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Quantitative pharmacokinetic model to characterize and extrapolate long-term FVIII activity levels in patients with severe hemophilia A treated with valoctocogene roxaparvovec

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Background

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is an rAAV gene therapy that uses an adeno-associated virus (AAV) vector to transfer a B-domain-deleted human factor VIII (FVIII) coding sequence to reduce bleeding and FVIII concentrate use in people with severe hemophilia A
- In GENEr8-1, an open-label, single-arm, multicenter, phase 3 trial,134 participants with severe hemophilia A received a single infusion of $6x10^{13}$ vg/kg valoctocogene roxaparvovec
- A previously published quantitative pharmacokinetic (PK) model based on 2-year data was updated to characterize and extrapolate individual chromogenic FVIII activities for 3, 4 and 5 years after valoctocogene roxaparvovec administration
- At year 3, observed FVIII activity data from 134 participants showed a mean and median FVIII activity of 18.7 and 8.3 IU/dL, respectively

Aims

- To characterize the long-term trajectory of transgene-derived FVIII activity using a linear mixed effects (LME) model to estimate half-life ($t_{1/2}$), mean and median FVIII activity levels up to 5 years following a peripheral vein infusion

Methods

- FVIII activity was assessed using chromogenic substrate assay on Day 8, weekly from Weeks 2-36, every other week from Weeks 38-52, every 4 weeks during Year 2, and every 6 weeks thereafter

Quantitative pharmacokinetic model

- The key assumption in the LME model development is that long-term FVIII activity follows first-order elimination kinetics beginning at week 76
- Selection of the linear model and start time of week 76 was based on ANOVA of linear vs. non-linear models & model diagnostics with varying start times
- Ln-transformed FVIII activity values from week 76 to 104 were fit to the LME model with random effects for participants on slope and intercept
- Precision of parameter estimates and model diagnostics were evaluated to confirm goodness-of-fit
- Individual fits were used to extrapolate FVIII activities for years 3, 4, 5

Data exclusions during model development

- Exclusion criteria included:
  1. FVIII assessments collected within 72 hours of exogenous FVIII use or after resumption of prophylactic FVIII use
  2. Subjects with insufficient follow-up, defined as actual relative time of last evaluable FVIII assessment <100 weeks (5 subjects)
  3. Subjects with ≥50% BLQ (below the limit of quantification) records in the lambda Z region (8 subjects)
  4. Subjects who resumed prophylactic FVIII or started emicizumab prior to end of lambda Z region (4 subjects)
- Total of 14 subjects were excluded (3 subjects met more than 1 rule)
- Final LME dataset included 928 observations from 120 subjects

Data imputations for extrapolation

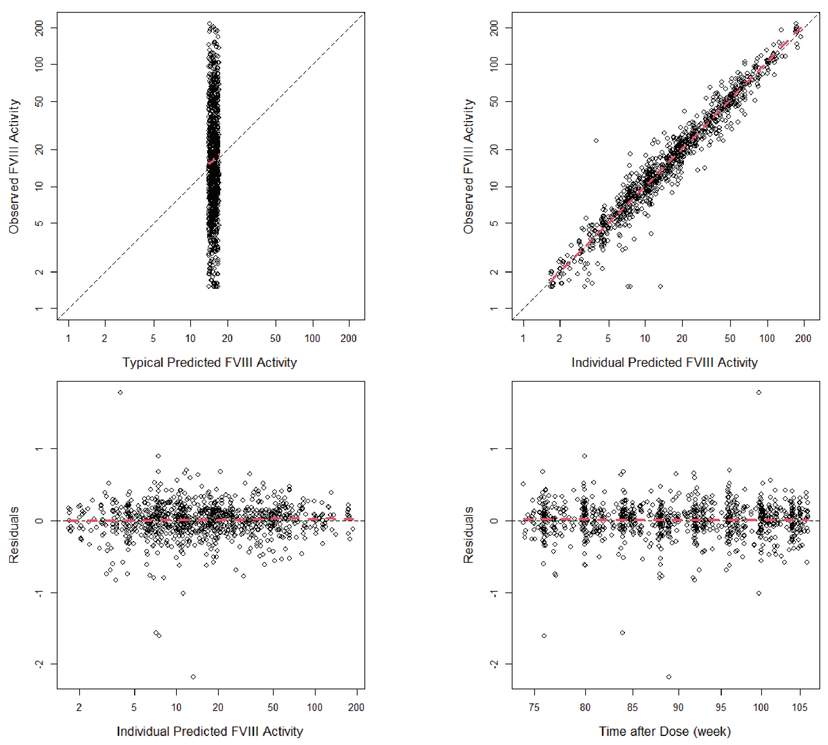
- Extrapolated FVIII activities set to 0 for subjects removed from LME due to ≥50% BLQ records in the lambda z region or resumption of prophylactic FVIII or start of emicizumab prior to end of lambda z region (values imputed for 11 subjects)
- Extrapolated values <LLOQ (1.5 IU/dL) were set to 0 for descriptive statistics

LME model qualification

- Model was qualified using internal dataset by comparing the observed and predicted values of 270-301 participants at year 3
- For external qualification, modeling approach was applied to participants in a phase 1/2 study to compare FVIII activity at year 5

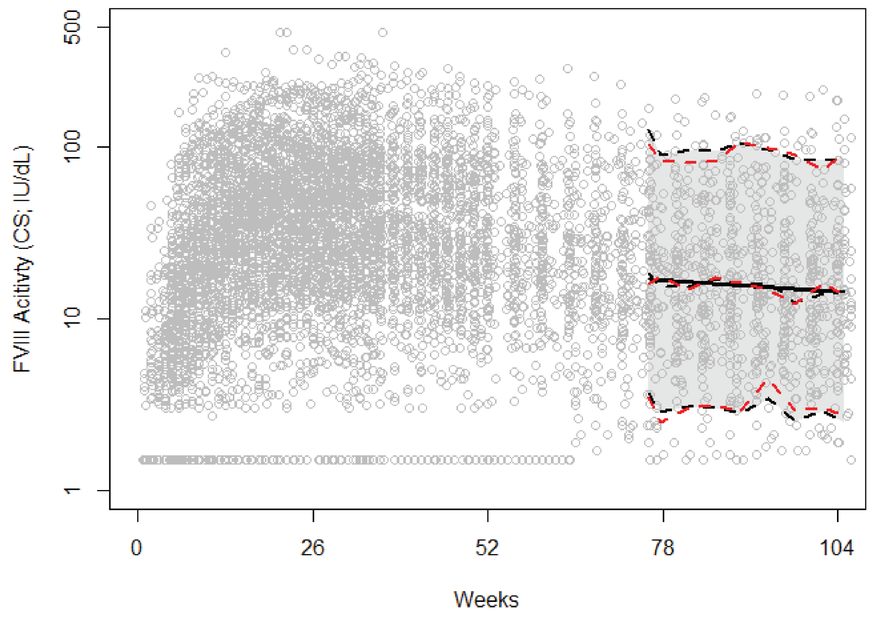
Results

Figure 1. Goodness-of-fit plots for the LME model



- Goodness-of-fit plots showed no major deficiencies

Figure 2. Visual predictive check for the LME model



CS, chromogenic substrate; FVIII, factor VIII; LME, linear mixed effects.
Circles denote individual observed data, and the dashed red lines denote 5th, 50th, and 95th percentiles of the observed data; the solid black line represents population fit and the dashed black lines denote the median and 90% prediction intervals calculated from simulations (n=1000)

- The estimated typical half-life of factor VIII was 115.1 weeks
- The goodness-of-fit plots and VPC support the first-order elimination kinetics starting at week 76 assumption

Table 1. Parameter estimates for the LME model

	Parameter	Typical Value	SE (%)	Lower 2.5th	Upper 97.5th
Fixed Effects	Intercept	3.285	4.67	2.983	3.587
	Slope	-6.03×10^{-3}	21.1	-8.52×10^{-3}	-3.52×10^{-3}
	Groups	**Name**	**Variance**	**SD**	**Correlation**
Random Effects	SUBJID	(Intercept)	1.839	1.356	
		Time (Weeks)	7.371×10^{-5}	8.59×10^{-3}	-0.64
	Residual		7.674×10^{-2}	0.277	

Table 2. Extrapolated FVIII activity

Visit	Predicted FVIII Activity (CS; IU/dL) N=131		Observed FVIII Activity (CS; IU/dL) N=134	
	Mean (SD)	Median [min, max]	Mean (SD)	Median [min, max]
Year 2	22.3 (29.9)	11.2 [BLQ, 173]	23.5 (33.2)	11.7 [BLQ, 187]
Year 3	17.0 (25.6)	8.83 [BLQ, 160]	18.7 (30.8)	8.3 [BLQ, 218]
Year 4	13.5 (23.1)	6.38 [BLQ, 149]		
Year 5	11.4 (21.4)	5.04 [BLQ, 139]		

- At 5 years, the estimated mean and median factor VIII levels were 11.4 IU/dL and 5.04 IU/dL, respectively, consistent with a mild hemophilia A phenotype

Summary/Conclusions

- The trajectory of factor VIII activity was consistent with first-order elimination kinetics starting at week 76, facilitating the development of an LME model
- Model prediction results were consistent with observed FVIII activity in phase 3 GENEr8-1 study at year 3 and phase 1/2 study at year 5 (data not shown), confirming adequacy of the current PK model
- Quantitative PK model indicated that factor VIII activity levels in subjects will remain in mild hemophilia range for at least 5 years after gene transfer, potentially providing consistent protection than factor VIII prophylaxis

References

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