Impact of gene therapy on the hemophilia-free mind: Outcomes before and after valoctocogene roxaparvovec in GENEr8-1 trial participants

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Background

- A "hemophilia-free mind" has been described as freedom from or significant alleviation of the typical physical and psychosocial burdens associated with hemophilia. Attaining a hemophilia-free mind has been proposed as the aspirational aim for hemophilia care[1,2]
- Ten "dimensions" have previously been proposed to comprise the hemophilia-free mind framework: bleeding risk, joint pain, medication, blood-born infections, treatment efficacy, injection schedule, physical activity, travel, employment/education, and affected family members and carriers[1,2]
- Recent advances in the treatment of hemophilia, including one-time therapies such as gene therapy, are allowing people with hemophilia to experience extended periods of time where their minds are not preoccupied by their hemophilia[3,4]
- Currently, there is no dedicated assessment of the hemophilia-free mind in people with hemophilia A (PwHA). The aims of this study were to explore the relevance of the framework's dimensions to gene therapy and to define attainment or movement towards a hemophilia-free mind, specifically in relation to the assessments in the GENEr8-1 study of valoctocogene roxaparvovec in males with severe hemophilia A

Methods

- Two advisory boards comprised of clinicians, a technical expert in patient-reported outcomes (PROs), and a patient expert, were convened to discuss how data from the phase 3 GENEr8-1 study of hemophilia A gene therapy valoctocogene roxaparvovec could be interpreted within a hemophilia-free mind framework
- Advisory board 1 (Apr 2024) aimed to define an operational structure for the hemophilia-free mind framework in the context of clinical trials and treatment decision making for PwHA
- Advisory board 2 (Dec 2024) aimed to assess the gene therapy-specific hemophilia-free mind framework developed in the first advisory board, through its application to clinical and PRO assessments used in the GENEr8-1 study[5]
- Performance of the framework using 104-week data from the GENEr8-1 study was applied to a select set of measures and thresholds
  - Change in status of hemophilia-free mind was measured for each dimension by calculating the proportion of participants achieving the stated threshold at baseline and 104 weeks

Results

- Advisors recognized the need for new approaches to treatment decision-making in hemophilia A and were aligned that annualized bleeding rate cannot be relied upon alone to assess treatment efficacy
- It was emphasized that the hemophilia-free mind is a continuum, and that PwHA can have partial or complete freedom, attainment of which may change over time. It was considered important to acknowledge the interrelationship between alleviation of the physical symptoms of hemophilia A and psychological freedom
- Of the 10 proposed hemophilia-free mind dimensions, seven were considered relevant and measurable in gene therapy for hemophilia A using existing outcome measures. Two dimensions were considered not applicable to gene therapy, and one overlapped conceptually with other dimensions
- Advisors aligned on suitable outcome measures from the GENEr8-1 trial and corresponding thresholds for each relevant hemophilia-free mind dimension (**Table 1**)
- Applying these measures and thresholds to GENEr8-1 trial data, the proportion of participants achieving hemophilia-free mind thresholds increased between baseline and week 104 in each dimension (**Figure 1**)
  - Percentage point increases ranged from +15 in the "joint pain" and "affected family members and carriers" dimensions to +60 in "injection schedule"

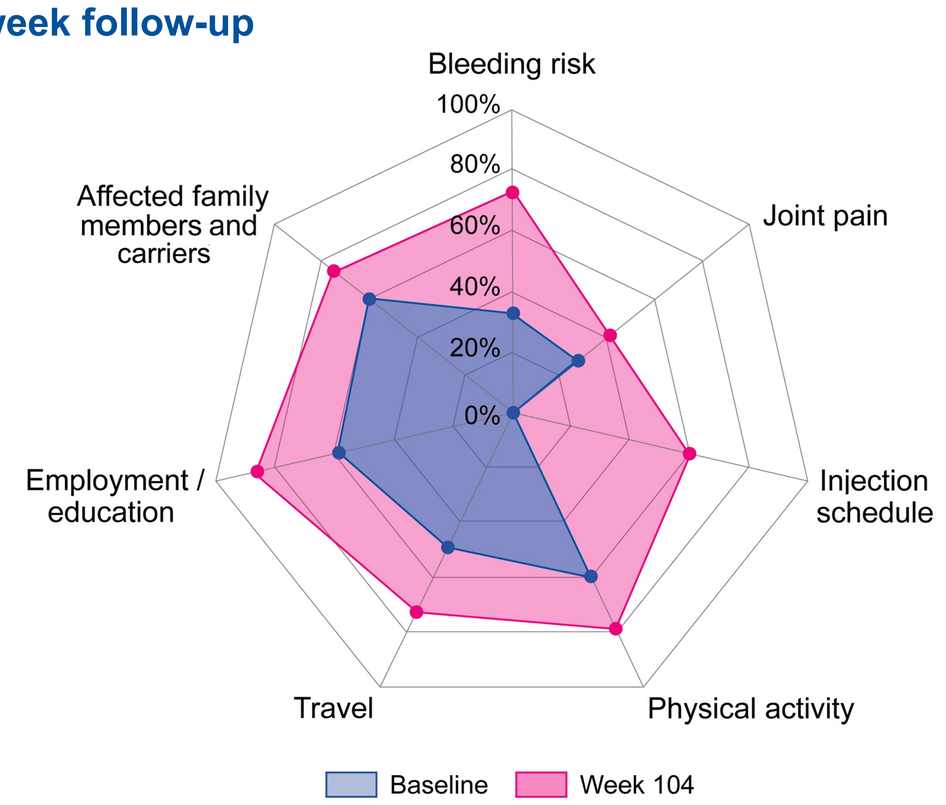
Table 1. Overview of hemophilia-free mind dimensions applied to the GENEr8-1 trial

Dimension	Measure	Item	Applied to GENEr8-1 participants
Bleeding risk	Clinical bleeding data	Treated bleeds	% with zero treated bleeds
Joint pain	Haemo-QoL-A	"I have to adjust my activities because of pain"	% reporting "None of the time"
Injection schedule	Exogenous FVIII use	Number of exogenous FVIII injections	% with no exogenous FVIII injections*
Physical activity	Haemo-QoL-A	Role Functioning domain	% with domain score ≥80 (out of 100)
Travel	Haemo-QoL-A	"I have difficulty travelling because of my hemophilia"	% reporting "None of the time"
Employment/ education	PROBE	Days of school/work missed	% reporting 0 days of school/work missed
Affected family members and carriers	Haemo-QoL-A	"I feel like a burden to my family"	% reporting "None of the time"

*FVIII use for invasive procedures was excluded.

FVIII: factor VIII; Haemo-QoL-A: Haemophilia-Specific Quality of Life Questionnaire for Adults; PROBE: Patient Reported Outcomes, Burdens and Experiences.

Figure 1. Proportion of GENEr8-1 participants achieving hemophilia-free mind thresholds at baseline and at 104-week follow-up



Conclusions

- This is the first initiative to assess the hemophilia-free mind concept using a visual, multidimensional method, demonstrating that it is feasible to measure this concept in clinical studies of hemophilia A gene therapy
- Quantification may be further refined with development of a validated tool for measuring the hemophilia-free mind concept and utilization of long-term data of PwHA treated with valoctocogene roxaparvovec
- The improvements in all dimensions observed at 104 weeks of follow-up among GENEr8-1 participants demonstrate progression towards a hemophilia-free mind after administration of valoctocogene roxaparvovec

References

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Disclosures

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