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

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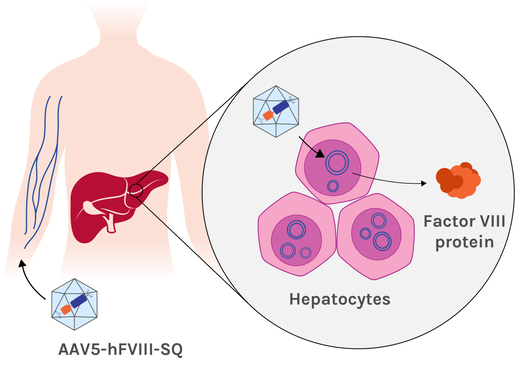
Background

- 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 (HA; 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 HA (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 characteristics

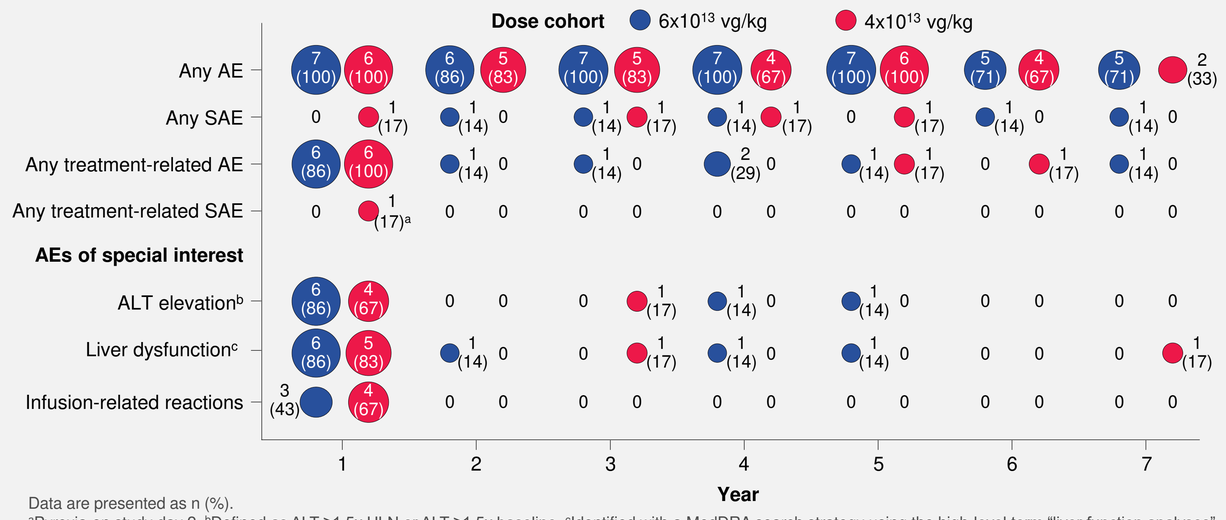
Baseline characteristic	6x10^{13} vg/kg cohort (n = 7)	4x10^{13} vg/kg cohort (n = 6)
Age, y		
Median (min, max)	30.0 (23.0, 42.0)	30.5 (22.0, 45.0)
ABR, bleeds/y		
Mean (SD)	17.6 (14.7)	12.2 (15.4)
Median (min, max)	24.0 (0.0, 40.0)	8.0 (0.0, 41.0)
AFR, infusions/y		
Mean (SD)	120.1 (45.9)	142.8 (48.8)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

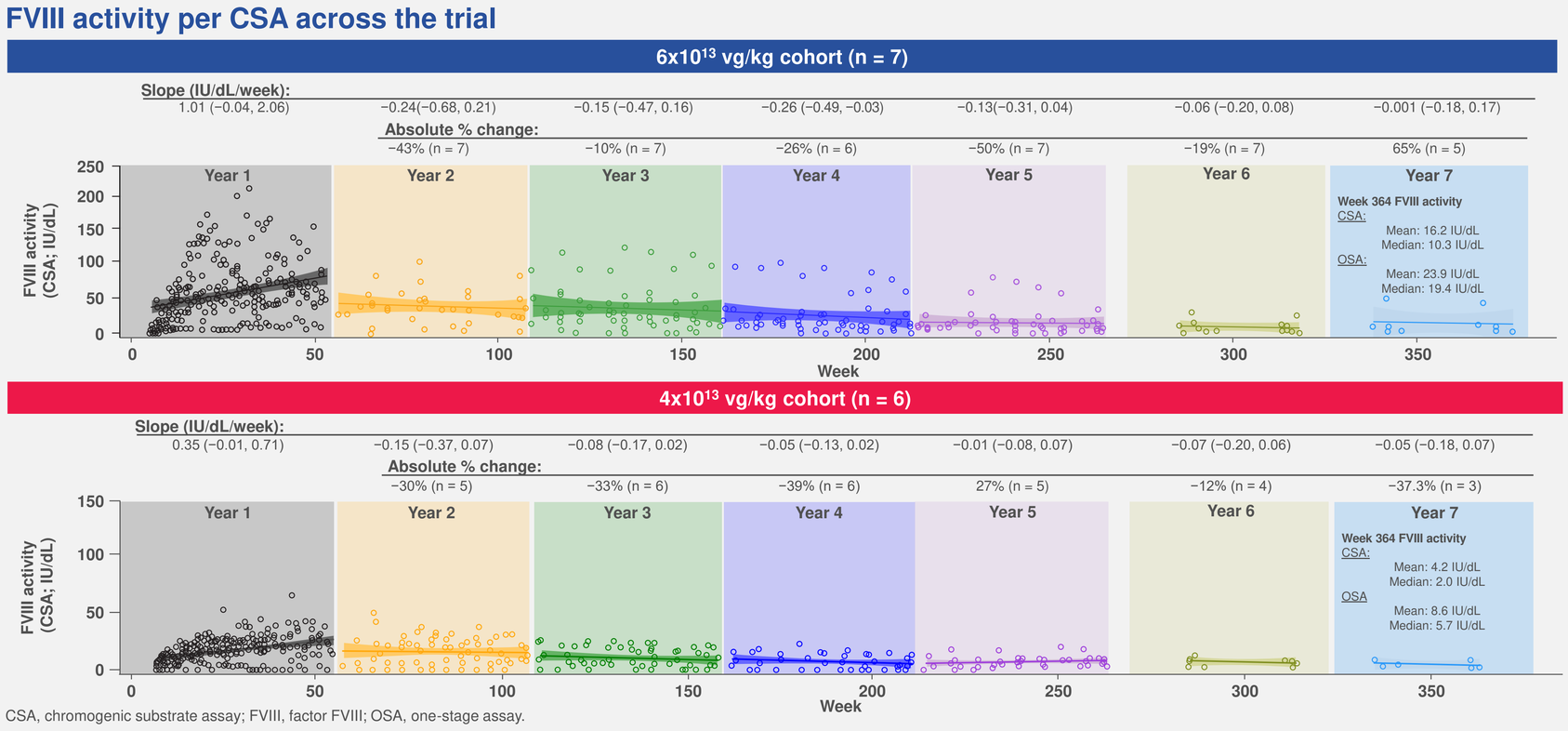
Summary of incidence of AEs in each year by cohort



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.

FVIII activity

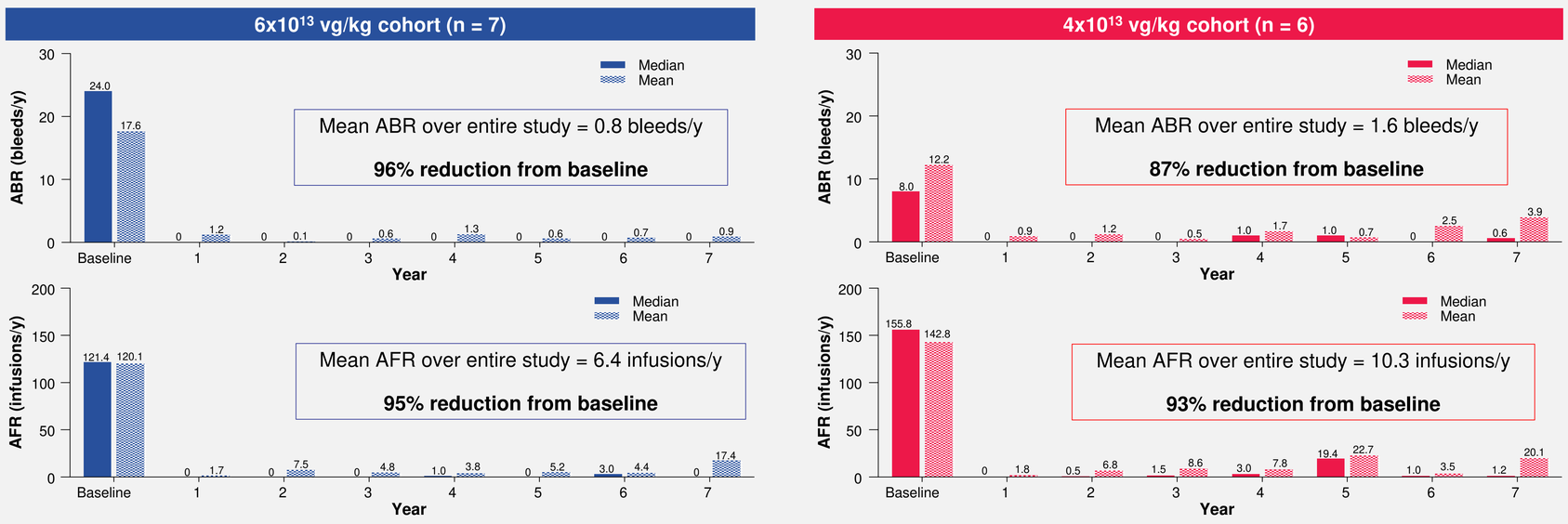
FVIII activity per CSA across the trial



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

References

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