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Results from the Taiwanese cohort in GENEr8-1: bleeding rates, factor VIII usage, quality of life and safety in severe hemophilia A patients after gene therapy

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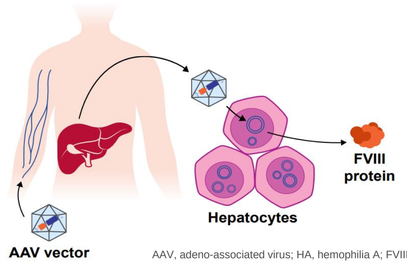
Introduction

- 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]
- In the global, open-label, phase 3 GENEr8-1 trial (NCT03370913), 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 in the Taiwanese cohort by reporting an exploratory analysis of the bleeding rate, annualized FVIII usage, infusion rates, quality of life and safety

Figure 1. Valoctocogene roxaparvovec for severe HA



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

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 originally from Taiwan (n = 10)**

Endpoints

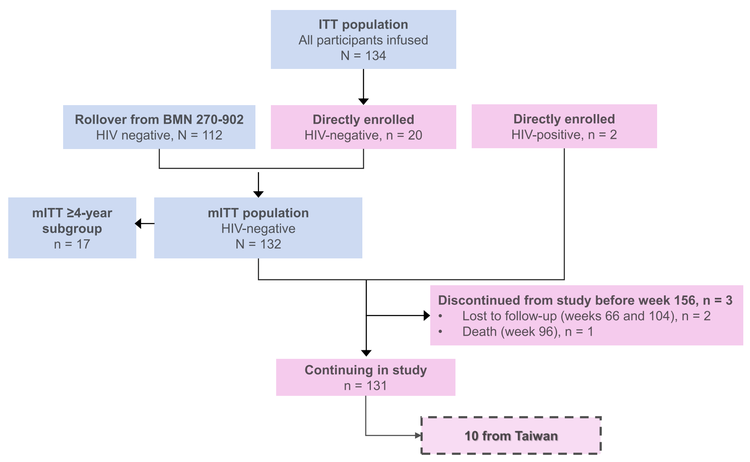
- Safety was assessed through recording of any grade 3 or above adverse events (AEs)
- Change from baseline in annualized bleeding rate (ABR) for treated bleeds
- Change from baseline in annualized FVIII utilization rate
- Health-related quality of life (HRQOL):
  - EQ-5D-5L Utility Index Score

Results

Participants

- At week 156, 10 participants from Taiwan who received valoctocogene roxaparvovec remained in the study (**Figure 2, Table 1**)

Figure 2. Participant disposition



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

Table 1. Demographics characteristics

Participants	Overall N = 10
Age (years), mean (SD)	37.2 (14.9)
Weight (kg), mean (SD)	71.7 (14.1)
Number of target joints, n (%)	
0	4 (40.0)
1	4 (40.0)
2	0
>3	2 (20.0)

Safety and corticosteroid use

- In year 3, AEs grade ≥3 were reported in 3 participants (30%) (**Table 2**)
- No treatment-related AEs or serious AEs (SAEs) grade ≥3 occurred in year 3
- No participants developed FVIII inhibitors
- The median duration of corticosteroid use was 136 days with a mean total dose of corticosteroid courses per subject of 3,499 mg (**Table 3**)

Table 2. AEs grade ≥3 in the Taiwanese cohort in 3 years post-gene transfer

Participants, n (%)	Overall N = 10
AE grade ≥3	3 (30)
Events	
Alanine aminotransferase increased	1 (10)
Coronary artery disease	1 (10)
Dyspnea	1 (10)
Macular hole	1 (10)
Pneumonia cytomegaloviral	1 (10)
Retinal detachment	1 (10)

Table 3. Corticosteroid therapy for ALT elevation within 3 years of follow-up in the Taiwanese cohort

Participants, n (%)	Overall N = 10
Subjects with any corticosteroid use, n (%)	5 (50.0)
Duration on days of corticosteroid courses per subject, mean ± SD	136.0 ± 71.0
Total dose on mg of corticosteroid courses per subject, mean ± SD	3,499.0 ± 1,283.9

FVIII activity levels

- FVIII activity levels presented with an initial rise to a peak around 6 months post-gene transfer, followed by a gradual decline (**Table 4**)

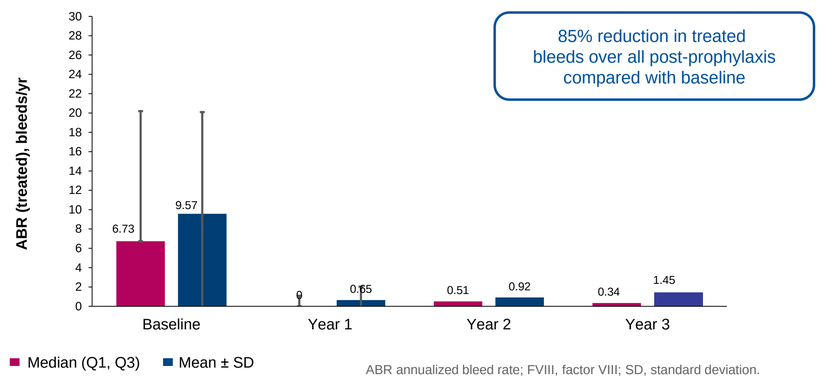
Table 4. FVIII activity levels (CSA) within 3 years of follow-up in the Taiwanese cohort

FVIII activity levels (IU/dL)	Week 23-26 (N = 10)	Week 49-52 (N = 10)	Year 2 (N = 10)	Year 3 (N = 10)	Year 3 mITT (N = 132)
<5	0 (0%)	0 (0%)	1 (10%)	3 (30%)	33%
5~14.9	0 (0%)	0 (0%)	2 (20%)	3 (30%)	36%
15~39.9	1 (10%)	5 (50%)	6 (60%)	3 (30%)	20%
≥40	9 (90%)	5 (50%)	1 (10%)	1 (10%)	11%

Bleeds

- During year 3 and during the entire post-prophylaxis period, mean ABR for treated bleeds was lower (**Figure 3**)

Figure 3. Mean and median ABR for treated bleeds

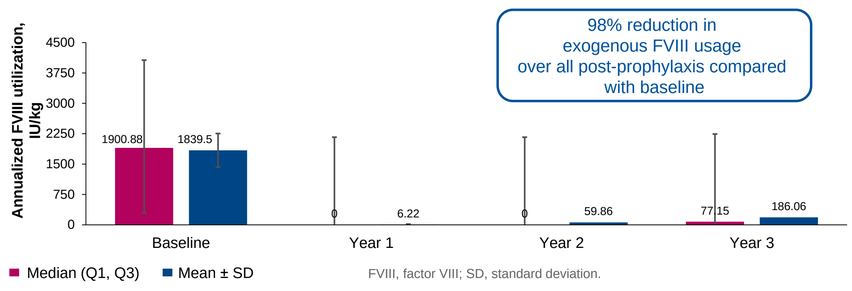


ABR annualized bleed rate; FVIII, factor VIII; SD, standard deviation.

Exogenous FVIII use

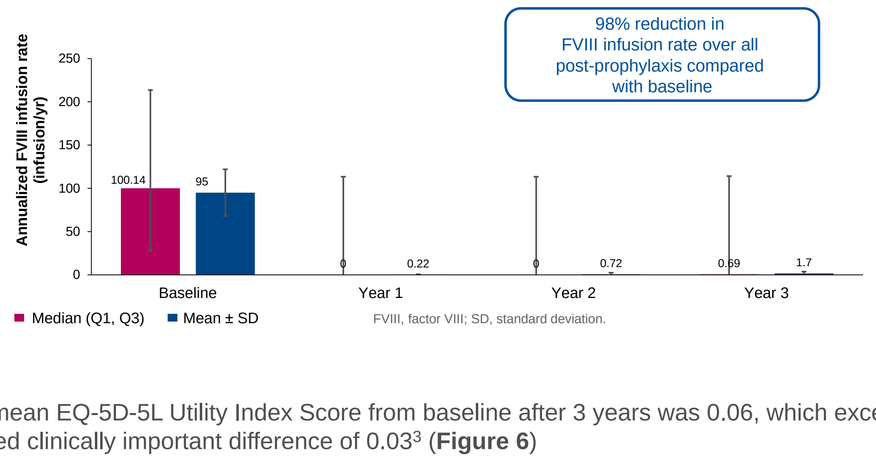
- Annualized FVIII utilization was reduced during year 3 and during the entire post-prophylaxis period compared with baseline (**Figure 4**)

Figure 4. Annualized exogenous FVIII use in the Taiwanese population



FVIII, factor VIII; SD, standard deviation.

Figure 5. Annualized FVIII infusion rate, infusions/year in the Taiwanese population

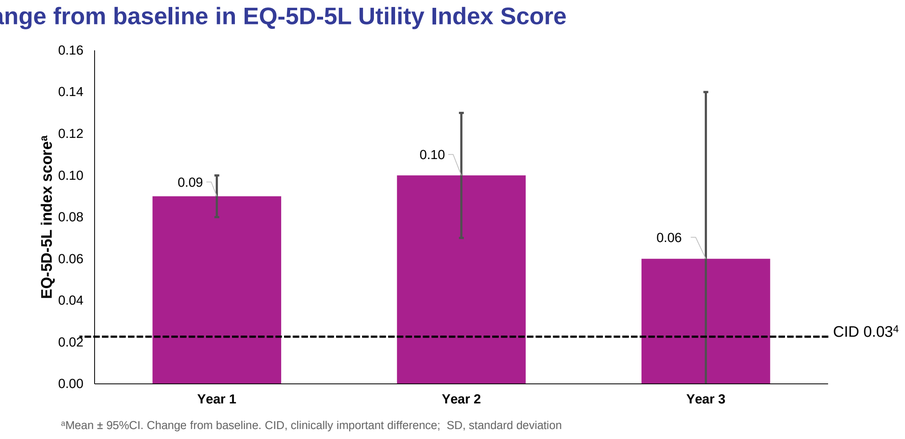


FVIII, factor VIII; SD, standard deviation.

HRQOL

- Change in mean EQ-5D-5L Utility Index Score from baseline after 3 years was 0.06, which exceeds the anchor-based clinically important difference of 0.03[3] (**Figure 6**)

Figure 6. Change from baseline in EQ-5D-5L Utility Index Score



[a]Mean ± 95%CI. Change from baseline. CID, clinically important difference; SD, standard deviation

Conclusions

- In Taiwanese patients, valoctocogene roxaparvovec provided robust hemostatic efficacy relative to FVIII prophylaxis for more than 3 years, with improvements in QOL and stable safety
- Clinically relevant improvements in EQ-5D-5L index score were observed
- The robust hemostatic efficacy relative to FVIII prophylaxis and the safety profile promoted by valoctocogene roxaparvovec in the Taiwanese cohort is not distinct from the one previously observed in the mITT population

References

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Disclosures

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