Final analysis of the phase 1/2 trial of valoctocogene roxaparvovec for severe hemophilia A

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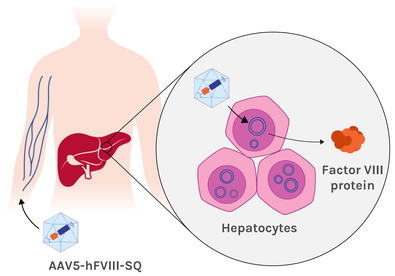
Background

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a factor VIII (FVIII) coding sequence to enable endogenous FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1]

Valoctocogene roxaparvovec for severe hemophilia A



AAV5, adeno-associated virus serotype 5; hFVIII-SQ, human FVIII, SQ variant

- Previously published results from this phase 1/2 trial (NCT02576795) and a phase 3 trial (GENEr8-1, NCT03370913) demonstrated the efficacy and safety of valoctocogene roxaparvovec[1-9]
- We present final efficacy and safety results and insights from across the full 7 years of the phase 1/2 trial

Methods

Study Design

- The design of this phase 1/2 trial has been described previously[1-5]
- Participants did not have a history of FVIII inhibitors, anti-AAV5 antibodies, significant liver dysfunction, significant liver fibrosis, or liver cirrhosis[1-5]

Endpoints

- Safety was assessed by adverse events (AEs)
- FVIII activity was assessed via chromogenic substrate assay and one-stage assay and are reported excluding data from participants who resumed prophylaxis
- Annualized treated bleeding rates (ABRs) and annualized FVIII infusion rates were calculated as described previously[1-5]
- Baseline ABRs were derived from the 12 months prior to enrollment

Statistics

- Data are presented with descriptive statistics
- Missing data were not imputed
- The yearly rate of change in FVIII activity was calculated using a linear regression model

Results

Participants

- Males aged ≥18 years of age with severe hemophilia A (FVIII ≤1 IU/dL) who were previously receiving exogenous FVIII received an infusion of 6x10^{13} (n = 7) or 4x10^{13} (n = 6) vg/kg valoctocogene roxaparvovec. All participants completed the study except 1 participant in the 4x10^{13} vg/kg cohort who was lost to follow-up by week 312

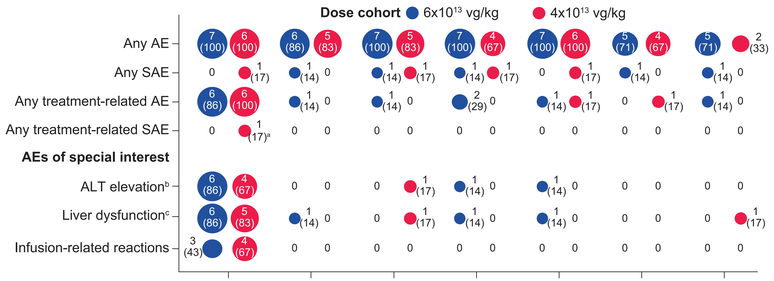
Baseline characteristic	6x10^{13} vg/kg cohort (n = 7)	4x10^{13} vg/kg cohort (n = 6)
Age, y		
Median (min, max)	30.0 (23.0, 42.0)	30.5 (22.0, 45.0)
ABR, bleeds/y		
Mean (SD)	17.6 (14.7)	12.2 (15.4)
Median (min, max)	24.0 (0.0, 40.0)	8.0 (0.0, 41.0)
AFR, infusions/y		
Mean (SD)	120.1 (45.9)	142.8 (48.8)
Median (min, max)	121.4 (27.4, 158.5)	155.8 (53.8, 184.3)

ABR, annualized bleeding rate; AFR, annualized factor VIII infusion rate; max, maximum; min, minimum; SD, standard deviation

Safety

- In year 1, the most common treatment-related AE was alanine aminotransferase (ALT) elevation
- No treatment-related serious AEs (SAEs) occurred after year 1
- No ALT elevations were reported after year 5
- In the last year, no new safety signals were reported
- Across the trial, no participants experienced thromboembolic events or developed FVIII inhibitors

Summary of incidence of AEs in each year by cohort



Data are presented as n (%).
[a]Pyrexia on study day 2. [b]Defined as ALT ≥1.5x ULN or ALT ≥1.5x baseline.
[c]Identified with a MedDRA search strategy using the high-level term "liver function analyses".
AE, adverse event; ALT, alanine aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious AE; ULN, upper limit of normal.

References

1. Rangarajan S, et al. *N Eng J Med.* 2017;3877(26):2519-30. **2.** Pasi KJ, et al. *N Eng J Med.* 2020;382:29-40. **3.** Pasi KJ, et al. *Haemophilia.* 2021;27(6):947-56. **4.** Symington E, et al. *Haemophilia.* 2024;30:320-30. **5.** Symington E, et al. *Haemophilia.* 2024;30(5):1138-47. **6.** Ozelo MC, et al. *N Eng J Med.* 2022;386:1013-25. **7.** Mahlangu J, et al. *N Eng J Med.* 2023;388(8):694-705. **8.** Madan B, et al. *J Thromb Haemost.* 2024;22(7):1880-93. **9.** Leavitt AD, et al. *RPTH.* 2024;8:e102615.

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Disclosures

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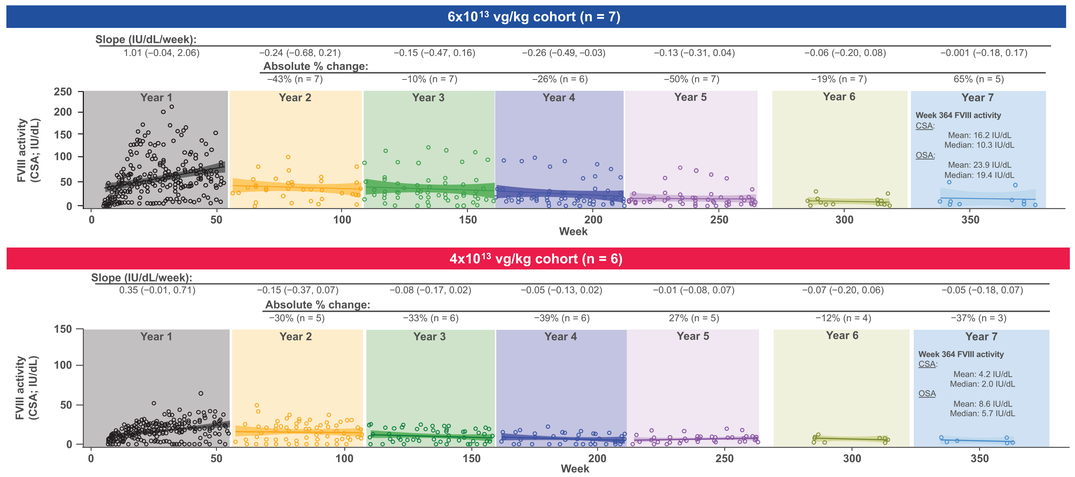
FVIII activity

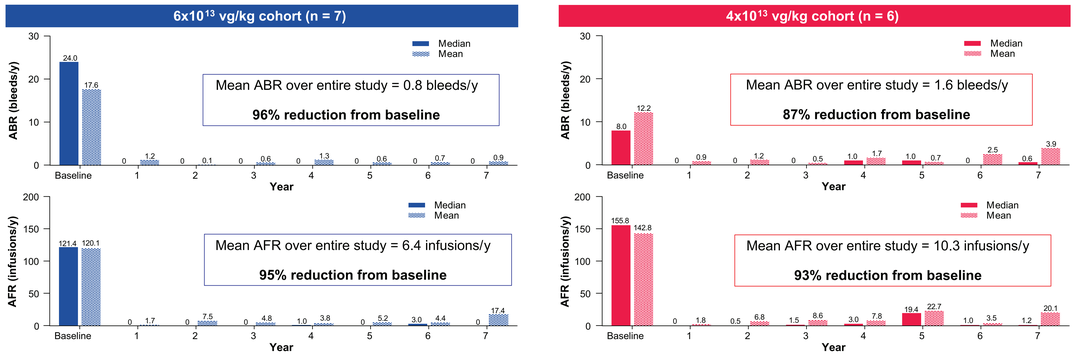
FVIII activity per CSA across the trial



CSA, chromogenic substrate assay; FVIII, factor FVIII; OSA, one-stage assay.

Hemostatic efficacy

- Overall, 5 of 7 participants in the 6x10^{13} cohort and 3 of 5 participants in the 4x10^{13} cohort remained off prophylaxis (1 participant in the 4x10^{13} cohort was lost to follow-up)[5]
- Reductions in treated bleeds and FVIII infusion rates were maintained across the trial



ABR, annualized bleeding rate; AFR, annualized FVIII infusion rate; FVIII, factor VIII.

Conclusions

- Safety outcomes following doses of 6x10^{13} and 4x10^{13} vg/kg valoctocogene roxaparvovec remained consistent with previous reports[1-5]
- The most common treatment-related AE in year 1 was ALT elevation; no treatment-related SAEs occurred after year 1
- No participants experienced thromboembolic events or developed FVIII inhibitors
- Despite the slow decline in FVIII levels, valoctocogene roxaparvovec continues to support hemostasis for the majority of participants
- Rates of treated bleeds declined 96% and 87% from baseline for the 6x10^{13} and 4x10^{13} vg/kg cohorts, respectively; FVIII infusion rates declined 95% and 93% from baseline

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