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Valoctocogene roxaparvovec estimated long-term durability of treatment effect: An extrapolation of the most recent clinical data

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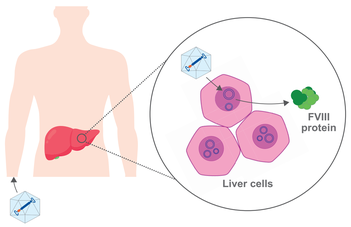
Introduction

Valoctocogene roxaparvovec for severe hemophilia A

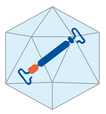
- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a B-domain-deleted FVIII coding sequence to enable FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1,2]
- In the phase 3 GENEr8-1 trial, participants who received 6x10[13] vg/kg valoctocogene roxaparvovec had improved protection from bleeds compared with regular FVIII prophylaxis over 4 years[1–4]
- **Here, we estimated the long-term durability of valoctocogene roxaparvovec treatment effect by extrapolating the most recent trial data (GENEr8-1 4–5-year and 270-201 7-year data)**



Methods

Study population

- All participants were adult (≥18 years) males with severe hemophilia A (with FVIII activity levels ≤1 IU/dL) who were previously receiving exogenous FVIII and had no history of FVIII inhibitors or anti-AAV5 antibodies



GENEr8-1:

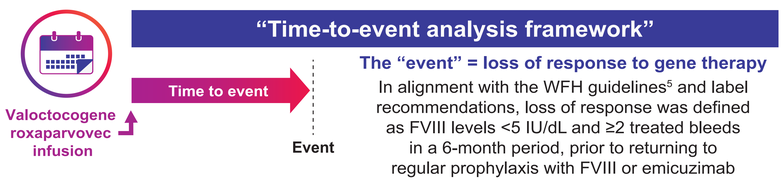
- A phase 3 clinical trial testing the efficacy and safety of valoctocogene roxaparvovec
- 134 participants received valoctocogene roxaparvovec (6x10[13] vg/kg) 4–5 years ago

270-201:

- A phase 1/2 clinical trial testing the safety, side effects, and best dose of valoctocogene roxaparvovec
- 7 participants received valoctocogene roxaparvovec (6x10[13] vg/kg) 7 years ago

Time to event analysis framework

- Using the 4–5-year data from GENEr8-1 and the 7-year data from 270-201, the durability of treatment effect was estimated using a "time-to-event analysis framework" in which loss of response data observed from the clinical trials were extrapolated using different parametric survival distributions. This resulted in a range of estimates for the predicted durability of treatment effect



- The primary objective was to estimate the long-term durability of valoctocogene roxaparvovec, defined using a composition of an objectively measurable biomarker (FVIII levels), clinical endpoints (bleeds), and a utilization metric (return to continuous prophylaxis)

Statistical analysis

- A parametric regression approach was used to extrapolate outcomes beyond the follow-up duration
- Parametric survival models of time from baseline until the event were estimated to extrapolate beyond the available follow-up. Six alternative parametric distributions were estimated (exponential, Weibull, loglogistic, lognormal, Gompertz, and generalized gamma)

Results

Study participants

- Demographics for these participants have been reported previously[1,6,7]
- Maximum follow-up was 233 weeks for GENEr8-1 and 314 weeks for 270-201 study participants

Durability modeling

- Table 1 summarizes the loss of response composite endpoint data and the alternative scenarios considered

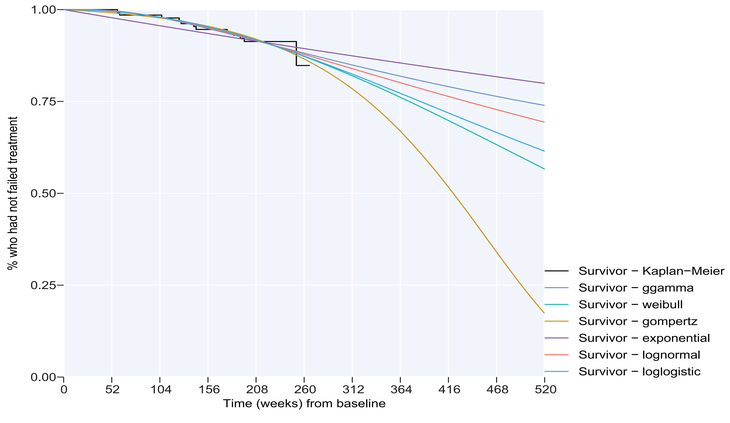
Table 1. Summary of scenarios and cohorts

Study/cohorts	Event	Criteria, n	N	Events, n
GENEr8-1 4–5Y	**FVIII <5 IU/dL and ≥2 treated bleeds in 6 months prior to RTP**	**3**	**134**	**12**
	FVIII <5 IU/dL and RTP	2	134	18
	RTP and ≥2 treated bleeds in 6 months prior to RTP	2	134	12
	FVIII <5 IU/dL and ≥2 subsequent treated bleeds in 6 months	2	134	18
	Return to continuous prophylaxis	1	134	23
GENEr8-1 4–5Y + 270-201 7Y (6x10[13] vg/kg cohort)	**FVIII <5 IU/dL and ≥2 treated bleeds in 6 months prior to RTP**	**3**	**141**	**12**
	FVIII <5 IU/dL and RTP	2	141	19
	RTP and ≥2 treated bleeds in 6 months prior to RTP	2	141	12
	FVIII <5 IU/dL and ≥2 subsequent treated bleeds in 6 months	2	141	20
	Return to continuous prophylaxis	1	141	25

Three-component composite definition of loss of response

- Within the GENEr8-1 study, eight (6.0%) participants experienced loss of response based on the three-component composite definition
- Using the three-component composite definition, the predicted median durability was estimated to range from 11.0–17.0 years using the three models with the best fit (Table 2)

Extrapolations (three-component composite definition; GENEr8-1)



References

1. Ozelo M, et al. *N Engl J Med.* 2022;386(11):1013–1025. **2.** Mahlangu J, et al. *N Engl J Med.* 2023;388:694–705. **3.** Madan B, et al. *J Thromb Haemost.* 2024;22(7):1880–1893. **4.** Leavitt AD, et al. *Res Pract Thromb Haemost.* 2024; in press. **5.** Srivastava A, et al. *Haemophilia.* 2020;26 Suppl 6:1–158. **6.** Rangarajan S, et al. *N Engl J Med.* 2017;377(26):2519–2530. **7.** Pasi KJ, et al. *N Engl J Med.* 2020;382:29–40.

Durability models: Full results

Table 2. Median durability in years for all scenarios

Study/cohorts	Criteria, n	Model scenario	Distribution	Median (95% CI)
GENEr8-1 4–5Y	**3**	**FVIII <5 IU/dL and ≥2 treated bleeds in 6 months prior to RTP**	**Weibull**	**11.0 (4.5, 17.4)**
			Lognormal	**17.0 (3.4, 30.6)**
			Loglogistic	**12.4 (4.3, 20.6)**
	2	FVIII <5 IU/dL and RTP	Weibull	8.9 (5.4, 12.5)
			Lognormal	12.2 (5.6, 18.7)
			Loglogistic	9.9 (5.5, 14.3)
	2	RTP and ≥2 treated bleeds in 6 months prior to RTP	Weibull	11.0 (4.5, 17.5)
			Lognormal	17.0 (3.4, 30.7)
			Loglogistic	12.4 (4.3, 20.6)
	2	FVIII <5 IU/dL and ≥2 subsequent treated bleeds in 6 months	Weibull	16.2 (4.1, 28.3)
			Lognormal	31.8 (–0.9, 64.4)
			Loglogistic	19.8 (3.3, 36.3)
	1	Return to continuous prophylaxis	Weibull	7.5 (5.4, 9.7)
			Lognormal	9.5 (5.8, 13.1)
			Loglogistic	8.1 (5.5, 10.8)
GENEr8-1 4–5Y + 270-201 7Y (6x10[13] vg/kg cohort)	**3**	**FVIII <5 IU/dL and ≥2 treated bleeds in 6 months prior to RTP**	**Weibull**	**13.2 (4.6, 21.8)**
			Lognormal	**20.4 (2.6, 38.2)**
			Loglogistic	**15.0 (4.2, 25.8)**
	2	FVIII <5 IU/dL and RTP	Weibull	9.6 (5.9, 13.2)
			Lognormal	12.9 (6.1, 19.6)
			Loglogistic	10.6 (6.0, 15.1)
	2	RTP and ≥2 treated bleeds in 6 months prior to RTP	Weibull	13.2 (4.6, 21.8)
			Lognormal	20.4 (2.5, 38.3)
			Loglogistic	15.0 (4.2, 25.8)
	2	FVIII <5 IU/dL and ≥2 subsequent treated bleeds in 6 months	Weibull	15.2 (5.2, 25.1)
			Lognormal	28.2 (2.4, 54.1)
			Loglogistic	18.2 (4.8, 31.7)
	1	Return to continuous prophylaxis	Weibull	7.8 (5.8, 9.8)
			Lognormal	9.6 (6.2, 13.1)
			Loglogistic	8.4 (5.9, 10.9)

Limitations

- Only a small number of events were observed to date in the valoctocogene roxaparvovec clinical trial program; therefore, small changes in the timing of events may have influenced the extrapolated outcomes
- The addition of data from the 270-201 study as a scenario analysis is subject to potential issues of between-study heterogeneity
- The durability measures presented are projected estimates using parametric durability extrapolations based on initial outcomes, whose precision may improve when incorporating future outcomes as they become available

Conclusions

- Therapeutic benefit of valoctocogene roxaparvovec is expected to extend beyond follow-up in existing clinical trials, with the estimated median durability of treatment effect ranging from 11–17 years using phase 3 data only and the three-component composite definition of loss of response, and 7.5–31.8 years using other scenarios and cohorts
- When combined with appropriate characterization of uncertainty, these results may be of value in informing the long-term outcomes for patients treated with valoctocogene roxaparvovec

Acknowledgements

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