PB0626

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

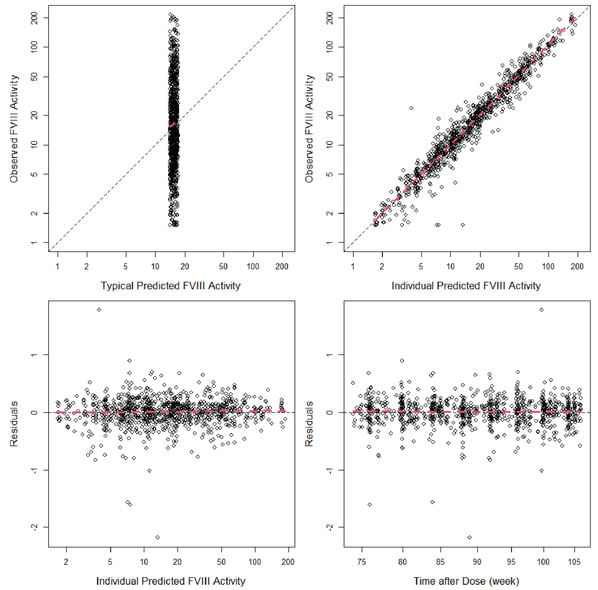
- Extrapolated FVIII activities set to 0 for subjects removed from LME due to ≥50% BLQ records in the lambda z region or resumption of prophylactic FVIII or start of emicizumab prior to end of lambda z region (values imputed for 11 subjects)
- Extrapolated values <LLOQ (1.5 IU/dL) were set to 0 for descriptive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

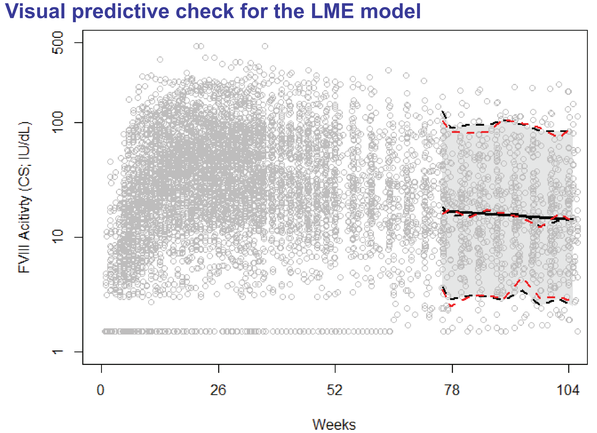
Results

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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2. Mahlangu J, Kaczmarek R, von Drygalski A, et al. Two-year safety and efficacy of valoctocogene roxaparvovec gene therapy in hemophilia A. *N Engl J Med* 2023;388:694-705.

Acknowledgments

We thank all the trial participants, their families, and study site personnel, BioMarin CMC team and Early Development, Study Execution, Clinical Development, and core teams.

Disclosures

SA, PC, TR, and JH are paid employees of BioMarin Pharmaceutical Inc. and hold stock ownership.
AT holds grants for research from BioMarin and receives Honoraria for consultancy.

Presented at the ISTH 2023 Annual Conference: 24–28 June, 2023, Montreal, Canada