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Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1

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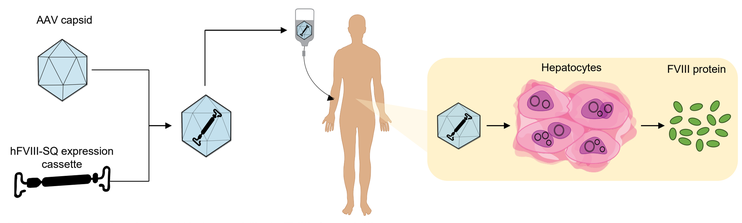
Introduction

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a factor VIII (FVIII) coding sequence that enables endogenous FVIII production in people with severe hemophilia A (HA; FVIII activity <1 IU/dL; **Figure 1**)[1,2]

Figure 1. Valoctocogene roxaparvovec for severe HA



AAV, adeno-associated virus; HA, hemophilia A; FVIII, factor VIII.

- In the global, open-label, phase 3 GENEr8-1 trial, participants who received 6x10^{13} vg/kg valoctocogene roxaparvovec achieved FVIII activity that provided improved protection from bleeds compared with FVIII prophylaxis over 104 weeks[1,2]
- Here, we present outcomes after 3 years post-gene transfer

Study design

Eligibility

- Adult men with severe HA (FVIII activity ≤1 IU/dL)
- Receiving routine FVIII prophylaxis at the time of enrollment
- No history of FVIII inhibitors or anti–adeno-associated virus serotype 5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

Study populations

- The intention-to-treat (ITT) population includes all participants who received an infusion of valoctocogene roxaparvovec
  - The ITT population included 112 participants who rolled over from a noninterventional study (270-902; rollover population) and 22 participants who enrolled directly
- The modified ITT (mITT) population excluded 2 participants who were human immunodeficiency virus-positive
  - A subset of the mITT population (n = 17) was dosed at least 4 years ago

Endpoints

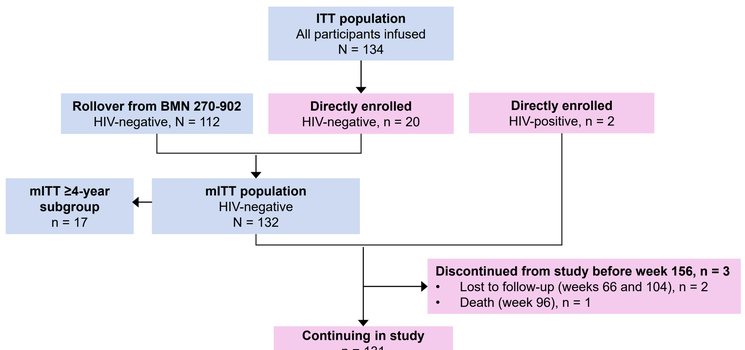
- Safety was assessed in the ITT population through recording of adverse events (AEs)
- FVIII activity was assessed in the mITT population by chromogenic substrate assay (CSA) and one-stage assay (OSA)
- Change from baseline in annualized bleeding rate (ABR) for treated bleeds was assessed in the rollover population
  - Bleeds were self-reported by participants
- Change from baseline in annualized FVIII utilization rate was assessed in the rollover population
- Health-related quality of life (HRQOL) was assessed in the mITT population
  - Haemophilia-Specific Quality of Life Questionnaire for Adults (Haemo-QOL-A)
  - Total Score and domain scores
  - EQ-5D-5L Utility Index Score
  - Hemophilia Activities List
  - Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Hemophilia Specific

Results

Participants

- At week 156, 131 of 134 participants who received valoctocogene roxaparvovec remained in the study (**Figure 2**)
- Median follow-up was 162.4 (range, 66.1–255.0) weeks

Figure 2. Participant disposition



HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified ITT.

Safety

- In year 3, alanine aminotransferase elevation was the most common AE (**Table 1**)
  - No participants initiated corticosteroids after week 104

Table 1. AEs in the ITT population

		ITT population			
Participants, n (%)		**Year 1 N = 134**	**Year 2 N = 134**	**Year 3 N = 132**	**Overall N = 132**
AEs		134 (100)	113 (84.3)	104 (78.8)	134 (100)
SAEs		21 (15.7)	6 (4.5)	9 (6.8)	32 (23.9)
Treatment-related AEs		123 (91.8)	28 (20.9)	13 (9.8)	123 (91.8)
Corticosteroid-related AEs		80 (59.7)	9 (6.7)	1 (0.8)	81 (60.4)
AEs of special interest	ALT elevation	114 (85.1)	40 (29.9)	31 (23.5)	121 (90.3)
	ALT elevation Grade ≥3	11 (8.2)	1 (0.7)	0	11 (8.2)
	Potential Hy's law case	0	0	0	0
	Infusion-related reactions[a]	12 (9.0)	0	0	12 (9.0)
	Systemic hypersensitivity	7 (5.2)	0	0	7 (5.2)
	Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	3 (2.2)
	Thromboembolic events	0	0	0	0
	Anti-FVIII neutralizing antibodies	0	0	0	0
	Malignancy (except non-melanoma skin cancer)	0	0	1 (0.8)	1 (0.7)

[a]Infusion-related reactions were defined as AEs occurring during valoctocogene roxaparvovec infusion or within 6 hours post-infusion. ALT, alanine aminotransferase; AE, adverse event; FVIII, factor VIII; ITT, intent to treat; SAE, serious AE.

- No treatment related serious AEs (SAEs) occurred in year 3
  - One case of B-cell acute lymphoblastic leukemia (B-ALL) was reported
- No participants developed FVIII inhibitors or thromboembolic events

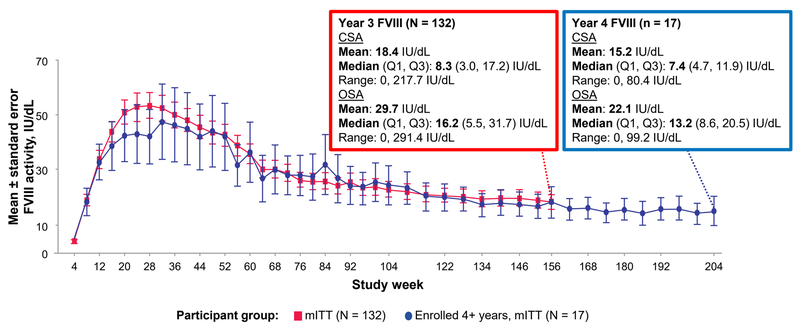
B-cell acute lymphoblastic leukemia

- One participant, dosed nearly 3 years ago with 6x10^{13} vg/kg valoctocogene roxaparvovec, was diagnosed via a bone marrow biopsy with an SAE of B-ALL
- Genetic testing and whole genome sequencing were performed on leukemic and healthy blood cells
  - A known driver mutation for B-ALL was detected in 85% of bone marrow cells via standard-of-care genetic workup
  - Extremely low levels of valoctocogene roxaparvovec vector DNA were found in 5 cell populations that underwent genomic analysis, with the lowest levels in tumor-containing samples
  - No vector-host integration sites were identified in any samples that underwent whole genome sequencing
- Based on these analyses, valoctocogene roxaparvovec was very unlikely to have played a role in the development of B-ALL in this study participant

FVIII activity

- FVIII activity persisted at hemostatic levels for up to 3 years in the mITT population and up to 4 years in the subset of mITT participants who were dosed at least 4 years ago (**Figure 3**)

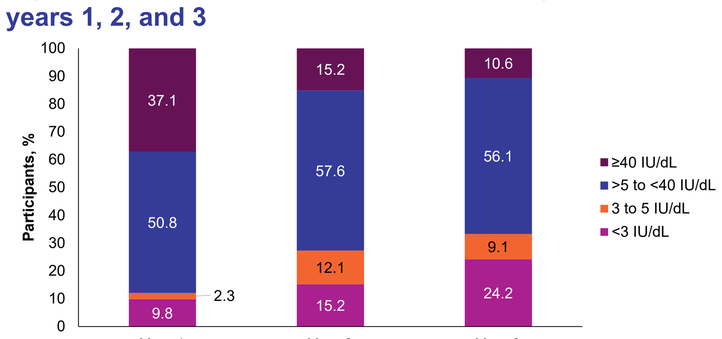
Figure 3. FVIII activity over time in the mITT population



For participants who discontinued the study, missing FVIII values post-discontinuation were imputed to be 0 IU/dL through the data cutoff date for the analysis. CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intent-to-treat; OSA, one-stage assay; Q, quartile.

- At year 3, more than half of participants had FVIII activity from >5 to <40 IU/dL per CSA (**Figure 4**)

Figure 4. Distribution of median FVIII activity at the end of years 1, 2, and 3

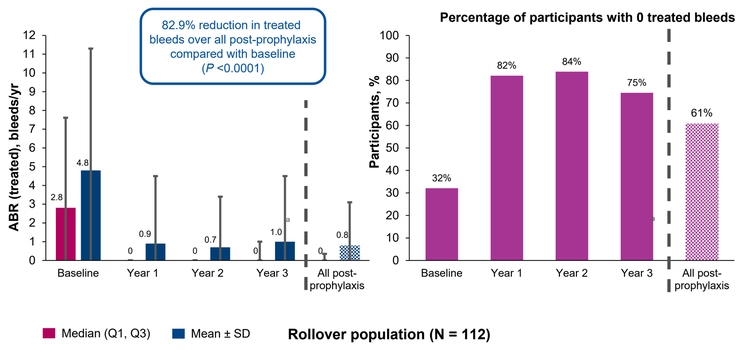


Values for participants who discontinued were imputed as 0 IU/dL. FVIII, factor VIII; mITT, modified intention-to-treat.

Bleeds

- During year 3 and during the entire post-prophylaxis period, mean ABR for treated bleeds was lower and the proportion of participants with 0 treated bleeds remained higher compared with baseline (**Figure 5**)

Figure 5. Mean and median ABR for treated bleeds in the rollover population (left) and proportion of rollover participants with 0 treated bleeds (right)

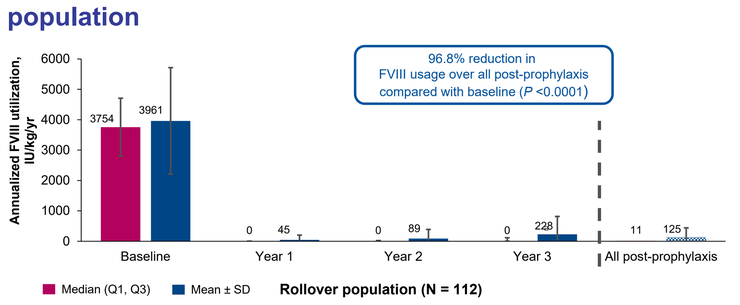


Missing data were not imputed. [a]Year 3 data were based on N = 110 due to participants who discontinued from the study. ABR, annualized bleeding rate; SD, standard deviation; Q, quartile.

Exogenous FVIII use

- Annualized FVIII utilization was reduced during year 3 and during the entire post-prophylaxis period compared with baseline (**Figure 6**)

Figure 6. Annualized exogenous FVIII use in the rollover population

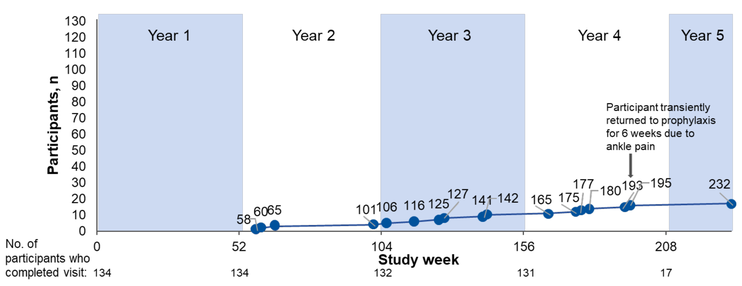


Missing data were not imputed. [a]Year 3 data were based on N = 110 due to participants who discontinued from the study. FVIII, factor VIII; Q, quartile; SD, standard deviation.

Return to prophylaxis

- To date, 17 participants have resumed prophylaxis (**Figure 7**)

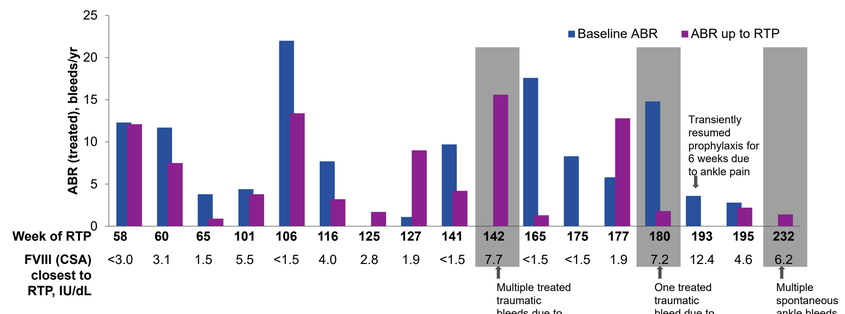
Figure 7. Timing of return to prophylaxis after receiving gene therapy in the ITT population



Participants who discontinued the study were not considered as returning to prophylaxis. Prophylaxis was defined as a FVIII infusion categorized as "usual FVIII prophylaxis" administered at least once a week for ≥4 consecutive weeks or ≥2 emicizumab injections in 1 month.
FVIII, factor VIII; ITT, intent-to-treat.

- The decision to return to prophylaxis was multifactorial and based on bleeds, physical activity, and personal preference (**Figure 8**)

Figure 8. ABR (treated) at baseline and up to return to prophylaxis and FVIII activity

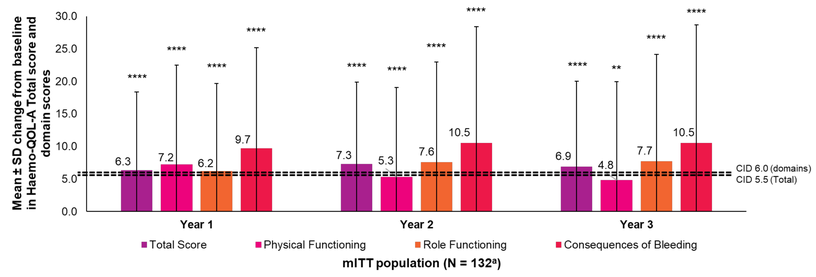


Prophylaxis was defined as a FVIII infusion categorized as "usual FVIII prophylaxis" administered at least once a week for ≥4 consecutive weeks or ≥2 emicizumab injections in one month. ABR, annualized bleeding rate; CSA, chromogenic substrate assay; FVIII, factor VIII; RTP, return to prophylaxis.

HRQOL

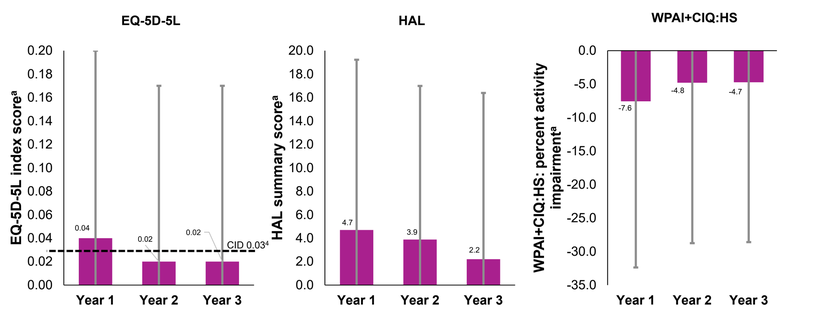
- Change in mean Haemo-QOL-A Total Score from baseline was 6.9, which exceeds the anchor-based clinically important difference of 5.5[3] (**Figure 9**)

Figure 9. Change from baseline in Haemo-QOL-A Total Score and domain scores



**P <0.01; ****P <0.0001 based on a 2-sided t-test against 0.
[a]Change from baseline in Haemo-QOL-A Total Score and domain score results are based on available data at each time point, which may differ from the given N. Participants who resumed prophylaxis were excluded, and missing data were not imputed. CID are per Quinn J, et al. *Patient Relat Outcome Meas*. 2022;13:169-80.
CID, clinically important difference; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; mITT, modified intent-to-treat; SD, standard deviation.

Figure 10. Change from baseline in EQ-5D-5L Utility Index Score (left), HAL summary score (middle), and WPAI+CIQ:HS (right)



[a]Mean ± SD change from baseline.
[b]Change from baseline results are based on available data at each time point, which may differ from the given N value. Missing data were not imputed.
CID, clinically important difference; HAL, Hemophilia Activities List; mITT, modified intent-to-treat; SD, standard deviation; WPAI+CIQ:HS, Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questionnaire: Hemophilia Specific.

Conclusions

- After 3 years of follow-up, the safety profile of valoctocogene roxaparvovec remains unchanged from previous reports
- Previously observed trends regarding change in FVIII activity were maintained
- A single infusion of valoctocogene roxaparvovec provided robust, durable hemostatic efficacy relative to FVIII prophylaxis over 3 years
- The decision to return to prophylaxis was influenced by FVIII activity levels, bleeds, desired physical activity level, and personal preferences

References

1. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25. **2.** Mahlangu J, et al. *N Engl J Med*. 2023;388(8):694-705. **3.** Quinn J, et al. *Patient Relat Outcome Meas*. 2022;13:169-80. **4.** Kaplan RM. *COPD*. 2005;2(1):91-7.

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