ORIGINAL ARTICLE

Fidanacogene Elaparvovec for Hemophilia B — A Multiyear Follow-up Study

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ABSTRACT

BACKGROUND

Treatment with fidanacogene elaparvovec, a recombinant adeno-associated virus (AAV) vector developed for the treatment of hemophilia B, led to sustained expression of the high-activity factor IX variant (FIX-R338L, or FIX-Padua) in a phase 1–2a study. The long-term safety and efficacy of this treatment are not known.

METHODS

In a 12-month study, 15 participants with severe or moderately severe hemophilia B (factor IX coagulant activity, ≤2% of the normal value) received fidanacogene elaparvovec at a dose of 5×10^{11} vector genomes (vg) per kilogram of body weight; thereafter, participants could enroll in a 5-year follow-up study. Safety end points included adverse events and changes in laboratory measures. Efficacy end points included the annualized rate of treated bleeding events (annualized bleeding rate) and factor IX activity.

RESULTS

A total of 14 participants provided consent and completed at least 3 years of follow-up (median, 5.5; range 3 to 6); participation was ongoing among 8 at the data cutoff. None of the participants reported treatment-related adverse events after year 1. Throughout follow-up, nine serious adverse events were noted in 4 participants; none were thrombotic or treatment-related. No factor IX inhibitors were detected. Throughout follow-up, mean factor IX activity was in the mild hemophilia range; the mean annualized bleeding rate was less than 1, and 10 participants had no treated bleeding episodes. Surveillance liver ultrasounds obtained from year 1 onward showed no evidence of cancer but showed steatosis in 4 participants who had weight gain and elevated aminotransferase levels (maximum alanine aminotransferase level, 77 U per liter). One participant with a history of hepatitis C, hepatitis B, human immunodeficiency virus infection, and an elevated body-mass index had progression of underlying advanced liver fibrosis. A total of 13 surgical procedures were performed in 8 participants; exogenous factor IX was administered for 10 procedures, and no associated unexpected bleeding complications occurred.

CONCLUSIONS

Fidanacogene elaparvovec was associated with no or only low-grade adverse effects over a period of 3 to 6 years. Efficacy was maintained in the long term at 5×10^{11} vg per kilogram, one of the lowest intravenous doses of AAV used for any indication. (Funded by Pfizer; ClinicalTrials.gov number, NCT03307980.)

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Hemophilia B, an X-linked disorder resulting from a deficiency in coagulation factor IX activity, can lead to lifelong spontaneous bleeding events or excessive bleeding after injury or surgery.[1] The natural history of severe hemophilia B involves the development of debilitating arthropathy as a result of recurrent hemarthroses.[1,2]

Current standard care for hemophilia B is prophylaxis by means of episodic intravenous administration of exogenous factor IX, which leads to peaks and troughs in factor IX levels. Although effective at reducing bleeding events and slowing long-term joint damage, factor IX replacement requires a high degree of adherence. Recombinant adeno-associated virus (AAV) vectors provide the opportunity to develop one-time disease-altering therapies for inherited monogenic disorders, including hemophilia.[3-5] A previous AAV trial in which wild-type *F9* was used showed durable factor IX expression for 10 years after treatment, with observation ongoing, but mean factor IX activity remained in the moderate range (<5%).[6,7]

Fidanacogene elaparvovec incorporates a hepatotropic AAV capsid and a high-activity factor IX transgene encoding FIX-R338L (also known as FIX-Padua).[8] FIX-R338L is a naturally occurring variant with a single amino acid substitution. Since FIX-R338L leads to an increase in factor IX–specific activity by a factor of 8 to 12 and consequently to a reduction in the vector dose needed to reach clinically meaningful factor IX activity levels, it has been widely adopted for hemophilia B gene transfer.[8-10] A phase 1–2a study evaluated the safety, side effects, and pharmacokinetics of fidanacogene elaparvovec expression in participants with severe or moderately severe hemophilia B.[8] After 1 year of follow-up, the first 10 participants had sustained factor IX expression in the mild hemophilia B (5 to 40% of normal) to normal (50 to 150% of normal) range.[8] These results indicated that a highly efficient vector administered at low doses can achieve therapeutic factor IX expression while minimizing the risk of an AAV capsid–directed immune response.[8] Here, we present data from an expanded cohort of 15 participants from the phase 1–2a study, including data from 14 participants enrolled in the long-term follow-up study (total study duration of up to 6 years).

METHODS

STUDY DESIGN AND OVERSIGHT

The study was funded by Pfizer, which accepted responsibility for the conduct of the study after transfer from Spark Therapeutics in July 2018. The study was designed by an academic author and three investigators who were employees of Spark Therapeutics at the time (one of whom is also an author of this article). Data were collected by site investigators, and analyses were performed by Pfizer. The academic authors recommended submission of the article, had access to the data, and could request additional analyses at their discretion. The submitted manuscript was written by a medical writer contracted by Pfizer, under the direction of the authors; the authors critically reviewed the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol, available with the full text of this article at NEJM.org.

PARTICIPANTS

The inclusion and exclusion criteria for the phase 1–2a study have been reported in detail previously.[8] Men 18 years of age or older with severe or moderately severe hemophilia B (factor IX activity, ≤2% of the normal value) were enrolled. Neutralizing antibody titers, assessed with a cell-based assay, were required to be less than 1:5 during screening in the phase 1–2a study (details are provided in the Methods section in the Supplementary Appendix, available at NEJM.org).

TRIAL PROCEDURES

The institutional review board at each study site approved the protocol. Written informed consent was obtained from all the participants at enrollment. A single intravenous infusion of 5×10^{11} vector genomes of fidanacogene elaparvovec per kilogram of body weight was administered as part of the phase 1–2a study (ClinicalTrials.gov number, NCT02484092).[8] One year after administration, participants could enroll in the 5-year follow-up study, thereby providing 6 years of data after treatment. Details of the study registration are provided in the Supplementary Methods. Factor IX activity levels were determined at the central laboratory with the use of the one-stage Actin FSL reagent on a BCS XP analyzer (Siemens Healthcare Diagnostics).

OBJECTIVES AND OUTCOMES

The primary objective of the 1-year phase 1–2a study was to assess the safety of fidanacogene elaparvovec,[8] with the follow-up study providing an additional 5 years of post-treatment data. A secondary objective of the follow-up study was to assess clinical outcomes after treatment, such as the rate of treated bleeding events and the use of exogenous factor IX.

For the first 2 years of the 5-year follow-up study (years 2 and 3 after vector administration), study visits took place at 13-week intervals (with a window of ±2 weeks); thereafter, study visits were scheduled to occur once every 26 weeks until the end of the study (see Supplementary Methods). Participants were contacted by telephone on a quarterly basis for the final 3 years of the study to review factor IX administration, adverse events, and the use of concomitant medications or therapies.

Safety assessments included physical examinations, liver-function testing, and evaluation of vital signs, adverse events, and factor IX inhibitor levels.[8] Humoral and cellular responses to the AAV capsid and factor IX were measured periodically after treatment with the use of a neutralizing antibody assay and an interferon-γ enzyme-linked immunosorbent spot (ELISpot) assay, respectively.[8] Liver health was monitored by annual qualitative liver ultrasound, physical examinations, laboratory assessments of liver function, and measurement of alpha-fetoprotein every 26 to 52 weeks after administration. Reporting of findings from liver ultrasounds was based on local site practice, in most cases without pretreatment comparators; no reporting guidelines were prespecified, and no protocol-specified definition of hepatic steatosis was used. During the 5-year follow-up study, only serious adverse events and treatment-related nonserious adverse events (or those of unknown causality) were documented; the determination of whether an adverse event was related to treatment was made by the investigators.

Efficacy assessments included the number of bleeding events treated with exogenous factor IX, the annualized rate of treated bleeding events (annualized bleeding rate), exogenous factor IX use, the number of participants with no treated bleeding events, and factor IX activity levels. Additional details of the assessments are provided in the Supplementary Appendix. Data on factor IX use during the year before vector administration were collected retrospectively at enrollment; data on factor IX use after vector administration were collected prospectively with the use of a paper diary.

STATISTICAL ANALYSIS

All the participants who received fidanacogene elaparvovec and consented to long-term follow-up were included in the efficacy and safety populations. Mean factor IX activity levels were calculated at each yearly visit. The annualized bleeding rate per participant was calculated as the annualized number of breakthrough bleeding events (spontaneous and traumatic) necessitating treatment with exogenous factor IX. The data-cutoff date was August 2, 2022. Durability was assessed (post hoc) as the mean paired difference (and 95% confidence interval) in factor IX activity levels in comparisons of three different time periods after administration of fidanacogene elaparvovec: year 1 (after week 12), years 2 and 3, and years 4 through 6. We calculated the confidence interval for the mean paired difference as a marker of stability, with the means for years 2 and 3 and years 4 through 6 each compared with the mean for year 1.

RESULTS

STUDY POPULATION

A total of 15 men 18 years of age or older with severe to moderately severe hemophilia B were enrolled and received fidanacogene elaparvovec in the phase 1–2a study[8]; 14 of the participants entered the follow-up study, and 1 (Participant 8) chose not to enroll for personal reasons. The demographic and baseline clinical characteristics of the participants are shown in Table S1 in the Supplementary Appendix. The median follow-up duration was 5.5 years (range, 3 to 6), and 8 participants were still participating at the time of the data cutoff. All 14 participants completed at least 3 years of follow-up (see Supplementary Results). Ten participants with hepatitis C, 7 with hepatitis B, and 2 with human immunodeficiency virus (HIV) infection were enrolled. Nine participants reported a history of arthropathy in one or more joints.

SAFETY

Previously, we reported the first-year safety and efficacy results from 10 participants who received fidanacogene elaparvovec.[8] An additional 5 participants were subsequently enrolled and are included in this analysis.

Overall, 14 of the 15 participants (93%) in the phase 1–2a study had adverse events during the first year after administration (Table S2). Of the 14 participants who consented to long-term follow-up, none reported treatment-related adverse events after year 1. Nine serious adverse events in 4 participants were reported; none were deemed to be related to vector or vector-related therapy, and all occurred more than 1 year after administration (Table 1). No adverse events resulted in discontinuation of participation in the study or in death. No thrombotic events or anti–factor IX antibodies were reported.

Three participants overall (7, 9, and 11) received glucocorticoids for elevated liver-enzyme levels during the first year after administration; none received treatment for elevated liver-enzyme levels in the follow-up study (after year 1). Two participants had elevated aminotransferase levels that were considered to be treatment-related (the event in one of these participants was included in the first-year safety and efficacy report).[8] ELISpot results for Participants 7 and 9 showed positivity for AAV capsid antigen after week 2 and week 4, respectively (Fig. S1).

Baseline ultrasound assessments were obtained for 4 participants (11 through 14), and 14 participants had surveillance ultrasound assessments; liver masses were not detected at any time. Ten participants had liver abnormalities noted (Table S3 and Participant Narratives in the Supplementary Appendix), 7 of whom did not have baseline ultrasounds. Hepatic steatosis was the most common abnormality, noted in 4 participants (1, 4, 5, and 7); each of these participants had a baseline body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of greater than 25 (range, 27 to 33) that increased during follow-up. (The body weight in Participant 1 increased each year, from 81.8 kg at screening to 101.7 kg in year 5; however, with purposeful weight loss, this participant's body weight subsequently decreased to 97.9 kg in year 6 [still above screening weight]. The body weight in Participant 5 decreased from screening to year 1 and subsequently increased, then was intentionally decreased between years 5 and 6.) Steatosis was noted on the first liver ultrasound obtained during year 1 after administration in 2 participants (4 and 5) and developed 3 to 6 years after administration in the other 2 participants (1 and 7). Participant 3 had progression of underlying liver fibrosis and scarring, beginning 5 years after administration. His medical history included hepatitis C, hepatitis B, and stage 3 fibrosis on liver biopsy 3 years before administration, as well as HIV infection (see Participant Narratives). Vibration-controlled transient elastography (FibroScan) at trial enrollment showed mild fibrosis (8.3 kPa, F1 fibrosis), a finding consistent with rapid regression after hepatitis C clearance. These ultrasound findings were not considered to be related to fidanacogene elaparvovec. Details of other liver abnormalities found on ultrasound (e.g., gallstones) are provided in the Participant Narratives.

Table 1. Serious Adverse Events during Years 2 through 6 after Vector Administration.

Participant No. and Event	Start Day of Event	Severity	Relationship to Fidanacogene Elaparvovec*	Factor IX Administered
1				
Appendicitis	1293	Severe	Not related	No
4				
Spinal stenosis	1224	Severe	Not related	No
Accident	1325	Mild	Not related	No
Joint dislocation	1325	Mild	Not related	No
Kidney contusion	1325	Mild	Not related	No
Liver contusion	1325	Mild	Not related	No
Rib fracture	1325	Mild	Not related	No
5				
Aortic dissection (type B)	1972	Severe	Not related	No
11				
Hemarthrosis†	704	Severe	Not related	Yes

* The investigator made the determination of whether an adverse event was related to fidanacogene elaparvovec.

† This spontaneous bleeding event occurred in a nontarget joint (i.e., a joint without repeated bleeding and without symptoms of preexisting repeated bleeding) and resulted in hospitalization. Factor IX activity determined by the central laboratory was 12.5% on the day before the bleeding event.

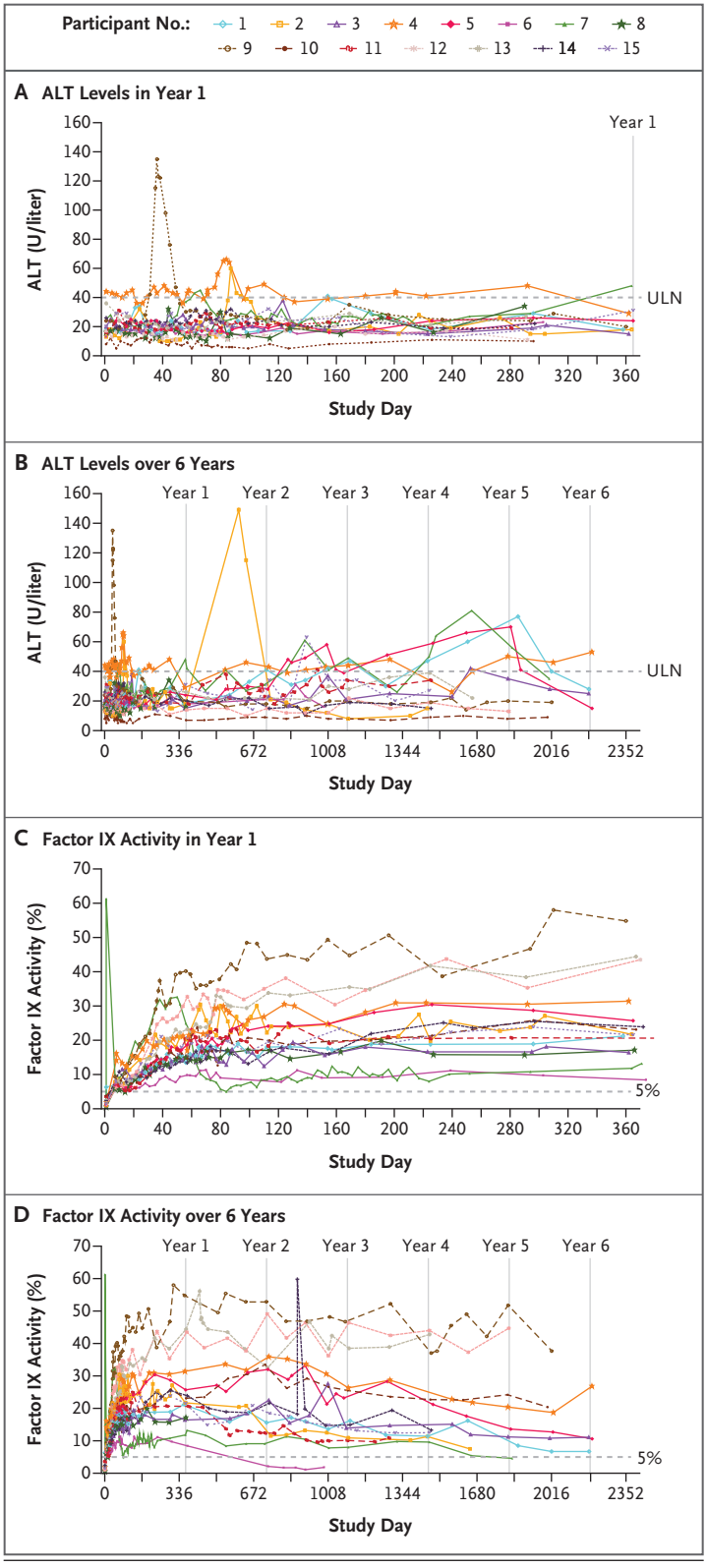

Figure 1. Alanine Aminotransferase Levels and Factor IX Activity (Safety Population).

Factor IX activity was determined by the central laboratory with an Actin FSL-based one-stage clotting assay. On day 869, Participant 14 had an original central laboratory result of 59.8% for factor IX activity; repeat testing on the spare plasma sample from the same date generated a result of 18.2%. (Additional information is provided in the Participant Narratives in the Supplementary Appendix.) Data for Participants 1 through 10 from baseline to year 1 were previously reported.[8] All the participants who received fidanacogene elaparvovec and consented to long-term follow-up were included in the safety population. ALT denotes alanine aminotransferase, and ULN upper limit of the normal range.

Key laboratory results, including liver-enzyme levels, are provided in Table S4. Fluctuations occurred in alanine aminotransferase (ALT) levels (Fig. 1A and 1B and Table S5) and aspartate aminotransferase (AST) levels (Fig. S2). Mean ALT and AST levels increased modestly during follow-up but remained below the upper limit of the normal range. ALT values above the upper limit of the normal range (maximum, 77 U per liter) tended to occur in participants who were found to have steatosis on ultrasound. The elevated levels were associated with weight gain (Table S3); in two participants with weight loss (1 and 5), ALT levels normalized with weight loss. No clinically relevant increases in alfa-fetoprotein levels were noted, and no cancers were detected.

All 15 participants had baseline anti-AAV neutralizing antibody titers of less than 1:5. Anti-AAV neutralizing antibodies developed rapidly after treatment administration and persisted at high levels during follow-up (Table S6).

CLINICAL OUTCOMES

Factor IX activity levels in each year overall and for each participant are shown in Figure 1C and 1D and Figure S3. Mean factor IX levels were sustained in the mild hemophilia range; the mean levels in years 4 through 6 ranged from 7.4 to 44.2% (Table 2). The 95% confidence interval for the difference between an individual participant's mean factor IX activity level in year 1 and in years 2 and 3 was –2.9 to 3.9 percentage points (among 14 participants), and that for the difference between year 1 and years 4 through 6

Table 2. Factor IX Activity.*

Participant No.	Mean in Year 1 (Range)	Mean in Years 2 and 3 (Range)	Mean in Years 4–6 (Range)	Mean Change, Year 1 to Years 2 and 3	Mean Change, Year 1 to Years 4–6
		percent		*percentage points*	
1	18.0 (15.2 to 21.2)	16.2 (13.6 to 18.8)	10.2 (6.7 to 16.2)	−1.8	−7.7
2	24.1 (19.8 to 30.0)	14.4 (10.9 to 20.8)	9.7 (7.5 to 11.3)	−9.6	−14.4
3	16.0 (12.4 to 19.4)	18.9 (13.9 to 27.6)	12.5 (10.8 to 15.1)	2.9	−3.6
4	28.6 (24.2 to 31.4)	32.4 (26.3 to 35.9)	23.2 (18.7 to 28.7)	3.8	−5.4
5	25.2 (20.6 to 30.4)	27.7 (21.3 to 33.2)	17.3 (10.6 to 28.3)	2.5	−7.9
6	9.2 (7.8 to 11.2)	1.7 (1.1 to 2.1)	—	−7.5	—
7†	9.5 (5.0 to 13.2)	9.5 (7.8 to 11.7)	7.4 (4.6 to 9.8)	<0.1	−2.1
8	16.7 (14.6 to 19.8)	—	—		
9†	46.7 (38.7 to 58.0)	49.9 (46.7 to 55.4)	44.2 (37.1 to 52.2)	3.2	−2.6
10	21.0 (18.7 to 25.8)	28.0 (23.5 to 33.5)	22.7 (20.4 to 24.2)	7.0	1.7
11†	20.7 (16.6 to 24.9)	12.4 (9.6 to 20.3)	10.3 (9.7 to 10.9)	−8.3	−10.4
12	36.1 (30.4 to 43.7)	42.2 (36.2 to 49.1)	42.1 (37.3 to 44.7)	6.1	6.0
13	35.1 (29.4 to 44.4)	44.2 (32.5 to 56.1)	40.9 (38.9 to 42.8)	9.1	5.7
14	19.8 (13.1 to 25.5)	23.0 (14.7 to 59.8)	16.4 (13.3 to 19.4)	3.2	−3.4
15	20.3 (16.4 to 23.8)	16.4 (13.1 to 20.8)	12.5 (12.4 to 12.5)	−4.0	−7.9
Overall					
95% CI				−2.9 to 3.9	−7.6 to −0.4
Mean				0.5±5.9	−4.0±6.0
With Participant 2 omitted					
95% CI				−2.0 to 4.5	−6.5 to 0.3
Mean				1.2±5.4	−3.1±5.3

* Plus–minus values are means ±SD. The arithmetic mean factor IX activity is shown for each period. Participant 8 did not participate in long-term follow-up. Summary data include only valid measurements in participants who had at least 96 hours of washout for plasma or recombinant factor IX or up to approximately 168 hours of washout for extended half-life recombinant factor IX before factor IX sample collection.
† Glucocorticoids were used in the first year after treatment.

was −7.6 to −0.4 percentage points (among 13 participants) (Table 2). Participant 2 had the largest decline from year 1 to years 4 through 6 (from 24.1% in year 1 to 9.7% after 4 years 6 months), which occurred immediately after a half-year period of abnormal liver-function testing that coincided with heavy alcohol consumption (Fig. S4 and Participant Narratives). After cessation of excessive alcohol intake, his factor IX activity level stabilized, as assessed over the subsequent 2 years. Exclusion of factor IX activity levels from Participant 2 that were associated with likely alcohol-related hepatitis resulted in a 95% confidence interval for the difference from year 1 to years 4 through 6 of −6.5 to 0.3 percentage points.

The mean annualized bleeding rate (±SD) decreased from 8.9±14.0 in the year before administration to 0.4±1.1 in year 1, 0.9±3.2 in year 2, 0.4±0.9 in year 3, 0.1±0.5 in year 4, 0.2±0.6 in year 5, and 0.4±0.8 in year 6 after treatment (Table S7). The median annualized bleeding rate was 0. Ten

Table 3. Observed Treated Bleeding Events in Each Year.

Measure	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
No. of participants	15	14	14	14	13	8	15
Participants with treated bleeding events — no. (%)	3 (20)	2 (14)	3 (21)	1 (7)	1 (8)	2 (25)	5 (33)
Spontaneous bleeding events — no.	6	9	3	2	1	2	23
Joint	5	7	3	2	0	1	18
Muscle or soft tissue	1	2	0	0	1	1	5
Traumatic bleeding events — no.	0	3	2	0	1	1	7
Joint	0	3	0	0	0	1	4
Muscle	0	0	2	0	1	0	3
Participants without treated bleeding events — no. (%)	12 (80)	12 (86)	11 (79)	13 (93)	12 (92)	6 (75)	10 (67)

participants (67%) had no treated bleeding episodes during the 5-year follow-up beginning 1 year after treatment (Fig. 2 and Table 3). Five participants had bleeding events during the study (Table 3 and Table S8). The most common bleeding events were spontaneous bleeds into joints. Measurements of factor IX activity were not always available at the time of each bleeding event. Figure S5 demarcates the timing of bleeding events in relation to individual factor IX levels over time, and factor IX activity before each bleed is shown in Table S8; all bleeding events occurred at times when the most recent determined factor IX activity level was less than 25% and were controlled with exogenous factor IX.

A total of 13 surgical procedures (in 8 participants) were performed after treatment. No bleeding events beyond expected blood loss were associated with surgery. For 10 procedures, exogenous factor IX was administered (Table S9). Three procedures were performed without exogenous factor IX and without complications (appendectomy [Participant 1; presurgery factor IX activity level, 11.8%], lumbar discectomy [Participant 4;

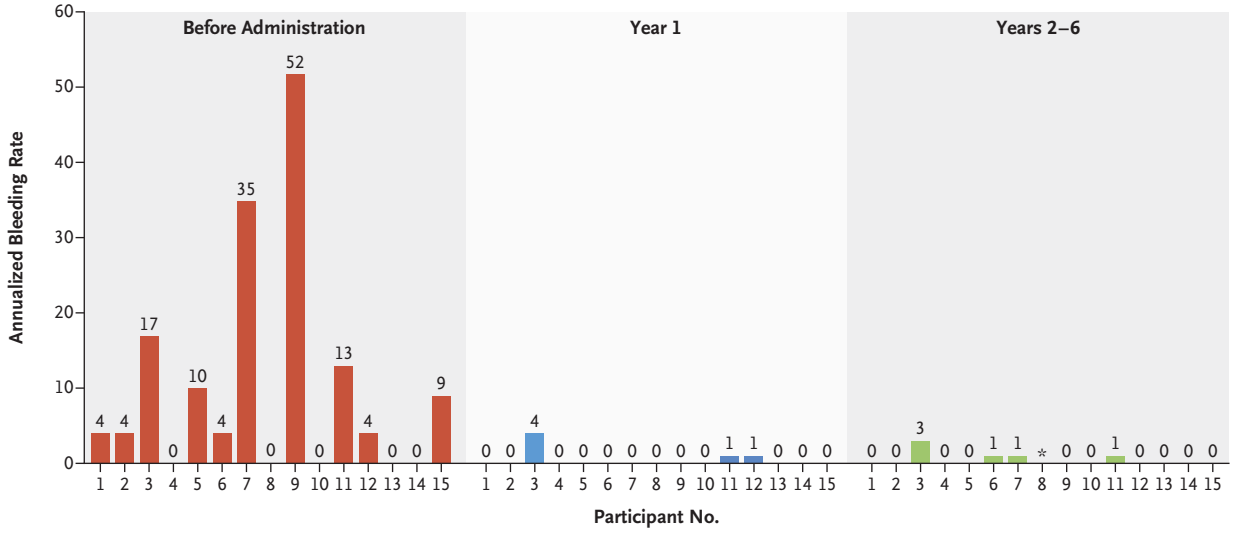

Figure 2. Annualized Rates of Treated Bleeding Events (Safety Population).

The annualized bleeding rate is calculated as follows: (number of treated bleeding events÷number of days in observation period)×365.25 days. Perioperative bleeding episodes are excluded. Participant 8 did not participate in long-term follow-up.

presurgery factor IX activity level, 26.3%], and polypectomy during colonoscopy [Participant 14; presurgery factor IX activity level, 14.9%]). Participant 4 had a downhill skiing accident that resulted in a separated shoulder, fractured ribs, and organ contusion. No exogenous factor IX was given, and no bleeding complications occurred. The factor IX activity level 38 days before the accident was 28.7%.

No participant resumed factor IX prophylaxis. The mean baseline annual infusion rate among the 11 participants who were using prophylaxis in the year before treatment was 71.2. The mean annual infusion rate during year 1 after treatment was 1.1 and remained low during follow-up (Fig. S6). Annualized factor IX consumption according to year, both overall and for each participant, is shown in Figures S7 and S8.

DISCUSSION

Liver-directed AAV-based gene therapy offers promise for people living with hemophilia B or other genetic disorders.[6,7,11-18] However, the long-term safety and efficacy of this approach remain unknown. Here, we have provided the results of follow-up for 3 to 6 years among patients with hemophilia B after AAV-based gene transfer of FIX-R338L, which resulted in sustained transgene expression. In addition, these data support the in vivo hemostatic function and low thrombotic risk at these levels of FIX-R338L. Fidanacogene elaparvovec is now approved in Canada, the United States, and Europe for the treatment of adults with hemophilia B.[19-21]

The overall safety results suggest that fidanacogene elaparvovec is generally safe. Asymptomatic liver abnormalities were identified in surveillance ultrasounds, including hepatic steatosis in four participants with overweight and progression to cirrhosis in one participant who had preexisting advanced liver fibrosis associated with iatrogenic hepatitis C virus infection. In accordance with the protocol, liver ultrasound studies were performed from year 1 onward as a safety measure to screen for hepatocellular carcinoma; the protocol did not require a baseline ultrasound and was not designed to rigorously assess abnormalities related to steatosis in a standardized manner. However, the prevalence of hepatic steatosis in this study is consistent with the approximate 40% prevalence among men[22] and the 40 to 50% prevalence among people living with hemophilia.[22-25] Some changes in liver-enzyme levels were noted, generally in participants in whom steatosis developed. Of note, in two participants with weight loss, ALT levels reverted to normal, which suggested that the hepatitis probably was related to metabolic dysfunction–associated steatotic liver disease. For all participants, mean ALT levels remained within normal limits and liver synthetic function appeared unaffected, as determined by laboratory evaluations. The investigators considered these liver abnormalities unlikely to be related to fidanacogene elaparvovec, but further monitoring is planned. No cases of cancer have been reported. The interplay between the progression of these liver diseases and AAV gene therapy remains unknown, which emphasizes the importance of continued follow-up of gene-therapy recipients.

The annualized bleeding rate remained low during follow-up. Although individual variation was observed, factor IX levels usually remained within the mild hemophilia range. This variation in transgene-product levels among participants is consistent with findings in other studies of AAV-based gene therapy for hemophilia, and its determinants should be examined in future studies. Factor IX activity levels were stable between year 1 and years 2 and 3, a finding consistent with a previous report of wild-type factor IX expression after AAV-mediated gene transfer.[7] The high specific activity of FIX-R338L probably magnifies subtle differences in factor IX antigen levels.[26] The decline in factor IX activity level in Participant 2 deviated from that in other participants and may have been due to toxic effects in the liver associated with heavy alcohol consumption. Although definitive conclusions cannot be drawn from observations of this single participant, his experience suggests the importance of avoiding heavy alcohol use after gene therapy.

The amelioration of bleeding in this cohort is generally consistent with the measured one-stage factor IX activity. Evidence that FIX-R338L had a substantial effect on bleeding in these participants also came from several major hemostatic challenges. Three participants underwent surgical procedures successfully without receiving exogenous factor IX, a finding consistent with that in a recent case report of an AAV-FIX-R338L recipient who underwent knee replacement.[27]

Glucocorticoid use, either prophylactic or in response to potential immune-mediated reactions to AAV capsid proteins, has been widely adopted in AAV-mediated gene-therapy trials. Three participants in our study received glucocorticoids, with their use limited to the first year after treatment.

Optimizing efficacy while minimizing potential toxicity is a goal of vector design. In this study, participants had clinical improvements that aligned with those seen in other gene-therapy studies in which much higher vector doses were used.[16-18,28] This efficacy with the use of a low vector dose has important implications for the reduction of potential risks, such as the risk of vector dose–dependent random AAV integration[29,30] and the associated risk of genotoxic effects leading to cancer, as well as the risk of vector being spread through bodily fluids.

This study has several limitations, including a small patient cohort and a lack of standardized liver imaging. Regardless, this study reflects long follow-up in a study of gene therapy for hemophilia B in which factor IX activity levels were sustained in the mild hemophilia range. The safety and efficacy in 2 participants with HIV infection were similar to those in the overall cohort, which suggests that chronic HIV infection in patients without detectable viral loads should not be an exclusion criterion in future studies, although the antiretroviral regimen must be assessed.[31] Among the 14 participants followed for more than 1 year, the therapy led to a sustained clinical response and generally no or low-grade adverse events, which suggests possible long-term clinical benefit with fidanacogene elaparvovec. In addition, this study supports the in vivo hemostatic efficacy of FIX-R338L. A phase 3 study of fidanacogene elaparvovec of up to 6 years' duration is ongoing (NCT03861273).

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Disclosure forms provided by the authors are available with the full text of this article.

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