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Bleeding Outcomes in Participants With Factor VIII Activity <5 IU/dL Post-Gene Transfer in GENEr8-1

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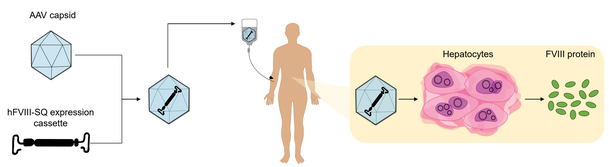
Introduction

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

Figure 1. Valoctocogene roxaparvovec for severe HA



AAV, adeno-associated virus; FVIII, factor VIII; HA, hemophilia A; hFVIII-SQ, human factor VIII, SQ variant.

- 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 156 weeks[1,2]
  - FVIII levels varied among participants despite receiving the same dose of valoctocogene roxaparvovec
  - The protective effect of low transgene-derived FVIII is unknown
- Here, we determined the clinical outcomes for participants with low FVIII 3 years post-gene transfer

Methods

Eligibility

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

Outcomes

- FVIII activity was assessed by chromogenic substrate assay (CSA) and one-stage assay (OSA)
  - The lower limit of quantification was 1.5 IU/dL (previously 3.0 IU/dL) for CSA and 1.0 IU/dL for OSA
  - For participants who resumed prophylaxis, the valid FVIII measurement closest to, but not after, return to prophylaxis is reported
  - Presented FVIII activity at a visit week is the median value in the 4- or 6-week window around the target date
  - Week 156 FVIII activity was imputed as 0 for participants who discontinued; other missing FVIII measurements (eg, if prophylaxis was resumed before week 156) were imputed as the smaller of the median values in the adjacent visits before or after week 156
- Bleeds were self-reported during baseline and after cessation of regular FVIII prophylaxis (post-prophylaxis period; scheduled for week 4 post-infusion)
- Return to prophylaxis was defined per protocol as usual FVIII prophylaxis administered ≥1 time/week for ≥4 consecutive weeks or ≥2 emicizumab injections/month
- Outcomes are reported for up to 156 weeks

Results

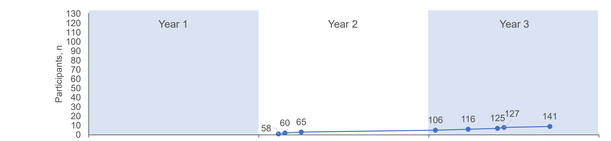
Participants with FVIII activity <5 IU/dL at week 156

- Of 134 participants who received an infusion of valoctocogene roxaparvovec (intent-to-treat [ITT] population), 131 completed the week 156 visit
- At week 156, 46 of 134 (34.3%) ITT participants had median FVIII activity <5 IU/dL (range, 0 to 4.9 IU/dL)

Participants who resumed prophylaxis

- Of the 46 participants with FVIII activity <5 IU/dL at week 156, 8 resumed prophylaxis before week 156 (**Figure 2**)
  - Week of return to prophylaxis ranged from week 58–141

Figure 2. Timing of return to prophylaxis



Prophylaxis was defined as an 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.

- These 8 participants had observed FVIII activity between <1.5 and 4.5 IU/dL per CSA temporally proximal to return to prophylaxis; 5 of 8 had median FVIII activity of 0 IU/dL at week 156 (**Figure 3**)
- For 2 of 8 (25.0%) participants who resumed prophylaxis before week 156, treated annualized bleeding rate (ABR) was higher during the post-prophylaxis period up to return to prophylaxis than at baseline; annualized FVIII utilization (AFU) was lower during the post-prophylaxis period than at baseline for 8 of 8 (100%) participants

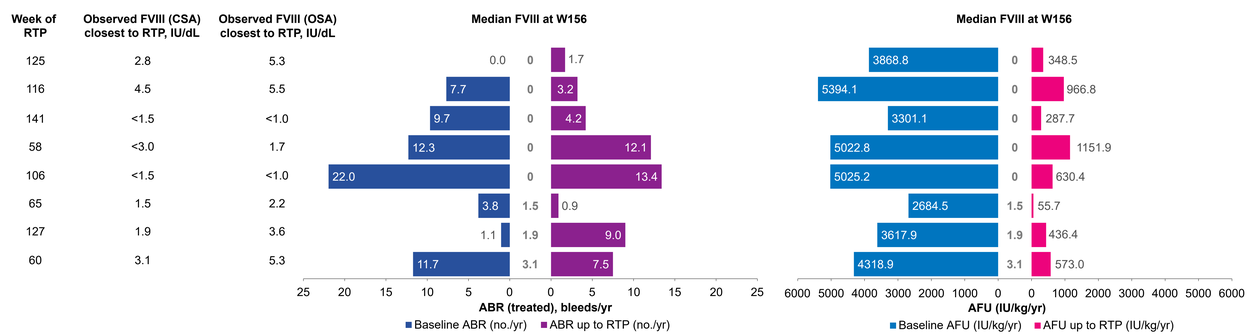
Participants who did not return to prophylaxis

- The remaining 38 participants with week 156 FVIII activity <5 IU/dL who did not resume prophylaxis by week 156 had median FVIII activity between 0 and 4.9 IU/dL per CSA at week 156 (**Figure 4**)
- Treated ABR and AFU were higher post-prophylaxis up to week 156 compared with baseline for 5 of 38 (13.2%) and 0 of 38 participants, respectively, who did not resume prophylaxis before week 156
- Most of the 38 participants who did not RTP before week 156 had lower ABR for treated bleeds compared with baseline, low post-prophylaxis ABRs for treated bleeds, or no substantial treated spontaneous bleeds
- Decisions to not RTP were multifactorial and based on participant-investigator shared decision-making

Conclusions

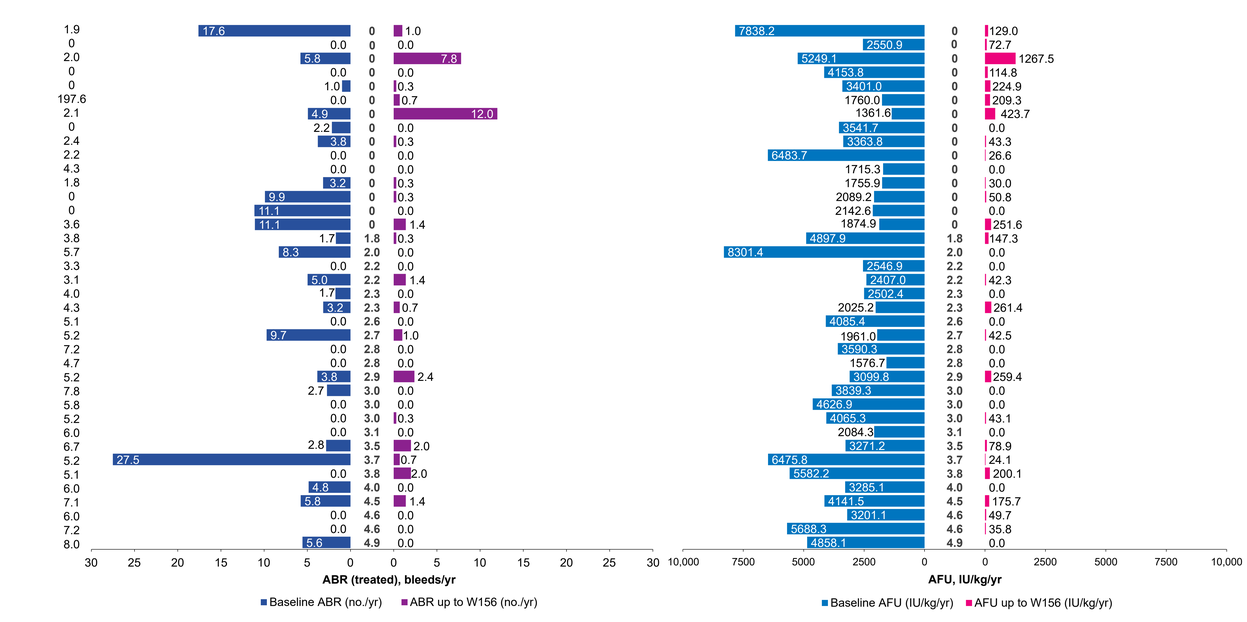
- Although most participants with low FVIII activity had low bleeding rates, early return to prophylaxis may indicate a lack of treatment effect on ABR
- AFU was not a predictor of return to prophylaxis before week 156
- The individual decision to RTP was multifactorial and influenced by FVIII activity, bleeding rates, desired physical activity levels, and personal preferences

Figure 3. ABR and AFU for participants who resumed prophylaxis before W156



ABR for treated bleeds and AFU at baseline and post-prophylaxis up to return to prophylaxis for ITT participants with W156 FVIII activity <5 IU/dL who resumed prophylaxis before W156. The valid FVIII measurement closest to RTP, but not after, was plotted. Median FVIII activity at W156 was imputed as the smaller of the median values in the adjacent visits before or after W156, or as 0 IU/dL if the measurements were below the LLOQ.
ABR, annualized bleeding rate; AFU, annualized FVIII utilization; CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantitation; OSA, one-stage assay; RTP, return to prophylaxis; W, week.

Figure 4. ABR and AFU for participants who did not resume prophylaxis before W156



ABR for treated bleeds and AFU at baseline and post-prophylaxis up to W156 for ITT participants with W156 FVIII activity <5 IU/dL who did not resume prophylaxis before W156.
ABR, annualized bleeding rate; AFU, annualized FVIII utilization; CSA, chromogenic substrate assay; FVIII, factor VIII; ITT, intent-to-treat; OSA, one-stage assay; RTP, return to prophylaxis; W, week.

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.

Acknowledgements

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