Health-Related Quality of Life Following Valoctocogene Roxaparvovec Gene Therapy for Severe Haemophilia A in the Phase 3 Trial GENEr8-1

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DISCLOSURE FOR **BRIAN O'MAHONY**

In compliance with COI policy, EAHAD requires the following disclosures to the session audience:

Shareholder	No relevant conflicts of interest to declare
Grant / Research Support	No relevant conflicts of interest to declare
Consultant	BioMarin Pharmaceutical Inc., and Freeline
Employee	No relevant conflicts of interest to declare
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Other	No relevant conflicts of interest to declare

Presentation includes discussion of the following off-label use of a drug or medical device:
<N/A>

INTRODUCTION

- Severe haemophilia A (plasma FVIII <1 IU/dL) is associated with increased risk of spontaneous bleeding and negatively impacts HRQOL through joint pain and disability[1]
- Improvement in chronic pain and mental health are core outcomes for haemophilia gene therapy trials[2]
- In the ongoing phase 3 trial GENEr8-1 (NCT03370913), 132 HIV-negative men with severe haemophilia A who received a $6x10^{13}$ vg/kg dose of valoctocogene roxaparvovec (AAV5-hFVIII-SQ) gene transfer had a meaningful increase in chromogenic FVIII activity at weeks 49–52 (mean ± SD, 42.9 ± 45.5 IU/dL) that resulted in reduced bleeding and FVIII utilisation from baseline through 52 weeks post-infusion[3]
- Here, we analysed the impact of valoctocogene roxaparvovec gene transfer on HRQOL in participants in GENEr8-1 over 52 weeks

METHODS

- Eligible participants were adult men with severe haemophilia A (plasma FVIII ≤1 IU/dL) previously receiving FVIII prophylaxis with no history of FVIII inhibitors or anti-AAV5 antibodies, no significant liver dysfunction, significant liver fibrosis, or liver cirrhosis, and no history of HIV infection
- Participants received a single $6x10^{13}$ vg/kg infusion of valoctocogene roxaparvovec
- Efficacy was assessed with change from baseline in FVIII activity and annualised rate of treated bleeding events over 52 weeks
- Participants completed PRO questionnaires (Haemo-QOL-A, EQ-5D-5L, HAL, and WPAI+CIQ:HS) at baseline and weeks 4, 12, 26, and 52 post infusion
- To evaluate change from baseline, exploratory P-values and 95% CI were generated using two-sided t-tests
- Post hoc analyses of Haemo-QOL-A results for participant subgroups based on problem joint status and bleeding events were performed
  - Problem joints were investigator-identified joints with chronic joint pain, chronic synovitis, haemophilic arthropathy, limited motion, or recurrent bleeding
- Clinically meaningful score changes were assessed with the following CID estimates:
  - For the Haemo-QOL-A, anchor-derived CID estimates of 5.5 and 6 were used for Total Score and domain scores (range, 0–100), respectively
  - For the EQ-5D-5L utility index score, 0.03 was considered a CID from baseline

RESULTS

Table 1. Baseline demographics and clinical characteristics

	mITT N = 132
Age (years), mean ± SD	31.4 ± 10.1
Race, n (%)	
White	94 (71.2)
Asian	19 (14.4)
Black or African American	15 (11.4)
Native Hawaiian or Pacific Islander	1 (0.8)
Not provided	3 (2.3)
Hispanic or Latino ethnicity, n (%)	7 (5.3)
BMI (kg/m^2), mean ± SD	25.3 ± 4.6
Medical history, n (%)	
Hepatitis B	18 (13.6)
Hepatitis C	39 (29.5)
Number of problem joints,* n (%)	
0	95 (72.0)
1	17 (12.9)
2	9 (6.8)
≥3	11 (8.3)

*Problem joints were those with chronic joint pain, chronic synovitis, haemophilic arthropathy, limited motion, or recurrent bleeding.

AAV5, adeno-associated virus serotype 5; BMI, body mass index; CI, confidence interval; CID, clinically important difference; EQ-5D-5L, EuroQol 5 Dimension 5 Level; FVIII, Factor VIII; Haemo-QOL-A, Haemophilia-specific Quality Of Life Questionnaire for Adults; HAL, Haemophilia Activities List; HIV, human immunodeficiency virus; HRQOL, health-related quality of life; mITT, modified intent-to-treat; PRO, patient reported outcome; SD, standard deviation; WPAI+CIQ:HS, Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific.

1. O'Hara et al. *Health and Quality of Life Outcomes*. 2018;16:84; 2. Iorio A et al. *Haemophilia*. 2018;24(4):e167–72; 3. Ozelo M et al. *N Engl J Med*. 2021;In Review.

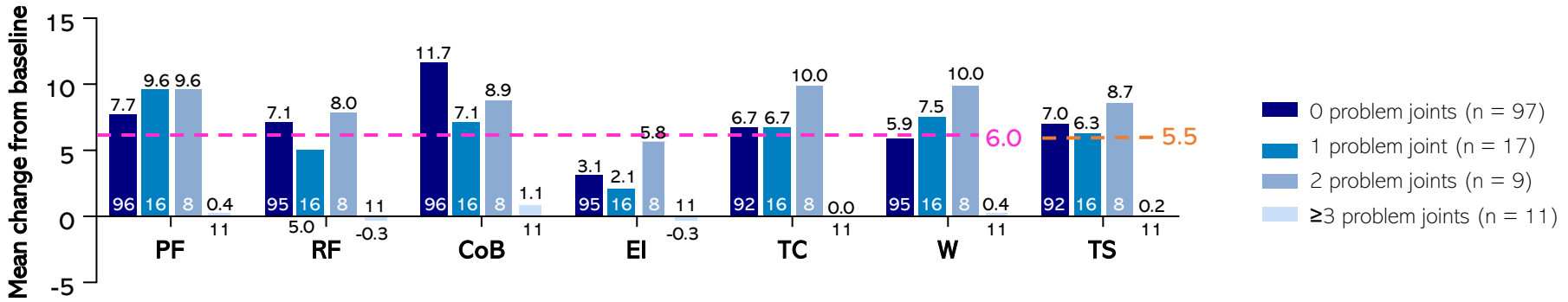
Haemo-QOL-A TOTAL AND DOMAIN SCORES AND SUBGROUP ANALYSES

- Overall, improvements in Haemo-QOL-A Total and domain scores above the CID were noted at weeks 26 and 52 (Table 2)

Table 2. Haemo-QOL-A Total and domain scores, mean (SD)

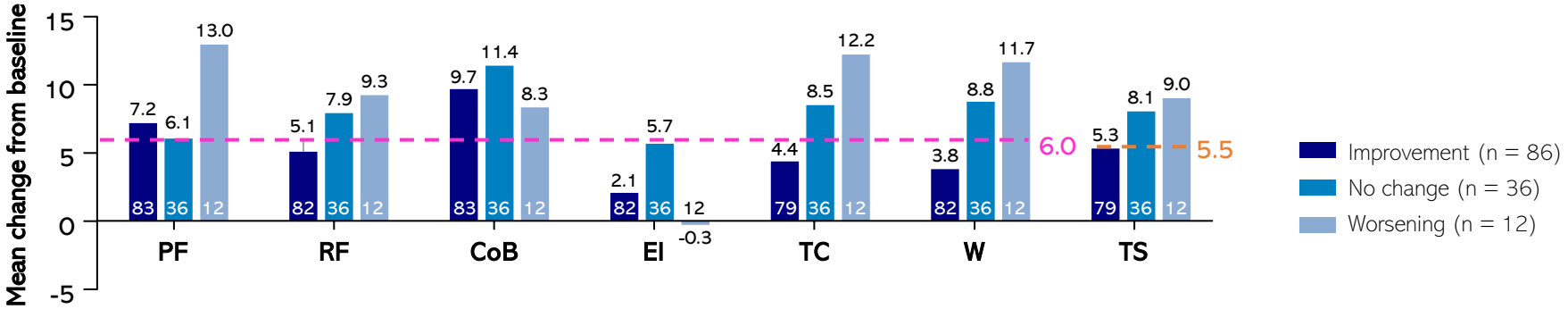
	Baseline	Week 26	CFB to week 26	Week 52	CFB to week 52
Physical Functioning	70.3 (20.8)	76.6 (19.9)	6.6 (13.4)[a]	77.7 (20.8)	7.4 (15.4)[a]
n	132	130	130	130	130
Role Functioning	78.2 (17.8)	84.7 (17.2)	6.6 (13.4)[a]	84.5 (15.7)	6.3 (13.4)[a]
n	131	128	127	130	129
Consequences of Bleeding	73.6 (21.7)	82.0 (19.3)	8.7 (15.0)[a]	83.4 (19.0)	10.0 (15.3)[a]
n	132	130	130	130	130
Worry	78.4 (22.7)	82.9 (21.6)	4.1 (15.6)[b]	84.2 (20.3)	5.8 (20.1)[b]
n	131	128	127	130	129
Emotional Impact	78.1 (16.5)	80.1 (19.6)	1.7 (14.2)	81.1 (16.7)	2.9 (15.5)[c]
n	131	128	127	130	129
Treatment Concern	76.2 (25.4)	81.0 (25.9)	5.2 (17.0)[d]	82.7 (24.5)	6.3 (18.5)[d]
n	130	128	126	129	127
Total Score	75.7 (16.7)	81.2 (16.9)	5.5[e] (10.7)[a]	82.2 (15.4)	6.4 (12.0)[a]
n	130	128	126	129	127

Figure 1A. Haemo-QOL-A change from baseline by number of problem joints



- Participants with ≥3 problem joints had lower baseline Physical Functioning, Role Functioning, and Total Score than the other groups (data not shown); clinically meaningful improvements in any domain were not observed for these participants (Figure 1A)

Figure 1B. Haemo-QOL-A change from baseline by ABR change over 52 weeks



- Patients whose ABRs worsened (n = 12) had significantly lower QoL scores at baseline (data not shown) and reported a large increase in scores at week 52, especially in Physical Functioning (Figure 1B)
- Participants with no change in ABR reported clinically meaningful improvements at week 52, especially in Consequences of Bleeding

[a]P <0.0001, [b]P <0.01, [c]P <0.05, and [d]P <0.001 were based on a two-sided t-test of CFB vs 0 without controlling for multiplicity. [e]Rounded up from 5.47 and therefore not above the CID. Boldface indicates that CFB had an exploratory P-value <0.05. Pink shading indicates a mean CFB ≥6 for domain scores, the CID for domain scores. Orange shading indicates mean CFB ≥5.5 for Total Score. Change in Haemo-QOL-A domain scores were groups by ABR improvement, worsening, or no change. All participants in the "No change" group had 0 bleeds. Red lines represent the CID for domains (6), and orange lines represent the CID for total score (5.5). Values in white are the number of participants responding.
ABR, annualised bleeding rate; CFB, change from baseline; CID, clinically important difference; CoB, Consequences of Bleeding; EI, Emotional Impact; Haemo-QOL-A, Haemophilia-specific Quality Of Life Questionnaire for Adults; PF, Physical Functioning; QoL, quality of life; RF, Role Functioning; SD, standard deviation; TC, Treatment Concern; TS, Total Score; W, Worry.

EQ-5D-5L VAS AND EQ-5D-5L UTILITY INDEX SCORE

- At baseline, EQ-5D-5L VAS mean ± SD was 80.1 ± 15.3 and increased by 2.5 ± 13.7 at week 26 ($P = 0.0384$) and by 4.5 ± 13.3 at week 52 ($P = 0.0002$)
- At baseline, EQ-5D-5L utility score (mean ± SD) was 0.78 ± 0.17
- EQ-5D-5L utility score change from baseline (mean ± SD) at week 26 (0.04 ± 0.14) and week 52 (0.04 ± 0.16) exceeded the CID of 0.03 ($P \leq 0.002$)

WPAI+CIQ:HS SCORES

- Decreased activity impairment, work impairment, and classroom impairment were observed
- Among the 129 participants, baseline mean ± SD activity impairment was 17.98% ± 21.37%; change from baseline was −6.98% ± 21.44% at week 26 ($P = 0.0004$) and −7.57% ± 24.80% at week 52 ($P = 0.0014$), signifying improvement
- At baseline, among the 101 employed participants, mean ± SD overall work impairment was 11.15% ± 17.27%; change from baseline was −3.25% ± 21.01% at week 26 and −2.69% ± 21.79% at week 52
- At baseline, among the 28 participants taking classes, mean ± SD overall classroom impairment was 12.59% ± 23.37%; mean ± SD change from baseline was −7.71% ± 21.63% at week 26 and −3.47% ± 18.36% at week 52

HAL DOMAIN SCORES

- Improvement from baseline was observed for all HAL individual components at week 26 and week 52 ($P < 0.05$) (Table 3)

Table 3. HAL domain scores, mean (SD)

	Baseline	Week 26	CFB to week 26	Week 52	CFB to week 52
Lying/sitting/ kneeling/standing	73.49 (22.64)	77.48 (22.05)	**4.17 (14.58)**[a]	78.12 (23.40)	**4.96 (16.31)**[a]
n	131	130	129	125	124
Functions of the legs	68.92 (26.51)	75.50 (25.66)	**6.88 (16.70)**[b]	76.05 (26.88)	**6.64 (17.63)**[b]
n	131	130	129	125	124
Functions of the arms	80.27 (21.12)	85.92 (19.03)	**5.85 (18.00)**[c]	85.36 (19.39)	**4.88 (20.51)**[a]
n	131	130	129	125	124
Use of transportation	83.64 (21.74)	88.50 (21.13)	**4.44 (16.48)**[a]	87.43 (21.88)	**3.68 (18.51)**[d]
n	120	113	108	109	105
Self-care	90.20 (15.53)	93.32 (13.55)	**3.22 (14.88)**[d]	93.47 (13.59)	**3.39 (14.70)**[d]
n	131	130	129	125	124
Household tasks	87.61 (16.87)	90.99 (14.82)	**3.57 (13.82)**[a]	91.01 (16.72)	**3.27 (16.27)**[d]
n	130	129	127	123	121
Leisure activities and sports	80.00 (19.77)	84.72 (19.37)	**5.49 (17.13)**[a]	86.62 (19.00)	**6.75 (18.16)**[c]
n	119	108	100	103	100

[a]$P < 0.01$, [b]$P < 0.0001$, [c]$P < 0.001$, and [d]$P < 0.05$ were based on a two-sided t-test of CFB vs 0 without controlling for multiplicity. CFB data are based on participants with data at both time points. Boldface indicates that CFB had an exploratory $P < 0.05$. CFB data are based on participants with data at both time points.

CONCLUSIONS

- Haemo-QOL-A results revealed meaningful improvements in HRQOL at week 52, with the largest impacts seen in the Physical Functioning and Consequences of Bleeding domains
  - Improvement in Haemo-QOL-A Total Score and domain scores was observed for participants with pre-existing problem joints, as well as those who had no change in bleeding or increased bleeding after gene therapy
  - Overall, the trend was towards net improvement across all domains, irrespective of baseline scores
- Clinically meaningful improvements in HRQOL were also seen with the EQ-5D-5L utility score
- HAL and WPAI+CIQ:HS scores reflected decreased impairment and increased activity post-gene transfer
- This study is ongoing, and additional analyses of these HRQOL outcomes will be conducted with week 104 results, once available

CFB, change from baseline; CID, clinically important difference; EQ-5D-5L, EuroQol 5 Dimension 5 Level; Haemo-QOL-A, Haemophilia-specific Quality Of Life Questionnaire for Adults; HAL, Haemophilia Activities List; HRQOL, health-related quality of life; SD, standard deviation; VAS, visual analogue scale; WPAI+CIQ:HS, Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific.