Final GENEr8-1 results confirm enduring efficacy, safety, and quality of life improvements 5 years after valoctocogene roxaparvovec gene transfer

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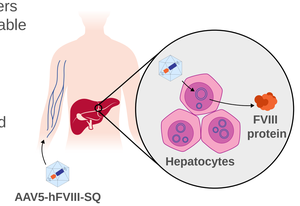
Introduction

Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is a liver-directed gene therapy that transfers a factor VIII (FVIII) coding sequence to enable FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1-4]
- In the open-label, phase 3 GENEr8-1 trial, participants who received 6x10^{13} vg/kg valoctocogene roxaparvovec had improved protection from bleeds compared with regular FVIII prophylaxis over 4 years[1-4]
- **Here, we present the final outcomes of the phase 3 GENEr8-1 trial 5 years after gene transfer**



FVIII, factor VIII.

Methods

Study design

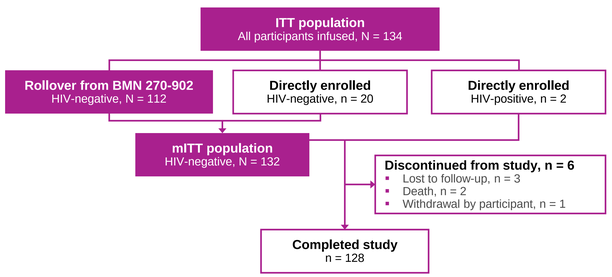
Eligibility	Endpoints
▪ Adult men with severe hemophilia A (FVIII ≤1 IU/dL) ▪ Previously receiving FVIII prophylaxis ▪ No history of FVIII inhibitors or anti-AAV5 antibodies ▪ No significant liver dysfunction, fibrosis, or cirrhosis	▪ FVIII activity (mITT population) ▪ Change from baseline (rollover population) – Annualized bleeding rate – Annualized FVIII infusion rate ▪ Safety (ITT population) ▪ Quality of life (mITT population)

The ITT population included all participants who received an infusion of valoctocogene roxaparvovec. The mITT population included all HIV-negative participants in the ITT population. The rollover population included all participants who rolled over from 207-902, a noninterventional study.
AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; ITT, intention-to-treat; LTFU, long-term follow-up; mITT, modified ITT; W, week.

Results

Participant disposition

- Overall, 128 of 134 participants completed the 5-year study



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

Baseline characteristics

Baseline characteristics	Rollover N = 112	mITT N = 132	ITT N = 134
Age, years, mean (range)	31.8 (19–70)	31.4 (18–70)	31.7 (18–70)
Race, n (%)			
White	78 (69.6)	94 (71.2)	96 (71.6)
Asian	17 (15.2)	19 (14.4)	19 (14.2)
Black or African American	14 (12.5)	15 (11.4)	15 (11.2)
Hawaiian or Pacific Islander	1 (0.9)	1 (0.8)	1 (0.7)
Not provided	2 (1.8)	3 (2.3)	3 (2.2)
Hispanic or Latino ethnicity, n (%)	5 (4.5)	7 (5.3)	7 (5.2)
BMI, kg/m^2, mean ± SD	25.2 ± 4.7	25.3 ± 4.6	25.3 ± 4.6
Medical history, n (%)			
Hepatitis B	17 (15.2)	18 (13.6)	20 (14.9)
Hepatitis C	33 (29.5)	39 (29.5)	41 (30.6)
HIV	0	0	2 (1.5)
Number of problem joints,[a] n (%)			
0	82 (73.2)	95 (72.0)	97 (72.4)
1	13 (11.6)	17 (12.9)	17 (12.7)
2	9 (8.0)	9 (6.8)	9 (6.7)
3	6 (5.4)	8 (6.1)	8 (6.0)
>3	2 (1.8)	3 (2.3)	3 (2.2)

[a]Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.
BMI, body mass index; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified ITT; SD, standard deviation.

Safety (intention-to-treat [ITT] population)

- In year 5, no new safety signals were reported
  - Low-grade, transient alanine aminotransferase (ALT) elevations remained the most common adverse event)
  - There were no treatment-related serious adverse events
- Across the entire trial, there were no treatment-related malignancies
- No participants developed FVIII inhibitors or experienced thromboembolic events

Participants, n (%)		Year 1 (N = 134)	Year 2 (N = 134)	Year 3 (N = 132)	Year 4 (N = 131)	Year 5 (N = 129)	All follow-up (N = 134)
AEs		134 (100.0)	112 (83.6)	104 (78.8)	98 (74.8)	102 (79.1)	134 (100.0)
SAEs		21 (15.7)	6 (4.5)	9 (6.8)	11 (8.4)	4 (3.1)	37 (27.6)
Treatment-related AEs[a]		124 (92.5)	27 (20.1)	14 (10.6)	8 (6.1)	5 (3.9)	124 (92.5)
Glucocorticoid-related AEs[a]		81 (60.4)	10 (7.5)	1 (0.8)	2 (1.5)	0 (0.0)	82 (61.2)
AEs of special interest	ALT elevation	116 (86.6)	39 (29.1)	31 (23.5)	49 (37.4)	52 (40.3)	125 (93.3)
	ALT elevation ≥grade 3	10 (7.5)	1 (0.7)	0	0	0	10 (7.5)
	Potential Hy's law case	0	0	0	0	0	0
	Infusion-related reactions[b]	12 (9.0)	0	0	0	0	12 (9.0)
	Systemic hypersensitivity	7 (5.2)	0	0	0	0	7 (5.2)
	Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	0	0	3 (2.2)
	Thromboembolic events	0	0	0	0	0	0
	Anti-FVIII neutralizing antibodies	0	0	0	0	0	0
	Malignancy (except nonmelanoma skin cancer)	0	0	1 (0.8)	0	0	1 (0.7)

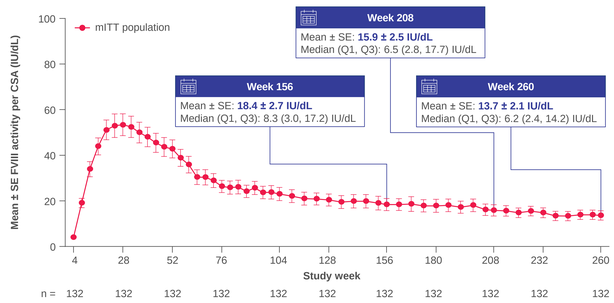
[a]Treatment-related and glucocorticoid-related AEs were assessed by the investigator.
[b]Infusion-related reactions were defined as AEs occurring during valoctocogene roxaparvovec infusion or within 6 hours post-infusion.
AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; SAE, serious AE.

ALT elevation and glucocorticoid use

- In year 5, 63 (48.8%) participants had an ALT elevation >1.5x baseline and 23 (17.8%) participants had an ALT elevation above the upper limit of normal
- Since year 2, no participants have used glucocorticoids to manage ALT elevations

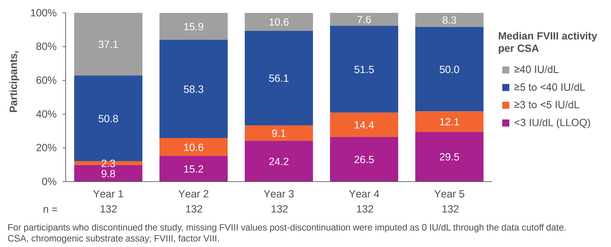
FVIII activity (modified ITT [mITT] population)

FVIII activity was nearly stable compared to year 4



For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intention-to-treat; Q, quartile; SE, standard error.

Most participants remain in the mild hemophilia range



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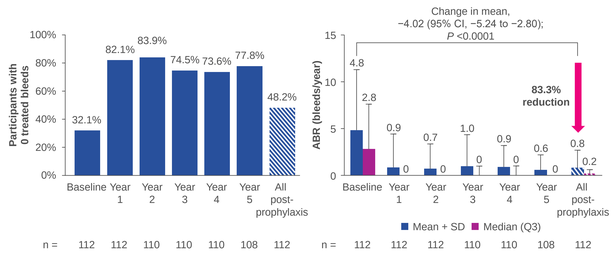
CSA, chromogenic substrate assay; FVIII, factor VIII.

Annualized bleeding rate (rollover population)

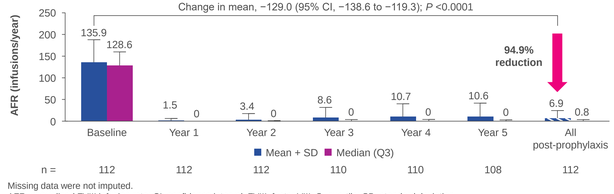
Reduction in treated bleeds was maintained over 5 years



Missing data were not imputed.
ABR, annualized bleeding rate; CI, confidence interval; Q, quartile; SD, standard deviation.

Annualized FVIII infusion rate (rollover population)

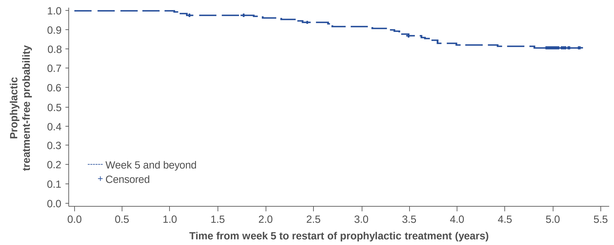
Reduction of FVIII infusion rate was maintained over 5 years



Missing data were not imputed.
AFR, annualized FVIII infusion rate; CI, confidence interval; FVIII, factor VIII; Q, quartile; SD, standard deviation.

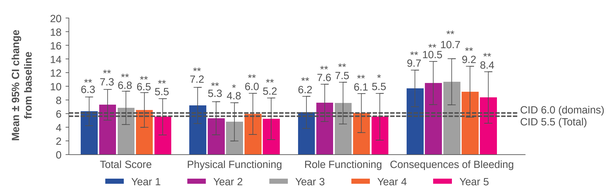
Return to prophylaxis (ITT population)

- Only 1 additional participant resumed prophylaxis in year 5 beyond those previously reported; 81.3% (109/134) of participants remain off prophylaxis
- Of 25 participants who resumed prophylaxis, 68% had a lower treated annualized bleeding rate before resuming vs baseline



Health-related quality of life (mITT population)

Consistent improvements in Haemo-QOL-A were maintained



*P <0.05; **P <0.001 based on a 2-tailed t-test against the null hypothesis of no change from baseline. Data after resuming prophylaxis were excluded.
CI, confidence interval; CID, clinically important difference; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults.

Conclusions

FVIII activity was maintained

- After 5 years, mean FVIII activity was in the mild hemophilia range (chromogenic, 13.7 IU/dL; one-stage, 24.0 IU/dL)

Durable hemostatic efficacy

- The rate of treated bleeds and FVIII infusions was reduced compared with FVIII prophylaxis 5 years after infusion, consistent with durable hemostatic efficacy

Most (81.3%) participants continue to remain off prophylaxis and experience a favorable impact on treatment burden 5 years after infusion

- Since the last data cut, only 1 additional participant resumed prophylaxis in year 5

For participants who did not return to prophylaxis, clinically meaningful improvements in health-related quality of life were maintained over 5 years

No new safety signals

- Across the trial, the most common adverse event was mild, transient ALT elevation

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;388:694–705.
3. Madan B, et al. *J Thromb Haemost*. 2024;22:1880–93. **4.** Leavitt A, et al. *Res Pract Thromb Haemost*. 2024;8:e102615.

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