CR13

Gene therapy in hemophilia A: The impact of valoctocogene roxaparvovec on patient outcomes – initial results from Patient Reported Outcomes, Burdens and Experiences (PROBE) from the GENEr8-1 trial

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Introduction

- Valoctocogene roxaparvovec (adeno-associated virus 5 [AAV5] human factor VIII [FVIII], SQ variant; AAV5-hFVIII-SQ) transfers a FVIII coding sequence that enables endogenous FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)
- In GENEr8-1, an open-label phase 3 trial, participants achieved FVIII activity providing improved protection from bleeding compared with prophylaxis for 52 and 104 weeks[1,2]
- Here, we describe patient-reported changes from the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire, a tertiary endpoint for the GENEr8-1 clinical trial

Methods

Phase 3 GENEr8-1 study design

- Participants received a single infusion of $6x10^{13}$ vg/kg valoctocogene roxaparvovec; quality of life (QOL) assessments were performed at baseline and weeks 52 and 104

Eligible participants

- Adult men with severe hemophilia A (FVIII ≤1 IU/dL)
- Receiving routine FVIII prophylaxis at the time of enrollment
- No history of FVIII inhibitors or AAV5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

Endpoints

- Safety
- FVIII activity
- Change from baseline during post-prophylaxis
  - Annualized bleeding rate
  - Annualized FVIII utilization rate
- QOL

PROBE questionnaire

- Contains hemophilia-specific outcomes that assess health status and QOL that are relevant to people with hemophilia[3]
  - Pain, independence, education, employment, family life, and mobility
  - Developed by people with hemophilia
- Designed with the intent to collect data to improve treatment of hemophilia and assess outcomes beyond bleeding frequency
- Total score and item-specific changes from baseline were calculated at weeks 52 and 104 post–valoctocogene roxaparvovec infusion
  - The total PROBE score ranges from 0 to 1 and the maximum score of 1 indicates the best health-related QOL (HRQOL)

Results

- Overall, 134 participants received valoctocogene roxaparvovec (**Table 1**); PROBE scores were completed at baseline by 124/134 (93%), at week 52 by 129/132 (98%), and at week 104 by 126/132 (95%) participants

Table 1. Participant characteristics and disposition

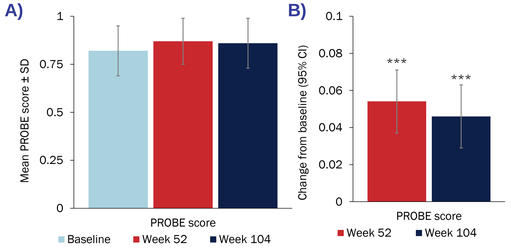
Baseline characteristics[1]	ITT (N = 134)
Age, years, mean ± SD	31.7 ± 10.3
Race, n (%)	
White	96 (71.6)
Asian	19 (14.2)
Black or African American	15 (11.2)
Hawaiian or Pacific Islander	1 (0.7)
Not provided	3 (2.2)
Hispanic or Latino ethnicity, n (%)	7 (5.2)
BMI, kg/m², mean ± SD	25.3 ± 4.6
Medical history, n (%)	
Hepatitis B	20 (14.9)
Hepatitis C	41 (30.6)
HIV	2 (1.5)
Number of problem joints,[a] n (%)	
0	97 (72.4)
1	17 (12.7)
2	9 (6.7)
3	8 (6.0)
>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, intent-to-treat; SD, standard deviation.

Results

- PROBE total scores improved at weeks 52 and 104 (**Figure 1**)

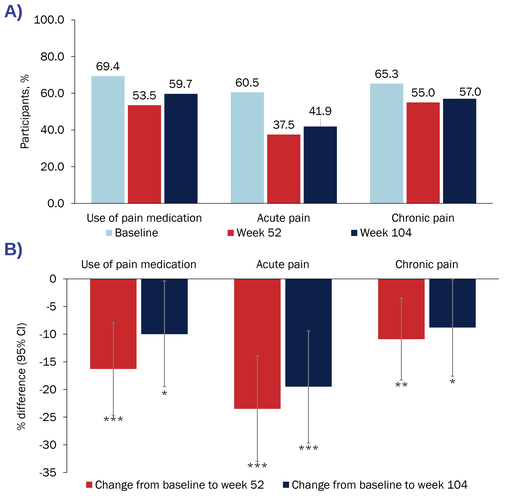
Figure 1. PROBE total scores. A) Mean PROBE score, and B) change from baseline



***P <0.001 compared to baseline using a linear mixed model. Data are mean ± SD or change from baseline (95% CI).
CI, confidence interval; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.

- Outcomes for pain improved from baseline (**Figure 2**)

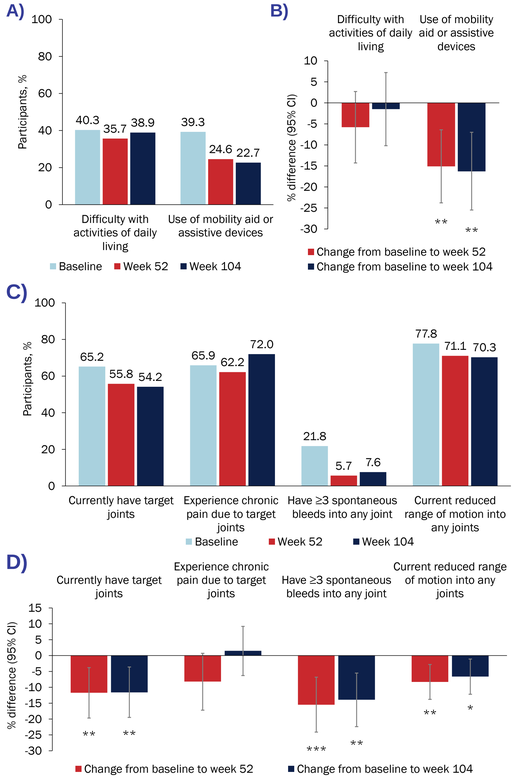
Figure 2. Outcomes for pain: A) percent of participants, and B) change from baseline



*P <0.05, **P <0.01, ***P <0.001 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

- Outcomes for activities of daily living and mobility improved (**Figure 3A**, **3B**)
- Outcomes for joint health improved (**Figure 3C**, **3D**)

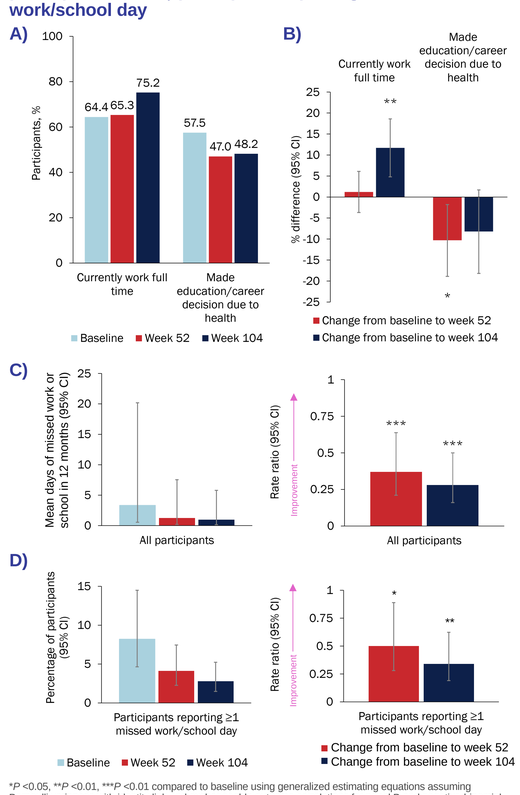
Figure 3. Outcomes for activities of daily living and mobility: A) percent of participants, and B) change from baseline; outcomes for joint health: C) percent of participants, and D) change from baseline



*P <0.05, **P <0.01, ***P <0.001 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

- Outcomes for work and school improved, and number of missed work or school days per person-year due to health-related reasons improved (**Figure 4**)

Figure 4. Outcomes for work and school: A) percent of participants, and B) change from baseline; outcomes for number of missed work or school days for C) all participants, and D) participants reporting ≥1 missed work/school day



*P <0.05, **P <0.01, ***P <0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations for panel B and negative-binomial regression models for panels C and D. Each person contributed 1 person-year.
CI, confidence interval.

Conclusions

- Valoctocogene roxaparvovec led to quantifiable changes in patient-reported outcomes 2 years after a single infusion
  - Improvements were observed in health and QOL outcomes
- PROBE score changes were generally consistent with EQ-5D-5L and Haemo-QOL-A results
- Further studies are needed to define a threshold for clinically meaningful changes in PROBE scores
- There are ongoing efforts to further interpret and identify underlying mechanisms for these results

References

1. Ozelo M, Mahlangu J, Pasi KJ, et al. *N Engl J Med*. 2022;386(11):1013-25. **2.** Mahlangu J, Kaczmarek R, von Drygalski A, et al. *N Engl J Med*. 2023;388(8):694-705. **3.** Skinner MW, Chai-Adisaksopha C, Curtis R, et al. *Pilot Feasibility Stud*. 2018;4:58.

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Disclosures

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