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Initial results of the impact of valoctocogene roxaparvovec on pain occurrence and interference: Insights from PROBE

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Introduction

- People with severe hemophilia A commonly present with intramuscular bleeding and hemarthrosis, leading to acute and chronic pain with an overall reduction in health-related quality of life
- Chronic pain was identified as an important core outcome to differentiate gene therapy from standard of care[1]
- The Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire was included in the phase 3, open-label, single-arm study (GENEr8-1) as a tertiary endpoint to assess the effect of a single 6x10[13] vg/kg dose of valoctocogene roxaparvovec on patient-reported health and life experiences[2]

Methods

- Here, we report results from the PROBE questionnaire for incidences of acute and chronic pain occurrences and interferences at baseline and week 104 post-gene therapy
- PROBE is a validated, hemophilia-specific, patient-reported outcomes questionnaire developed by people with hemophilia for people with hemophilia[1]
- While further validation to understand the performance of PROBE in this context of use is ongoing, this study summarized pain-related outcomes collected within the PROBE questionnaire

PROBE questionnaire pain-related questions

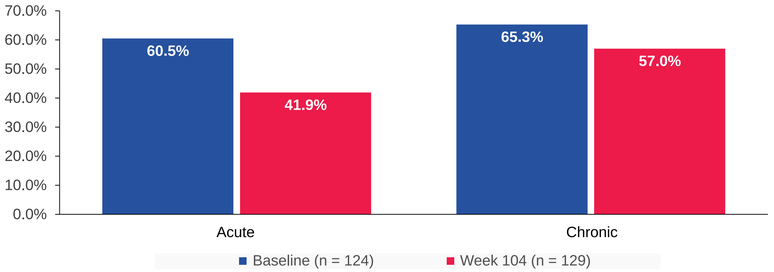
1. Any occurrence of acute and chronic pain (recall: 12 months)
   - "Acute pain" is defined as pain that arises in response to an event (like an injury or bleeding episode)
   - "Chronic pain" is defined as pain from a persistent cause; it can vary in frequency and intensity (like back pain, pain from sore joints, or arthropathy). "Chronic pain" does not include "acute pain"
2. Pain occurrence during 8 activities (walking, stair-climbing, nighttime, resting, weight bearing, playing, after falling/trauma, other)
3. Pain interference in 11 aspects of life (general activity, mood, walking ability, normal work, attending school, relations with others, sleep, enjoyment of life, playing/participating in sports/exercising, lifting, other)
4. Use and frequency of pain medication (not reported)
5. Chronic pain in target joints (not reported)

Results

Comparison of participants reporting chronic or acute pain at baseline and week 104

- Data were available for 124 participants at baseline and 129 at week 104
  - Intent-to-treat study population (N = 134; median age, 30.0; range, 18–70)
- Self-reported acute and chronic pain decreased post-gene therapy (**Figure 1**)
  - Acute pain decreased from 60.5% to 41.9%
  - Chronic pain decreased from 65.3% to 57.0%

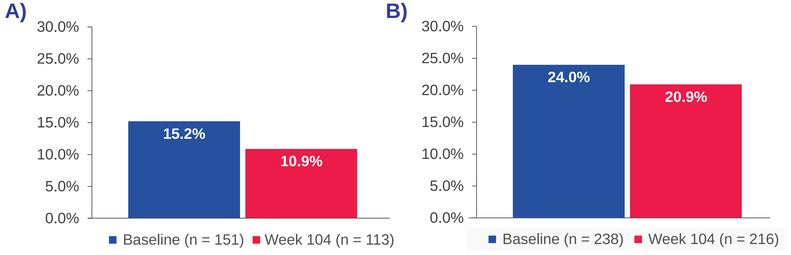
Figure 1. Percent of participants reporting chronic or acute pain at baseline and week 104



Aggregate instances of pain occurrence

- Aggregate instances of self-reported pain occurrence (8 activities including "Other"; **Figure 2**; **Table 1**)
  - Acute pain occurrence instances decreased from 151/992 (15.2%) to 113/1032 (10.9%)
  - Chronic pain occurrence instances decreased from 238/992 (24.0%) to 216/1032 (20.9%)

Figure 2. Comparison of participants reporting A) chronic and B) acute pain at baseline and week 104



Participants were allowed to select multiple options of pain interference or occurrence.

Table 1. Intra-patient comparison of pain occurrence

	Walking	Stair-climbing	Nighttime	Resting	Weight bearing	Play sport exercise	After fall trauma	Other	Aggregate
Intra-patient comparison of reported instances of acute pain occurrence									
% difference (95% CI)	−8.5 (−17.6, 0.6)	−6.3 (−13.7, 1.1)	−3.6 (−10.2, 3.0)	−0.4 (−6.2, 5.5)	−1.5 (−10.0, 7.1)	−0.4 (−8.3, 7.6)	−15.1 (−23.3, −6.8)	−0.3 (−6.5, 5.9)	**−4.7 (−8.7, −0.6)**
P-value	0.068	0.097	0.288	0.901	0.732	0.924	<0.001	0.929	**0.026**
Intra-patient comparison of reported instances of chronic pain occurrence									
% difference (95% CI)	−5.4 (−13.9, 3.0)	−0.5 (−9.4, 8.3)	−2.6 (−9.9, 4.7)	−5.1 (−12.6, 2.4)	−0.4 (−9.1, 8.3)	−4.8 (−12.8, 3.2)	−7.3 (−13.7, −0.9)	−2.6 (−6.8, 1.5)	**−3.7 (−7.8, 0.4)**
P-value	0.209	0.906	0.486	0.183	0.930	0.240	0.026	0.217	**0.073**

Pink color indicates intra-patient % difference >5%. Intra-personal incidences were compared between the 2 visits (% difference with 95% CI and *P*-value) using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations within participant visits nested in centers. Data from intermediate study visits were considered in the regression.
CI, confidence interval.

Aggregate instances of pain interference

- Aggregate instances of self-reported pain interference (11 activities including "Other"; **Figure 3**; **Table 2**)
  - Acute pain interference instances decreased from 294/1364 (21.6%) to 204/1419 (14.4%)
  - Chronic pain interference instances decreased from 332/1364 (24.3%) to 262/1419 (18.5%)

Figure 3. Aggregate instances of pain interference for A) acute pain, and B) chronic pain at baseline and week 104

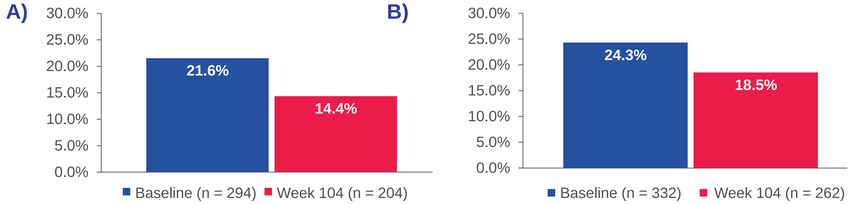


Table 2. Intra-patient comparison of pain interference

	Activity	Mood	Walking	Work	School	Relationships	Sleep	Enjoyment	Playing	Lifting	Other	Aggregate
Intra-patient comparison of reported instances of acute pain interference												
% difference (95% CI)	−7.4 (−17.4, 2.7)	−8.0 (−17.2, 1.2)	−10.3 (−20.8, 0.1)	−14.4 (−23.4, −5.4)	−1.6 (−4.7, 1.5)	1.2 (−3.8, 6.1)	−7.8 (−16.4, 0.8)	−10.3 (−19.2, −1.4)	−11.5 (−20.2, −2.8)	−10.3 (−19.4, −1.2)	−1.7 (−5.5, 2.2)	**−7.6 (−12.7, −2.5)**
P-value	0.151	0.088	0.052	0.002	0.312	0.647	0.076	0.023	0.010	0.026	0.394	**0.003**
Intra-patient comparison of reported instances of chronic pain interference												
% difference (95% CI)	−6.8 (−16.3, 2.7)	−8.0 (−17.1, 1.0)	−4.4 (−13.5, 4.7)	−10.5 (−20.3, −0.7)	−1.6 (−6.1, 2.8)	−0.2 (−5.2, 4.8)	−7.6 (−15.3, 0.1)	−9.9 (−18.4, −1.5)	−8.1 (−17.1, 0.9)	−14.0 (−23.0, −4.9)	¥	**−6.8 (−11.4, −2.3)**
P-value	0.163	0.082	0.341	0.036	0.466	0.936	0.054	0.021	0.077	0.003	¥	**0.003**

Pink color indicates intra-patient % difference >5%. Intra-personal incidences were compared between the 2 visits (% difference with 95% CI and *P*-value) using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations within participant visits nested in centers. Data from intermediate study visits were considered in the regression.
¥, model did not converge; CI, confidence interval.

Conclusions

- This analysis adds to previous findings from GENEr8-1 of the efficacy and safety of a single infusion of valoctocogene roxaparvovec relative to FVIII prophylaxis
- Pain is one of the core outcomes of importance to people with hemophilia
- Initial analysis of PROBE data demonstrates that valoctocogene roxaparvovec may be associated with a decrease in self-reported acute and chronic pain occurrence and interference with daily life in the study cohort
- The impact of gene therapy on pain, particularly chronic pain as demonstrated from PROBE, a hemophilia-specific tool, has important implications on treatment decision-making and continued disease management

References

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Acknowledgements

The authors wish to thank the participants in the GENEr8-1 study for their participation in the PROBE study data collection. Editorial support was provided by Tony Sallese, PhD, of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc.

Disclosures

MWS reports his institution received research support for the PROBE study, an independent investigator-initiated research project; he is a director, officer, or employee of Institute for Clinical and Economic Review, Institute for Policy Advancement Ltd., McMaster University, National Organization for Hemophilia Disorders, Patient Outcomes Research Group Ltd., and World Federation of Hemophilia USA; has received honoraria or fees for attending advisory boards or educational presentations from Bayer, BioMarin Pharmaceutical Inc., Novo Nordisk, Roche/Genentech, Pfizer, and Takeda; has served on advisory committees for Blue Cross Blue Shield, National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council, Pfizer (a Data and Safety Monitoring Board), and Spark; and has served as a consultant for NHF and Sanofi. **ER, MK,** and **MJ** are employees and stockholders of BioMarin Pharmaceutical Inc. **QI** reports nothing to disclose. **BOM** reports consulting fees from BioMarin Pharmaceutical Inc., and Freeline. **AK** is an employee of Patient Outcomes Research Group Ltd. **FG** reports his institution has received research funds from Novo Nordisk, Roche, Takeda, Bayer, Pfizer, BioMarin Pharmaceutical Inc., CSL, Freeline, Grifols, Octapharma, Sanofi, Spark, and Uniqure. **EC** is an employee of Institute for Policy Advancement Ltd.

Presented at the National Hemophilia Foundation Bleeding Disorders Conference 2023: August 17–19, National Harbor, Maryland