Health-Related Quality of Life in Adults With Hemophilia B After Receiving Gene Therapy With Fidanacogene Elaparvovec

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BACKGROUND

- Hemophilia B is an X-linked (*F9* gene) disorder of hemostasis that results in insufficient endogenous factor IX (FIX) activity.[1]
- As disease severity worsens, people with hemophilia B experience more bleeding episodes, a greater loss of productivity and higher direct (e.g., clotting factor usage, hospitalization, outpatient services) and indirect (e.g., loss of earnings, absenteeism) costs.[2]
- The current standard of care for severe hemophilia B is prophylaxis with regular factor replacement therapy via intravenous (IV) infusions; this requires adequate venous access, a continual supply of therapy, and adherence to treatment regimen.[1]
- The burden of the management and clinical sequelae of hemophilia B negatively impacts health-related quality of life (HRQoL) and self-reported health status.[3]
- Adeno-associated virus (AAV)–based gene therapy for hemophilia B has the potential to produce sustained endogenous FIX production, providing protection against spontaneous bleeding episodes and chronic arthropathy while avoiding problems of suboptimal adherence.[4]
- Fidanacogene elaparvovec (PF-06838435, formerly SPK-9001) is an AAV-based gene therapy vector transferring the high activity variant of the human FIX, FIX-R338L/FIX-Padua, aimed at enabling endogenous FIX expression in individuals with hemophilia B.[5]

OBJECTIVE

- To present descriptive data of the impact on HRQoL for participants with hemophilia B who received fidanacogene elaparvovec.

METHODS

Study Design

- Following completion of a phase 1/2a study (52-week duration), participants were eligible to enroll in a long-term follow-up (LTFU) study evaluating the long-term safety, durability, and efficacy of fidanacogene elaparvovec.

Participant Population

- Participants: males aged ≥18 years with moderately severe to severe hemophilia B (FIX activity ≤2%).
- Key inclusion and exclusion criteria are shown in **Table 1**.

Table 1: Key inclusion and exclusion criteria for the phase 1/2a and LTFU studies

Key Inclusion Criteria	Key Exclusion Criteria
• ≥50 prior exposure days to any plasma-derived or recombinant FIX product	• Active hepatitis B or C or currently on antiviral therapy for hepatitis B or C
• Prophylaxis participants: bleeding events and/or FIX infusions in last 12 wks	• Significant liver disease or liver fibrosis
• On-demand participants: ≥4 bleeding events in last year and/or chronic arthropathy	• HIV-1 or HIV-2 with CD4 counts ≤200/mm^3
• No FIX inhibitors	• NAb titers ≥1:5
• Hemoglobin, platelets, ALT, AST, alkaline phosphatase, bilirubin, and creatine in acceptable range	• History of chronic infection, chronic disease, or clinically significant major disease
	• Participation in previous gene therapy trial (in past 52 wks) or clinical study with investigational drug (in past 12 wks)

ALT=alanine transaminase; AST=aspartate aminotransferase; FIX=factor IX; LTFU=long-term follow-up; NAb=neutralizing antibody

Study Procedures

- 15 participants were enrolled in the phase 1/2a (NCT02484092), open-label, nonrandomized, multicenter study to evaluate the safety, tolerability, and kinetics of fidanacogene elaparvovec.
- Fidanacogene elaparvovec was delivered via a single IV infusion (5e11 vg/kg).
- Participants were followed for ≥1 year (52 ± 2 weeks).
- Participants were then eligible to participate in a LTFU study for an additional 5-year follow-up (NCT03307980).
- Participants in both studies completed patient-reported outcome (PRO) assessments every 6 months through 3 years post infusion and then once annually during the LTFU study.
  - The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)[6,7]:
    - Consists of 46 items pertaining to 10 domains to assess HRQoL.
    - Individual items are recoded, and domain scores and the Total Score are transformed, ranging from 0 to 100.
    - High scores indicate high impairment in HRQoL.
    - A 7-point reduction in the Total Score and a 10-point reduction in "Physical Health" and "Sport and Leisure" domain scores are considered clinically meaningful.[8,9]
  - The EQ-5D visual analog scale (EQ-VAS)[10]:
    - Participants rate their current health state for endpoints of 100 (best imaginable health) to 0 (worst imaginable health).
    - A score change of 7 points is considered clinically meaningful (i.e., the minimally important difference [MID]).[11]
  - The Change in Level of Activity questionnaire:
    - Participants assess whether they have been doing more / the same / lower amount or intensity of physical activities in the past month.
- The data cutoff date was August 2, 2022. The LTFU study is ongoing.

RESULTS

- All 15 participants completed the phase 1/2a study, and 14 enrolled in the LTFU study (1 participant declined).
- Participants who enrolled in the LTFU study were followed for a total of 3–6 years post gene therapy.
- Of the 14 participants, 13 had HRQoL data available through 3 years post infusion; beyond this time point there were too few participants (between 3 and 10) with both before and after gene therapy (baseline) values, so these data were not included.
- Participant demographics at baseline are shown in **Table 2**.

Table 2: Participant demographics pre-vector infusion for participants who entered the LTFU study

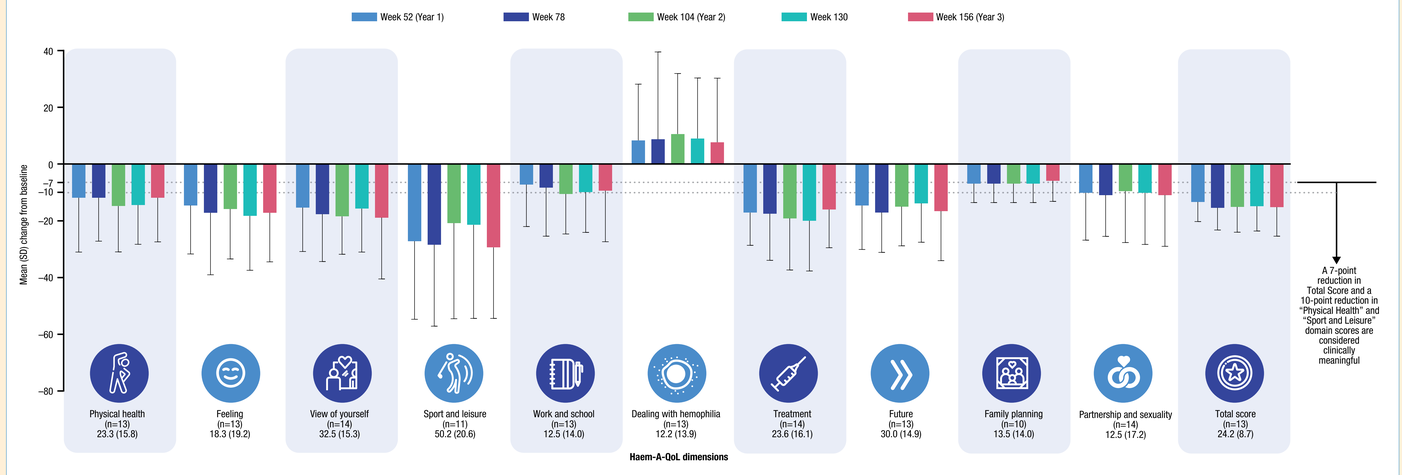
Characteristic, n (%)[a]		N=14
Age, y	Mean (SD)	42.0 (13.7)
	Median	44.0
	Min, max	20.0, 63.0
Gender	Male	14 (100)
Race	Black or African American	1 (7.1)
	Native Hawaiian or other Pacific Islander	1 (7.1)
	White	12 (85.7)
Severity	<1%	9 (64.3)
	1–2%	5 (35.7)
Target joint(s) in past 52 wks	No	5 (35.7)
	Yes	9 (64.3)
History of HIV infection	No	12 (85.7)
	Yes	2 (14.3)
HIV maintained on anti-retroviral therapy	Yes	2 (14.3)

[a] Unless otherwise noted.
LTFU=long-term follow-up; max=maximum; min=minimum

Haem-A-QoL Questionnaire

- Overall, 12 participants had data at baseline through Year 3. For these participants, the mean (SD) Total Score at Year 3 decreased by 15.2 (10.3) from pre-vector infusion, indicating a clinically meaningful improvement in HRQoL (**Figure 1**).

Figure 1: Change in HRQoL (Haem-A-QoL) from baseline over time



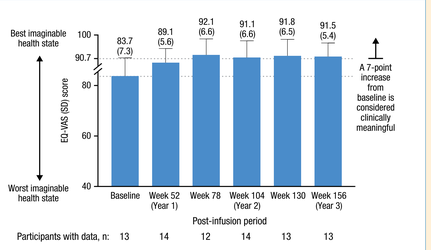
Week 52 (Year 1) assessment was from the End of Study visit in the phase 1 dosing study or Visit 1 of the LTFU study. Scoring was performed by averaging the non-missing item responses for each domain, and then rescaled to 0 to 100.
Change from baseline = post-baseline value − baseline value.
Numbers shown on x-axis represent the number of participants with responses for each individual domain at baseline and mean (SD) score at baseline; numbers of participants may be lower at subsequent timepoints. For the change from baseline, only participants with a value at both baseline visit and the specified post-baseline visit were included.
Haem-A-QoL=Haemophilia Quality of Life Questionnaire for Adults; HRQoL=health-related quality of life; LTFU=long-term follow-up

- Of the 12 participants with data at baseline through to Year 3, 8 had Total Score decreases ≥7 (indicating a clinically meaningful improvement in HRQoL) at each visit through Year 3.
- Similarly, participant scores for each individual domain decreased (indicating an improvement in HRQoL) over time from pre-vector infusion in all instances except for the "Dealing with Hemophilia" domain (**Figure 1**).
  - The mean (SD) "Physical Health" domain score at Year 3 decreased by 11.9 (15.6) from pre-vector infusion.
  - The mean (SD) "Sport and Leisure" domain score at Year 3 decreased by 29.4 (25.0) from pre-vector infusion.

EQ-VAS Assessment

- Mean scores were above mean baseline score and after Year 1, mean changes from baseline were consistently 7 to 8 points (indicating an improvement in overall health status) (**Figure 2**).
- At Year 3, the EQ-VAS score increased from baseline by mean (SD) of 7.2 (6.2) in 12 participants with data at both visits (**Figure 2**).

Figure 2: EQ-VAS score over time

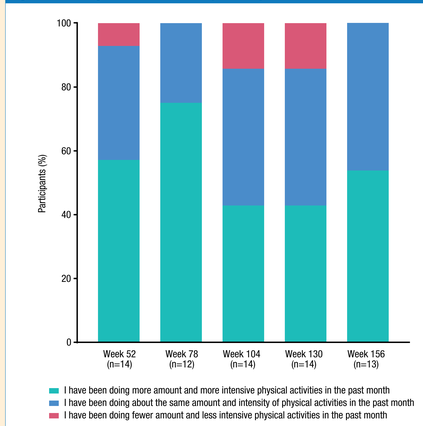


EQ-VAS=EQ visual analog scale

Change in Level of Activity Questionnaire

- Responses showed that a greater proportion of participants at each visit up to Year 3 (n=12–14) reported doing the same or more intensive physical activities in the past month (**Figure 3**).
- None of the 13 participants reported a reduction in the amount or intensity of physical activities at Year 3 (**Figure 3**).

Figure 3: Change in level of activity in the past month over time



Week 52 assessment was from the End of Study visit in the phase 1 dosing study or Visit 1 of the LTFU study.

CONCLUSIONS

- HRQoL improvements after gene therapy are an indicator that fidanacogene elaparvovec can reduce the burden associated with hemophilia.
- PRO assessments will be a part of BENEGENE-2, an ongoing pivotal phase 3 study to investigate the efficacy of fidanacogene elaparvovec.
  - BENEGENE-2 will provide additional insights via the analyses of secondary endpoints of the HRQoL benefits for participants with hemophilia B following gene therapy with fidanacogene elaparvovec.

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