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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Presentation learning objectives

- Understand application of a novel, hemophilia-specific, patient-reported outcome measure in a clinical trial involving a phase 3 gene therapy
- Understand the effect of a one-time infusion of valoctocogene roxaparvovec on health outcomes, burdens, and experiences identified as important by people living with hemophilia
- Understand the future direction for generation of real-world evidence using patient-centered outcomes with novel hemophilia treatments

Disclosures for Mark W. Skinner

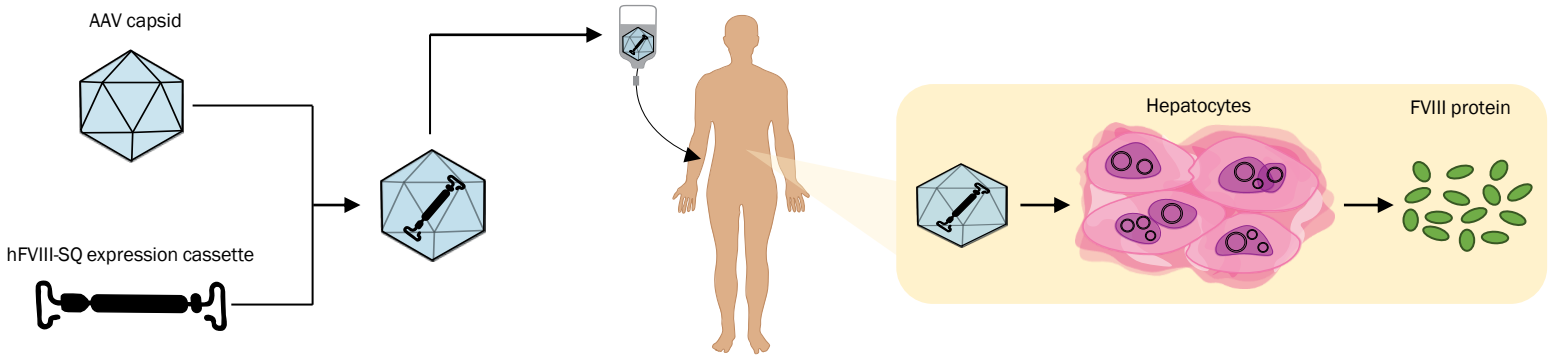
I have the following potential conflict(s) of interest to report:

- **Research support:** Institution received research support for the PROBE study, an independent investigator-initiated research project
- **Director, officer, employee:** ICER, Institute for Policy Advancement Ltd., McMaster University, NORD, Patient Outcomes Research Group Ltd., and WFH USA
- **Honoraria:** Institution received honoraria or fees for attending advisory boards or educational presentations from Bayer, BioMarin Pharmaceutical Inc., Novo Nordisk, Roche/Genentech, Pfizer, and Takeda
- **Advisory committee:** Blue Cross Blue Shield, NHF MASAC, DSMB - Pfizer, Spark
- **Consultant:** NHF and Sanofi

DSMB, Data and Safety Monitoring Board; ICER, Institute for Clinical and Economic Review; PROBE, Patient Reported Outcomes, Burdens and Experiences; MASAC, Medical and Scientific Advisory Council; NHF, National Hemophilia Foundation; NORD, National Organization for Hemophilia Disorders; WFH, World Federation of Hemophilia.

Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence that enables endogenous FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1,2]
- 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 PROBE questionnaire, a tertiary endpoint for the GENEr8-1 clinical trial



AAV, adeno-associated virus; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant; PROBE, Patient Reported Outcomes, Burdens and Experiences.

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.

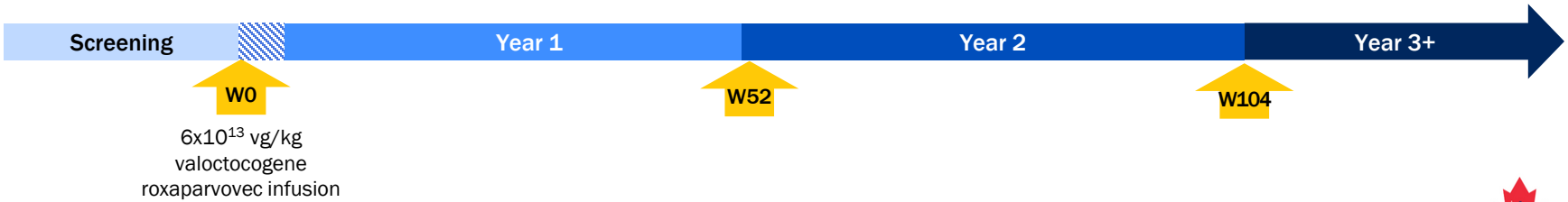
Phase 3 GENEr8-1 study design

Eligible participants

- Adult men with severe hemophilia A (FVIII ≤1 IU/dL)
- Receiving routine FVIII prophylaxis at time of enrollment
- No history of FVIII inhibitors or anti-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



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; QoL, quality of life; W, week.

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.

PROBE questionnaire

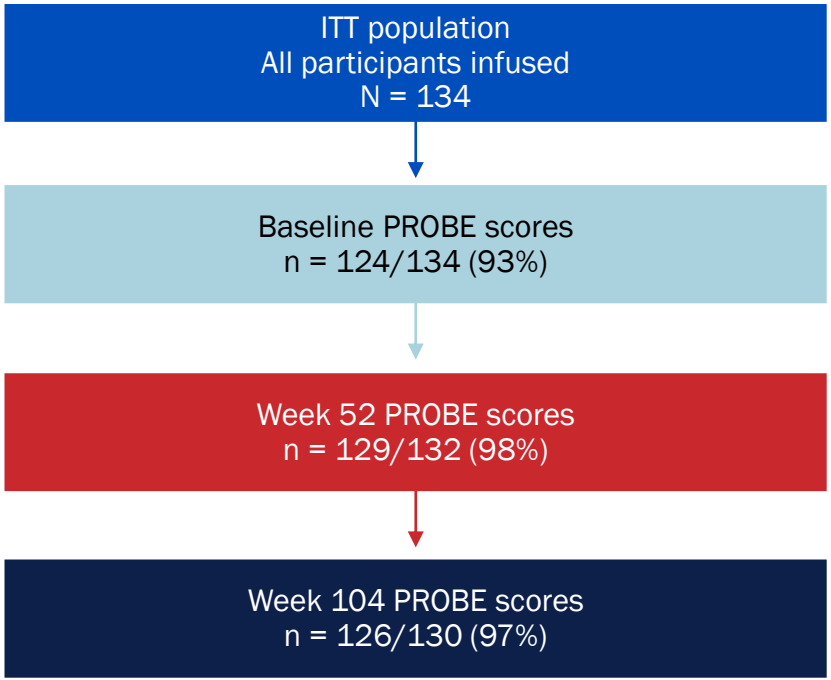
- Contains hemophilia-specific outcomes that assess health status and quality of life that are relevant to people with hemophilia[1]
  - Pain, independence, education, employment, family life, and mobility
  - Developed by people with hemophilia
- Designed with the intent to collect data to improve treatment 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 HRQoL

HRQoL, Health-related quality of life; PROBE, Patient Reported Outcomes, Burdens and Experiences.

1. Skinner MW, et al. *Pilot Feasibility Stud*. 2018;4:58.

Participant characteristics and disposition

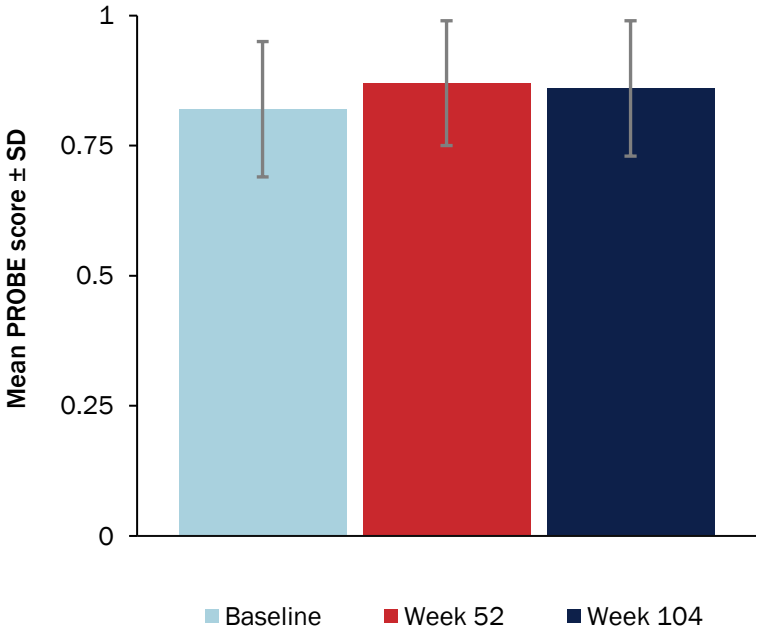
Baseline characteristics[1]	ITT (N = 134)
Age, years, mean ± SD	31.7 ± 10.3
Race, n (%)	
White	96 (71.6)
Asian	19 (14.2)
Black or African American	15 (11.2)
Hawaiian or Pacific Islander	1 (0.7)
Not provided	3 (2.2)
Hispanic or Latino ethnicity, n (%)	7 (5.2)
BMI, kg/m^2, mean ± SD	25.3 ± 4.6
Medical 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)

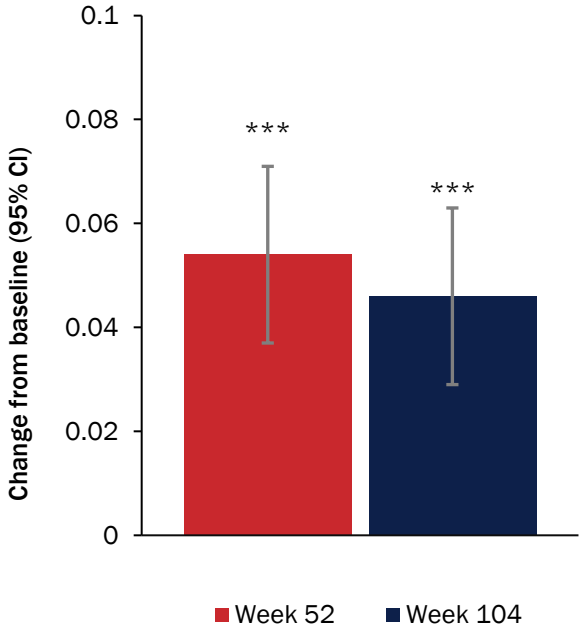


[a]Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.
BMI, body mass index; HIV, human immunodeficiency virus; ITT, intent-to-treat; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.

1. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25.

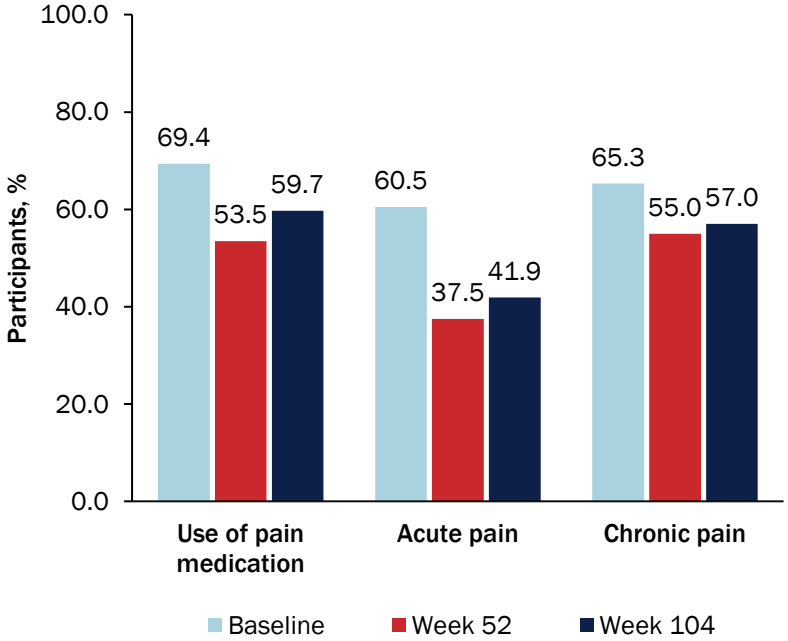
PROBE total scores improved at weeks 52 and 104

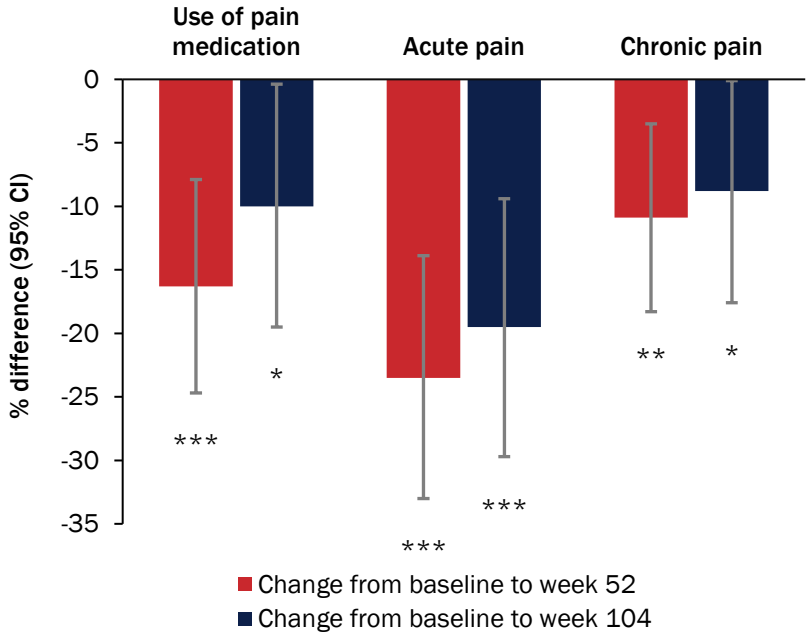




****P* <0.001 compared to baseline using a linear mixed model. Data are mean ± SD or change from baseline (95% CI).
CI, confidence interval; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.

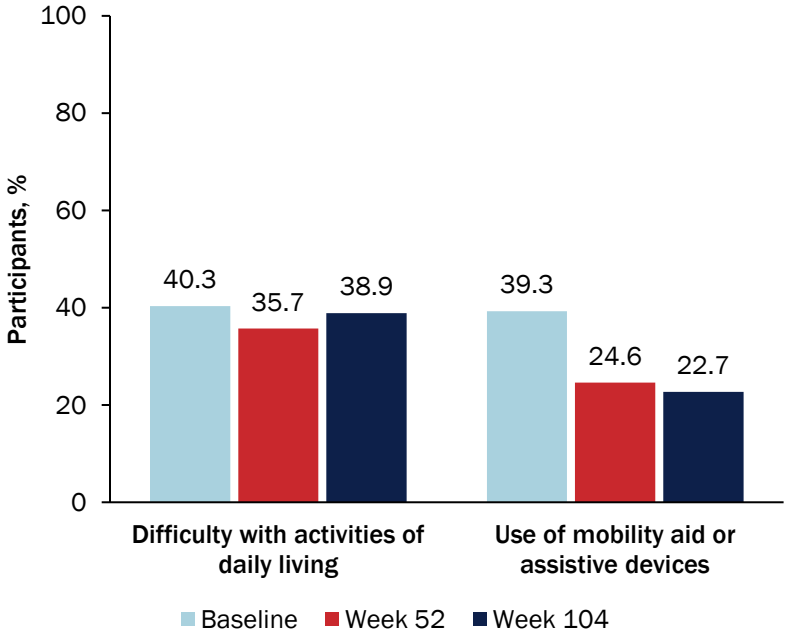
Outcomes for pain improved

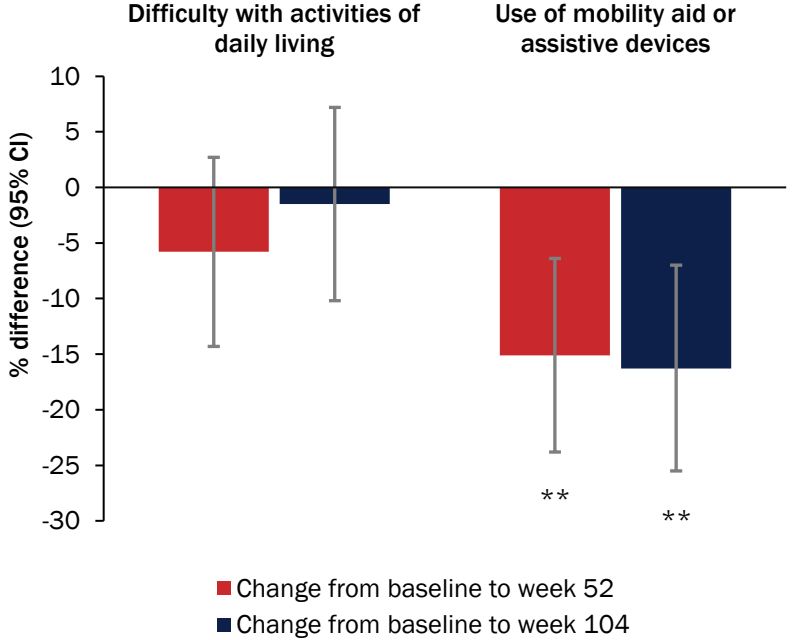




*P <0.05, **P <0.01, ***P <0.001 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

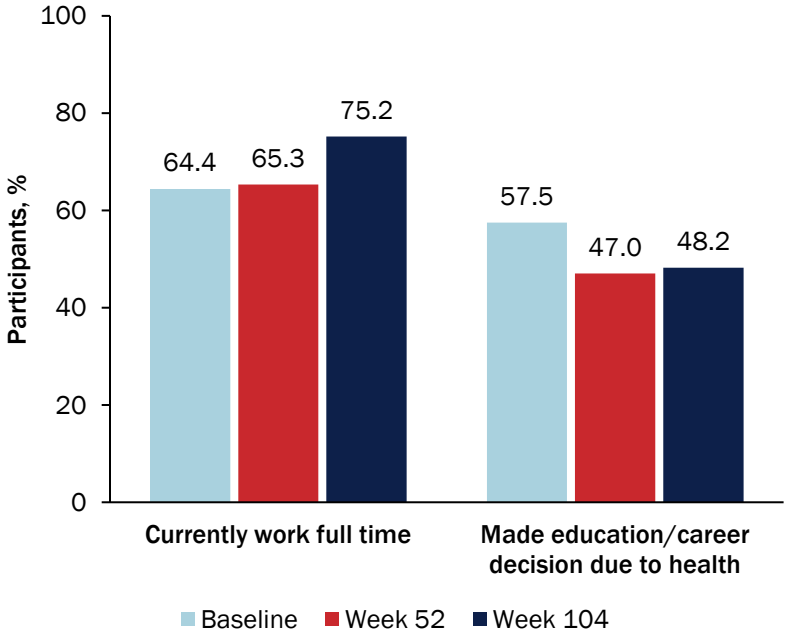
Outcomes for activities of daily living and mobility improved

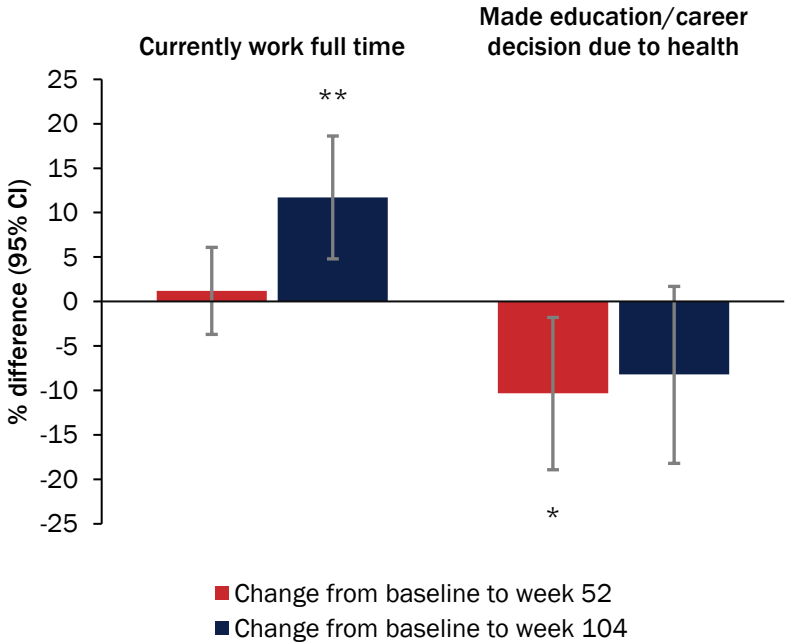




**P <0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

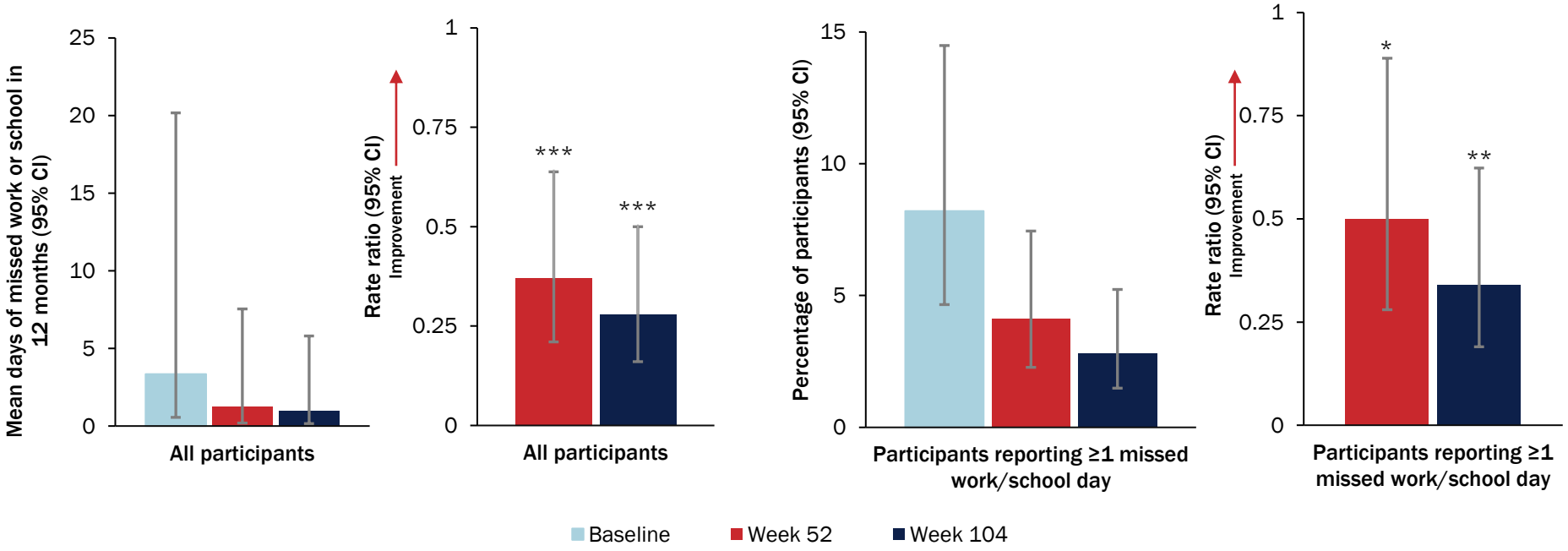
Outcomes for work and school improved





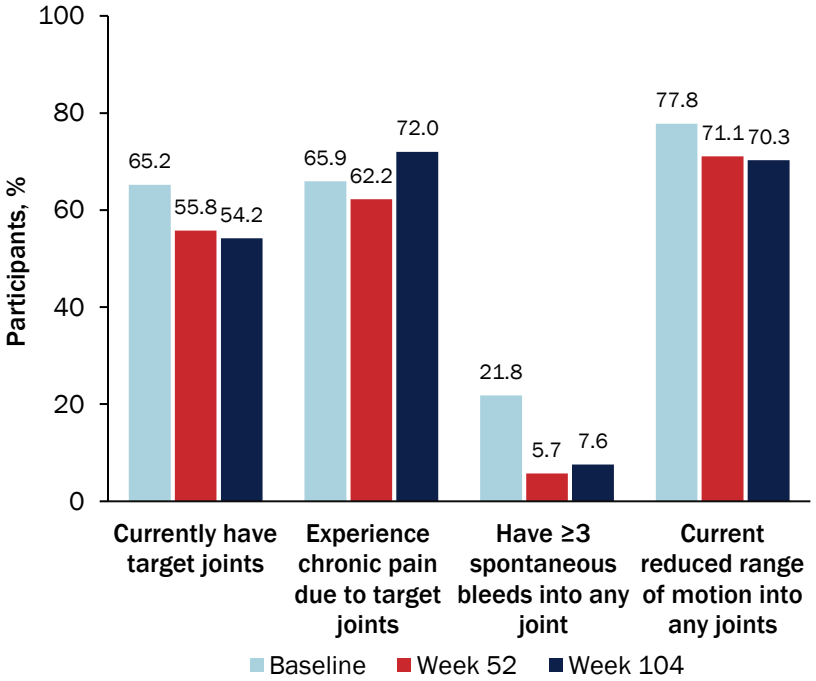
*P <0.05, **P <0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.
CI, confidence interval.

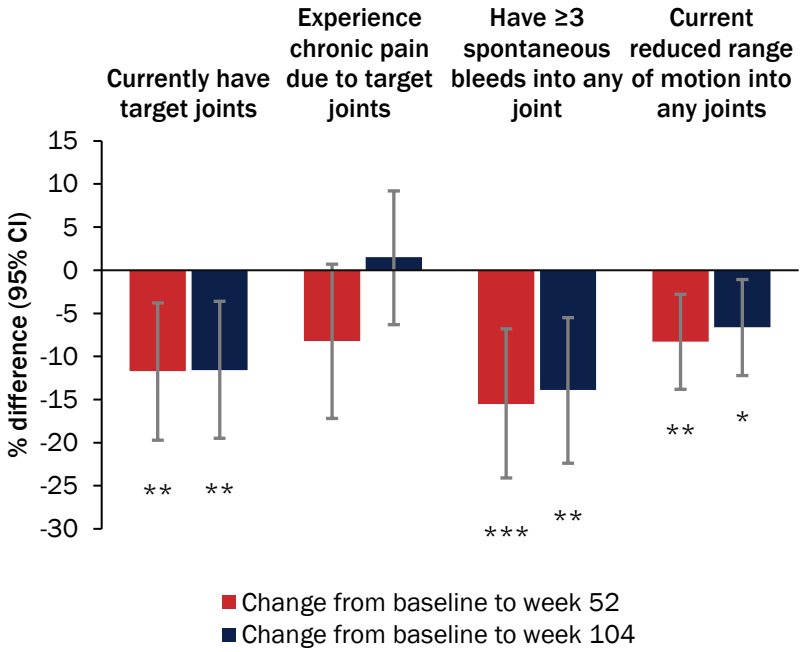
Outcomes for number of missed work or school days per person-year due to health-related reasons improved



*P <0.05, **P <0.01, ***P <0.01 compared to baseline using negative-binomial regression models. Each person contributed 1 person-year.
CI, confidence interval.

Outcomes for joint health improved





*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.

Conclusion

- Valoctocogene roxaparvovec led to quantifiable changes in patient-reported outcomes 2 years after a single infusion
  - Improvements were observed in health and quality of life 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

Haemo-QoL- A, haemophilia-specific quality of life questionnaire for adults; PROBE, Patient Reported Outcomes, Burdens and Experiences.

Acknowledgments

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  - Brian O'Mahony
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  - Er Chen
  - Milad Karimi
  - Mohit Jain
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PROBE, Patient Reported Outcomes, Burdens and Experiences.