A Multi-Year Follow-Up Study of Fidanacogene Elaparvovec Gene Therapy for Hemophilia B

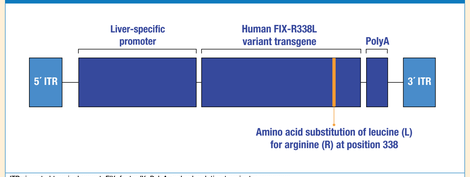
Benjamin J Samelson-Jones[1,2*], Lindsey A George[1,2], John EJ Rasko[3,4], Adam Giermasz[5], Jerome M Teitel[6], Catherine E McGuinn[7], Jonathan M Ducore[5], Sharon Pennington[8], Katherine A High[2], Jeremy Rupon[9], Francesca Biondo[10], Annie Fang[11], Lynne M Smith[9], Matko Kalac[11], Amit Chhabra[11], Frank Plonski[9]

[1]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [4]Gene and Stem Cell Therapy Program, Centenary Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; [5]Hemophilia Treatment Center, University of California Davis, Sacramento, CA, USA; [6]St. Michael's Hospital, University of Toronto, Toronto, Canada; [7]Weill Cornell Medicine, New York, NY, USA; [8]Mississippi Center for Advanced Medicine, Madison, MS, USA; [9]Pfizer Inc, Collegeville, PA, USA; [10]Pfizer Srl, Rome, Italy; [11]Pfizer Inc, New York, NY, USA; *Presenting author

INTRODUCTION

- The current standard of care for people with hemophilia B requires frequent intravenous (IV) infusions of exogenous factor IX (FIX) to prevent bleeding and avoid development of arthropathy.[1,2]
- Adeno-associated virus (AAV)–based gene therapy has the potential to produce sustained FIX activity following a single infusion.[3]
- Fidanacogene elaparvovec (PF-06838435), currently in development for the treatment of hemophilia B, is a hepatotropic recombinant AAV gene therapy vector encoding a codon-optimized, high-activity FIX variant (FIX-R338L)[4] (**Figure 1**).
- The R338L variant produces FIX with increased clotting activity,[5] allowing clinically meaningful FIX activity levels to be achieved with a lower vector dose that minimizes safety risks associated with anti-AAV immune responses.[6]
- In a phase 1/2a study, participants safely achieved therapeutic levels of FIX expression with a low dose of fidanacogene elaparvovec.[4] Subsequently, a long-term follow-up (LTFU) study was initiated to assess the multi-year safety and efficacy of fidanacogene elaparvovec in these participants.

Figure 1: Fidanacogene elaparvovec gene therapy



ITR=inverted terminal repeat; FIX, factor IX; PolyA=polyadenylation terminator sequence

OBJECTIVE

- Present results of a LTFU study of participants with hemophilia B followed for ≤6 years post treatment with fidanacogene elaparvovec.

METHODS

Study Design

- Following completion of a phase 1/2a study (NCT02484092) to evaluate the safety, tolerability, and kinetics of fidanacogene elaparvovec, participants were eligible to enroll in a LTFU study (NCT03307980) to evaluate the long-term safety, durability, and efficacy of fidanacogene elaparvovec.

Participant Population

- Male adults (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 study

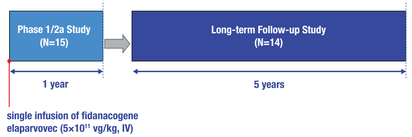
Key inclusion criteria	Key exclusion criteria
• ≥50 prior exposure days to any plasma-derived or recombinant FIX product • Prophylaxis participants: bleeding events and/or FIX infusions in last 12 weeks • On-demand participants: ≥4 bleeding events in last year and/or chronic arthropathy • No FIX inhibitors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

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

Study Procedures

- The study timeline is shown in **Figure 2**.
- 15 participants were enrolled in the phase 1/2a, open-label, nonrandomized, multicenter study.
- Fidanacogene elaparvovec was delivered via a single IV infusion (5×10^{11} vg/kg).
- Participants were followed for ≥1 year (52 weeks) as part of the phase 1/2a study.
- Participants were then eligible to participate in a LTFU study for ≤5 years.
- We present data from the LTFU study with up to 6 years of follow-up post vector infusion.

Figure 2: Study timeline



IV=intravenous; vg=vector genomes

RESULTS

Participant Disposition and Demographics

- All 15 participants completed the phase 1/2a study, and 14 enrolled in the LTFU study.
- As of the data cutoff date (August 2023), all 14 participants completed ≥3 years of follow-up post infusion.
- 7 participants have completed 6 years of follow-up, 2 participants discontinued from the study, 1 participant was lost to follow-up, and 4 participants remain ongoing in the trial.
- Overall, participants who enrolled in the LTFU study were followed for a total of 36–72 months (3–6 years) post vector infusion.
- Participant demographics at baseline are shown in **Table 2**.

Table 2: Participant demographics at baseline for the LTFU study

Characteristic	Cohort 1 (5×10^{11} vg/kg) N=14
Age, years	
Mean (SD)	40.1 (13.8)
Median	42.5
Min, max	18.0, 61.0
Gender, n (%)	
Male	14 (100)
Race, n (%)	
Black or African American	1 (7.1)
Native Hawaiian or other Pacific Islander	1 (7.1)
White	12 (85.7)
Ethnicity, n (%)	
Hispanic or Latino	0 (0)
Not Hispanic or Latino	14 (100)
Severe criteria, n (%)	
<1%	9 (64.3)
1–2% (inclusive)	5 (35.7)
Target joint(s)[a] in past 52 weeks, n (%)	
Yes	9 (64.3)
No	5 (35.7)
HIV+	
Yes	2 (14.3)
No	12 (85.7)
HIV maintained on anti-retroviral therapy	
Yes	2 (14.3)

[a] Target joint defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, ankle) into which repeated bleeding occurs (≥3 bleeding episodes into the same joint in a consecutive 12 week period) and with symptoms of pre-existing target joint involvement (eg, synovitis, persistent swelling, effusion, limitation of range of motion).
LTFU=long-term follow-up; min, max=minimum, maximum

Safety

- There were 9 serious adverse events (SAEs) in 4 participants; no SAEs were classified as treatment-related, and each occurred >1 year post infusion (**Table 3**).
- After the first year post infusion, asymptomatic liver enzyme levels above the normal range were reported in 9 participants; none of these events were treated with corticosteroids or considered treatment-related AEs.
- No liver masses or malignancies, thrombotic events, FIX inhibitors, or deaths were reported.

Table 3: Serious adverse events during the LTFU study

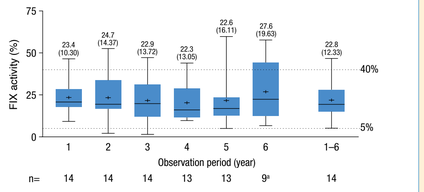
Participant #	Event	Severity	Relationship to fidanacogene elaparvovec
1	Appendicitis	Severe	Not related
4	Spinal stenosis	Severe	Not related
	Accident	Mild	Not related
	Joint dislocation	Mild	Not related
	Kidney contusion	Mild	Not related
	Liver contusion	Mild	Not related
	Rib fracture	Mild	Not related
5	Type B aortic dissection	Severe	Not related
11	Hemarthrosis	Severe	Not related

LTFU=long-term follow-up

Efficacy

- Geometric mean FIX activity generally remained in the mild hemophilia to normal range post infusion (**Figure 3**).

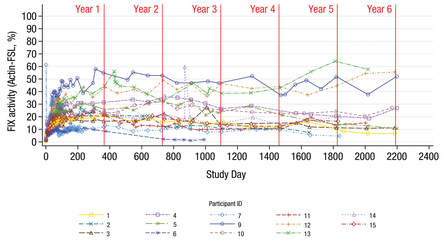
Figure 3: Geometric mean FIX activity (measured by Actin-FSL one-stage assay) for all participants in the LTFU study



Boxplots show minimum, quartile 1, median, quartile 3, and maximum.
+ indicates mean. Mean (SD) FIX activity values shown above bars.
Dotted lines represent mild disease severity range (5–40%) as per WFH definition. The classification of individuals with levels between 40 and 50% remains unresolved.[7]
[a] Includes Year 6 measurements for 2 participants who have not yet completed the study.
FIX=factor IX; LTFU=long-term follow-up; WFH=World Federation of Hemophilia

- FIX activity levels over time by participant are shown in **Figure 4**.

Figure 4: FIX Activity level over time for all participants in the LTFU study

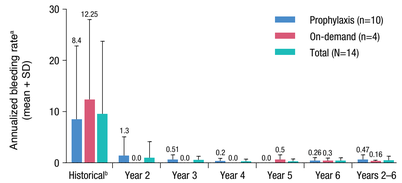


Participant # 8 did not enter the LTFU study.
FIX=factor IX; LTFU=long-term follow-up

- Annualized bleeding rates (ABRs) were reduced throughout the duration of the LTFU study compared with prior to infusion (**Figure 5**).
- In an exploratory analysis, participants had fewer bleeds per year during Years 2–6 post vector infusion compared with the 52 weeks prior to vector infusion (negative binomial estimate[a] −9.15 [95% CI −16.41, −1.90]).

[a] Mixed-effect model with repeated measures with treatment (pre vector infusion, post vector infusion) and duration as factors and participant as random effect.

Figure 5: Annualized bleeding rate for all participants in the LTFU study by baseline regimen (prophylaxis or on-demand)

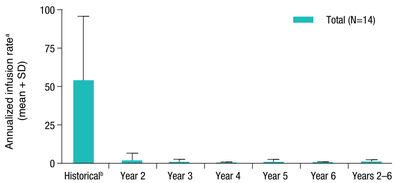


Observation Period	Historical	Year 2	Year 3	Year 4	Year 5	Year 6	Years 2–6
Mean (SD)	9.5 (14.35)	0.9 (3.19)	0.4 (0.87)	0.1 (0.54)	0.2 (0.56)	0.3 (0.66)	0.4 (0.89)
Median (min, max)	4.0 (0.0, 48.0)	0.0 (0.0, 12.0)	0.0 (0.0, 3.1)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.1)	0.0 (0.0, 3.3)
Total participants, n	14	14	14	14	13[c]	12[c]	14

Mean values for baseline prophylactic and on-demand participants shown above bars.
[a] ABR = (number of bleeds/days in the observation period) × 365.25 days/y; includes both spontaneous and traumatic bleeds; excludes bleeding episodes during surgical period.
[b] Historical = 52 weeks before vector infusion. Historical ABR did not distinguish between treated and untreated bleeds. Post-infusion ABR includes only treated bleeds.
[c] Includes all participants that entered designated year.
ABR=annualized bleeding rate; FIX=factor IX; LTFU=long-term follow-up; min, max=minimum, maximum

- 10 of 14 (71%) participants had no bleeding events during the LTFU.
- 4 of 14 participants experienced a total of 24 bleeding events during the LTFU.
  - 3 participants had a total of 17 spontaneous bleeds, 13 of which occurred in joints.
  - 4 participants had a total of 7 traumatic bleeds, 4 of which occurred in joints.
- 9/17 (53%) joint bleeds were in joints affected by chronic arthropathy.
- Overall, bleeding events occurred when FIX activity levels were less than ~25% (Actin-FSL one-stage assay).
- Annualized infusion rates (AIRs) were low throughout the duration of the LTFU study (**Figure 6**).
- No participant resumed prophylaxis.

Figure 6: Annualized infusion rate for all participants in the LTFU study



Observation period	Historical	Year 2	Year 3	Year 4	Year 5	Year 6	Years 2–6
Mean (SD)	53.9 (41.74)	1.6 (4.93)	0.7 (1.79)	0.2 (0.58)	0.5 (1.94)	0.3 (0.66)	0.7 (1.45)
Median (min, max)	49.5 (0.0, 156.0)	0.0 (0.0, 18.5)	0.0 (0.0, 6.3)	0.0 (0.0, 2.0)	0.0 (0.0, 7.0)	0.0 (0.0, 2.1)	0.0 (0.0, 5.2)
Total participants, n	14	14	14	14	13[c]	12[c]	14

[a] AIR = (number of FIX infusions/days in the observation period) × 365.25 days/y; excludes infusions for surgery.
[b] Historical = 52 weeks pre vector infusion.
Historical AIR included the total number of infusions (in prior 52 weeks) for participants on a baseline on-demand regimen but only the number of prophylactic infusions (in prior 52 weeks) for participants on a baseline prophylactic regimen.
[c] Includes all participants that entered designated year.
FIX=factor IX; LTFU=long-term follow-up; min, max=minimum, maximum

CONCLUSIONS

- The results of this ongoing LTFU study demonstrate that a single infusion of fidanacogene elaparvovec gene therapy in participants with hemophilia B remains generally well tolerated over a period of up to 6 years post infusion:
  - No participants experienced treatment-related AEs or SAEs in the LTFU study.
  - Mean FIX activity generally remained in the mild to normal range.
  - Participants in the LTFU had low ABRs and AIRs.
  - A majority (71%) of participants experienced no bleeds during the LTFU, and no participant resumed prophylaxis.
- These results reflect some of the longest follow-up of participants with hemophilia B in a gene therapy trial to date.
- An ongoing phase 3 trial (NCT03861273) is further investigating the efficacy and safety of fidanacogene elaparvovec in people with moderately severe to severe hemophilia B.

REFERENCES

1. Srivastava A, et al. Haemophilia 2020;26(suppl 6):1-158.
2. National Hemophilia Foundation (NHF). MASAC Document #267. March 11, 2022.
3. Leebeek FWG, et al. Blood 2021;138:923-31.
4. George LA, et al. N Engl J Med 2017;377:2215-27.
5. Simioni P, et al. N Engl J Med 2009;361:1671-5.
6. Mingozzi, F, et al. Blood 2013;122:23-36.
7. Blanchette VS, et al. J Thromb Haemos 2014;12:1935-9.

DISCLOSURES

BJS-J: Honoraria from Pfizer; advisory board for Amarna, Biomarin, Genentech, and GeneVentiv. **LAG:** Grants, royalties, and patents from AskBio; consulting fees from Bayer, Regeneron, and Spark Therapeutics; advisory board for Avrobio; leadership/fiduciary role in STRM.BIO. JEJR: Honoraria from BeiGene, Rarecyte, Novartis, Bluebird Bio, Spark Therapeutics, Cynata, and Pfizer; consulting fees from Pfizer; stock/stock options in RareCyte and Woke. **AG:** Grants from ATHEN, Bayer, BioMarin, CSL Behring, Sangamo Therapeutics, Spark Therapeutics, and UniQure; consulting fees from ATHEN, Alexion, Bayer, Genentech, Hema Biologics, Novo Nordisk, Pfizer, and Sanofi; honoraria from Alexion, BioMarin, Genentech, and Sanofi; advisory board for Adrenas Therapeutics. **JMT:** Clinical trial investigator with Pfizer and Spark Therapeutics; consulting fees from Bayer, Octapharma, and Sanofi; advisory board for BioMarin and Vega Therapeutics. **CEM:** Clinical trial investigator with Roche/Genentech, Sanofi, and Takeda; consulting fees from Bayer, BPL, CSL Behring, Genentech, HEMA Biologics, and Octapharma; meetings/travel support from BPL; advisory board for Bayer, CSL Behring, Genentech, HEMA Biologics, and Octapharma. **JMD:** Consulting fees from Bayer. **SP:** No conflicts to disclose. **KAH:** Consulting fees from Pfizer; patents from Spark Therapeutics; former employee/equity holder in Spark Therapeutics. AC, FB, AF, MK, FP, JR, and **LMS:** Employees/shareholders in Pfizer.

ACKNOWLEDGMENTS

This study was funded by Pfizer. Medical writing support was provided by Courtney Cameron, PhD, of Engage Scientific Solutions and funded by Pfizer.

Electronic Poster
Please scan this QR code with your smartphone app to view or obtain a copy of this poster.
If you don't have a smartphone, access the poster via the Internet at:
https://scientificpubs.congressposter.com/p/bz8j2uq08rjh0qqk

Presented at the Thrombosis & Hemostasis Societies of North America (THSNA) Summit, April 4–6, 2024, Chicago, IL, USA