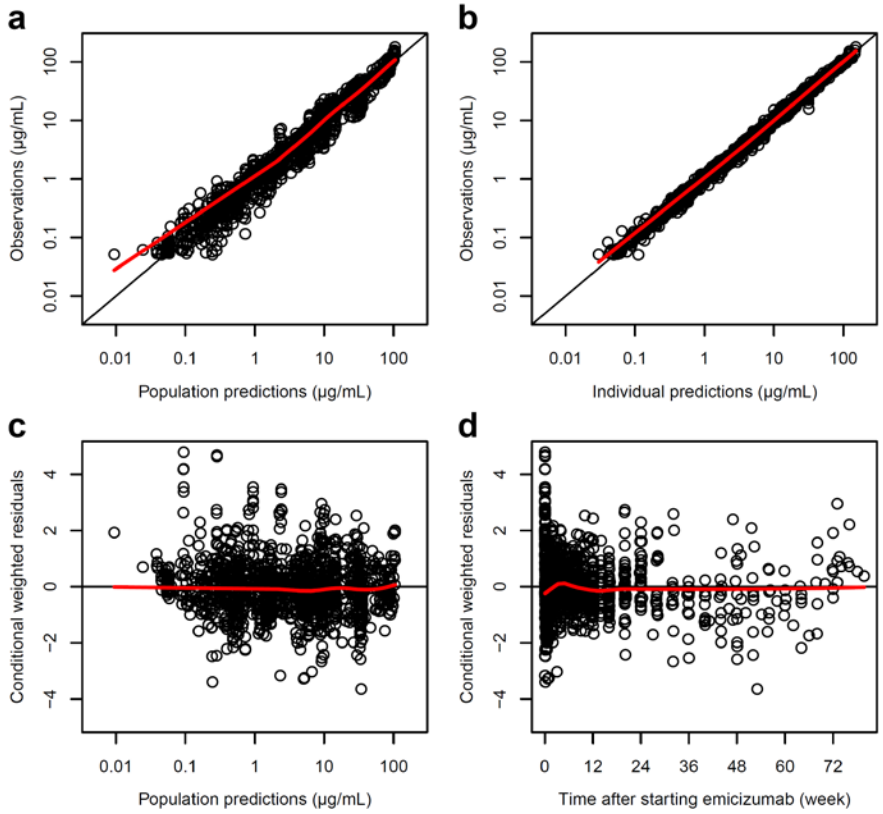


Fig. S4 Prediction-corrected visual predictive check plot for the validation of the developed population pharmacokinetic model using data becoming available since the data cutoff for Phase 3 dose selection. *Red solid line* observed median, *red dashed lines* observed 5th (*lower*) and 95th (*upper*) percentiles, *shaded areas* simulated 95% confidence intervals of 5th percentile (*blue bottom*), median (*red middle*), and 95th percentile (*blue top*)

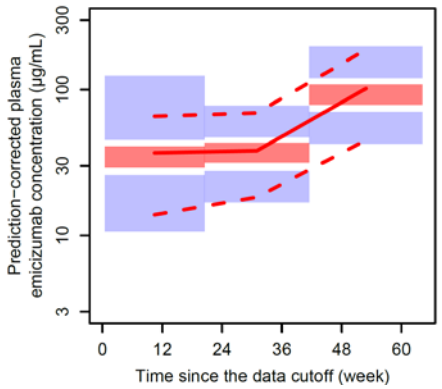


Fig. S5 Posterior predictive check plots for the developed repeated time-to-event model. Data before (**a**) and after (**b**) the start of emicizumab treatment are presented. *Open circles* observations, *solid lines* simulated expectations, *shaded areas* simulated 95% confidence intervals

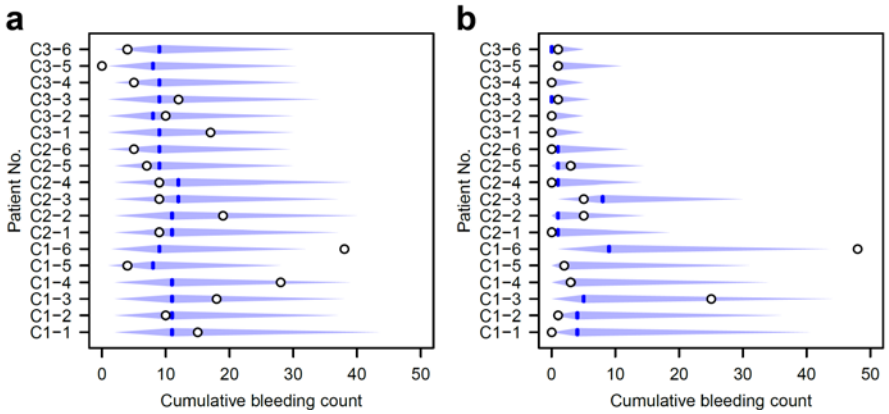
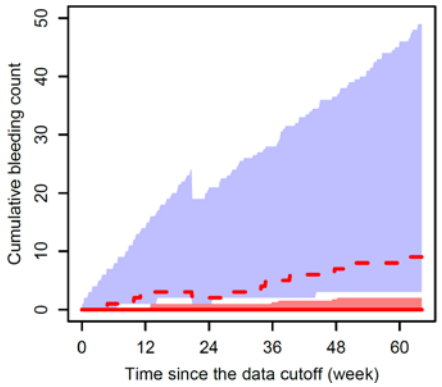


Fig. S6 Visual predictive check plot for the validation of the developed repeated time-to-event model using data becoming available since the data cutoff for Phase 3 dose selection. *Red solid line* observed median, *red dashed lines* observed minimum (*lower*) and maximum (*upper*), *shaded areas* simulated 95% confidence intervals of minimum (*blue bottom*), median (*red middle*), and maximum (*blue top*)



Supplementary Tables

Table S1 Derived pharmacokinetic parameters from the population pharmacokinetic simulations for the selected Phase 3 dosing regimens

Parameter	Maintenance dose		
	1.5 mg/kg QW SC	3 mg/kg Q2W SC	6 mg/kg Q4W SC
Peak level at steady state[a]	54.6 μg/mL	56.8 μg/mL	63.4 μg/mL
Time to peak level at steady state[b]	2 days	3 days	6 days
Trough level at steady state[c]	51.5 μg/mL	48.0 μg/mL	40.7 μg/mL
Peak:trough ratio at steady state	1.06	1.18	1.56

QW once weekly, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SC* subcutaneous

[a] Highest simulated median plasma emicizumab concentration within the dosing interval following the last administration during 52-week emicizumab treatment (i.e., between the 358th and 365th days post-dose for 1.5 mg/kg QW SC, between the 351st and 365th days post-dose for 3 mg/kg Q2W SC, and between the 337th and 365th days post-dose for 6 mg/kg Q4W SC)

[b] Days taken to reach the highest simulated median plasma emicizumab concentration within the dosing interval following the last administration during 52-week emicizumab treatment (i.e., between the 358th and 365th days post-dose for 1.5 mg/kg QW SC, between the 351st and 365th days post-dose for 3 mg/kg Q2W SC, and between the 337th and 365th days post-dose for 6 mg/kg Q4W SC)

[c] Simulated median plasma emicizumab concentration at trough following the last administration during 52-week emicizumab treatment (i.e., on the 365th day post-dose)

Supplementary Appendices

Appendix S1 NONMEM control stream for the developed repeated time-to-event model

```
$PROB  RTTE modeling
$INPUT ID TIME EVID CMT AMT DV MDV DVID AGE BW ADA PAT INH PLX IET1 IET2 IET3
$DATA  data_rtte.csv IGNORE=@
$SUB   ADVAN6 TOL=9

$MODEL
  COMP=(DEPOT)
  COMP=(CENTRAL)
  COMP=(CUMHAZ)

$THETA
;--- PK ---
  0.222  FIX  ; CL   [L/day]
  10.2   FIX  ; V2   [L]
  1.56   FIX  ; T12  [day]
  0.75   FIX  ; BW(CL)
  1      FIX  ; BW(V2)
  2.01   FIX  ; EADA
  33.4   FIX  ; TADA [day]
  0.232  FIX  ; PAT(CL)
  0.175  FIX  ; PAT(V2)
  0.0149 FIX  ; Add  [ug/mL]
  0.128  FIX  ; Prop

;--- E-R ---
 (0,21.9)     ; BASABR [event/year]
 (0,1.19)     ; EC50   [ug/mL]
 (0,0.314)    ; EPLX

; $OMEGA
;--- PK ---
$OMEGA BLOCK(2)
  0.0737 FIX     ; CL
  0.0278 0.0455  ; V2
$OMEGA
  0.502  FIX     ; T12

;--- E-R ---
  0.340  ; BASABR
  2.53   ; EC50

; $SIGMA
;   1 FIX

$PK
;--- PK ---
  CL  = THETA(1)*EXP(IET1)*(BW/70)**THETA(4)*EXP(THETA(8)*PAT)   ; IET1 = EBE of ETA(1)
  V2  = THETA(2)*EXP(IET2)*(BW/70)**THETA(5)*EXP(THETA(9)*PAT)   ; IET2 = EBE of ETA(2)
  T12 = THETA(3)*EXP(IET3)                                       ; IET3 = EBE of ETA(3)
```

```
  S2  = V2  ; [mg/L] = [ug/mL]
  K12 = LOG(2)/T12

  TADA = 9999
  IF (ADA.EQ.2)  TADA = THETA(7)  ; NAb positive
  MTIME(1) = TADA
  EADA = THETA(6)

;--- E-R ---
  FPLX = 0
  IF (PLX.NE.0)  FPLX = 1  ; Another prophylaxis

  BASABR = THETA(12)*EXP(ETA(4))
  EC50   = THETA(13)*EXP(ETA(5))
  EPLX   = THETA(14)

  BASHAZ = BASABR/365.25

$DES
;--- PK ---
  CLT  = CL*EXP(MPAST(1)*EADA)
  K20T = CLT/V2

  DADT(1) = -K12*A(1)
  DADT(2) =  K12*A(1) - K20T*A(2)

;--- E-R ---
  CP1 = A(2)/S2
  HAZNOW1 = BASHAZ*(1-(CP1/EC50+EPLX*FPLX)/(1+CP1/EC50+EPLX*FPLX))

  DADT(3) = HAZNOW1

$ERR
;--- PK ---
;   IPRED = 0
;   W     = 0
;   IRES  = 0
;   IWRES = 0
;     IF (F.NE.0)       IPRED = F
;     IF (IPRED.NE.0)   W     = SQRT(THETA(10)**2+(IPRED*THETA(11))**2)
;     IF (IPRED.NE.0)   IRES  = DV-IPRED
;     IF (IPRED.NE.0)   IWRES = IRES/W
;   Y = IPRED+W*EPS(1)

;--- E-R ---
  IF (NEWIND.NE.2)  CUMHAZOLD = 0
  CUMHAZ = A(3)-CUMHAZOLD
  SUR    = EXP(-CUMHAZ)

  CP2 = A(2)/S2
  HAZNOW2 = BASHAZ*(1-(CP2/EC50+EPLX*FPLX)/(1+CP2/EC50+EPLX*FPLX))
```

```
  Y = 0
  IF (DVID.EQ.2.AND.DV.EQ.0) THEN  ; Censored event
    Y = SUR
    CUMHAZOLD = A(3)
  ENDIF
  IF (DVID.EQ.2.AND.DV.EQ.1) THEN  ; Event onset
    Y = SUR*HAZNOW2
    CUMHAZOLD = A(3)
  ENDIF

; $EST METHOD=1 INTER NOABORT NSIG=3 SIGL=9 MAXEVAL=9999 PRINT=5
$EST METHOD=1 LAPLACE LIKE NOABORT NSIG=3 SIGL=9 MAXEVAL=9999 PRINT=5
$COV PRINT=E
;
```