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Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

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ABSTRACT

BACKGROUND

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is an adeno-associated virus 5 (AAV5)–based gene-therapy vector containing a coagulation factor VIII complementary DNA driven by a liver-selective promoter. The efficacy and safety of the therapy were previously evaluated in men with severe hemophilia A in a phase 1–2 dose-escalation study.

METHODS

We conducted an open-label, single-group, multicenter, phase 3 study to evaluate the efficacy and safety of valoctocogene roxaparvovec in men with severe hemophilia A, defined as a factor VIII level of 1 IU per deciliter or lower. Participants who were at least 18 years of age and did not have preexisting anti-AAV5 antibodies or a history of development of factor VIII inhibitors and who had been receiving prophylaxis with factor VIII concentrate received a single infusion of 6×10^{13} vector genomes of valoctocogene roxaparvovec per kilogram of body weight. The primary end point was the change from baseline in factor VIII activity (measured with a chromogenic substrate assay) during weeks 49 through 52 after infusion. Secondary end points included the change in annualized factor VIII concentrate use and bleeding rates. Safety was assessed as adverse events and laboratory test results.

RESULTS

Overall, 134 participants received an infusion and completed more than 51 weeks of follow-up. Among the 132 human immunodeficiency virus–negative participants, the mean factor VIII activity level at weeks 49 through 52 had increased by 41.9 IU per deciliter (95% confidence interval [CI], 34.1 to 49.7; P<0.001; median change, 22.9 IU per deciliter; interquartile range, 10.9 to 61.3). Among the 112 participants enrolled from a prospective noninterventional study, the mean annualized rates of factor VIII concentrate use and treated bleeding after week 4 had decreased after infusion by 98.6% and 83.8%, respectively (P<0.001 for both comparisons). All the participants had at least one adverse event; 22 of 134 (16.4%) reported serious adverse events. Elevations in alanine aminotransferase levels occurred in 115 of 134 participants (85.8%) and were managed with immune suppressants. The other most common adverse events were headache (38.1%), nausea (37.3%), and elevations in aspartate aminotransferase levels (35.1%). No development of factor VIII inhibitors or thrombosis occurred in any of the participants.

CONCLUSIONS

In patients with severe hemophilia A, valoctocogene roxaparvovec treatment provided endogenous factor VIII production and significantly reduced bleeding and factor VIII concentrate use relative to factor VIII prophylaxis. (Funded by BioMarin Pharmaceutical; GENEr8-1 ClinicalTrials.gov number, NCT03370913.)

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*A list of the members of the GENEr8-1 Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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The X-linked bleeding disorder hemophilia A is caused by pathologic genetic variants in the gene encoding coagulation factor VIII.[1] People with severe hemophilia A (factor VIII activity level, <1 IU per deciliter) have bleeding into soft tissues and joints that results in chronic pain and reduced mobility from hemophilic arthropathy.[1-3] Prophylactic regimens of exogenous factor VIII or emicizumab, a bispecific monoclonal antibody mimicking activated factor VIII, have improved outcomes for people with hemophilia A but do not eliminate breakthrough bleeding.[4-7]

Adeno-associated virus (AAV) vector gene therapy may improve hemophilia A outcomes and reduce treatment burden. Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is an AAV5-based gene-therapy vector that expresses a B-domain–deleted human factor VIII coding sequence from a hepatocyte-selective promoter.[8-10]

In a phase 1–2 study, valoctocogene roxaparvovec provided sustained endogenous factor VIII production and reductions in both bleeding and factor VIII use for up to 5 years.[8-10] The most common adverse event was an increase in the alanine aminotransferase level, usually occurring within 26 weeks after infusion and resolving with glucocorticoid treatment.[8-10]

GENEr8-1 is an open-label, single-group, multicenter, phase 3 study in which the efficacy and safety of valoctocogene roxaparvovec is being evaluated in people with hemophilia A. Here, we present the primary 52-week results and 2-year results from a subgroup of participants.

METHODS

STUDY DESIGN

We enrolled men who were at least 18 years of age, had severe congenital hemophilia A (factor VIII activity level, ≤1 IU per deciliter), had been receiving prophylaxis with factor VIII concentrates for at least 1 year before enrollment, and were negative for factor VIII inhibitors. Key exclusion criteria included anti-AAV5 capsid antibodies (total binding antibodies, as described previously[11]), human immunodeficiency virus (HIV) infection (added as a criterion after a protocol amendment), and substantial liver dysfunction, substantial liver fibrosis, or liver cirrhosis (see the Supplementary Appendix and the protocol, available with the full text of this article at NEJM.org). We planned to enroll 20 participants directly and to enroll 110 participants from the prospective, noninterventional 270-902 study, in which historical data and at least 6 months of prospective data on bleeding and factor VIII use with standard-of-care prophylaxis were collected.[12]

After informed consent had been obtained and screening and baseline assessments had been performed, participants received valoctocogene roxaparvovec at a dose of 6×10^{13} vector genomes (vg) per kilogram of body weight through peripheral vein infusion. Factor VIII prophylaxis continued through 4 weeks after infusion; thereafter, factor VIII was used as needed. Additional study procedures are described in the Supplementary Appendix.

If an elevation in the alanine aminotransferase level occurred, initiation of an immunosuppressant was considered (see the Supplementary Appendix). Treatment with oral prednisone or prednisolone was started at a dose of 60 mg per day and was tapered over a period of at least 8 weeks. Other immunosuppressants were administered if the investigator, after consulting the medical monitor, determined that glucocorticoids were contraindicated, caused unacceptable side effects, or resulted in poor or no response.

END POINTS

The primary efficacy end point was the change from baseline in factor VIII activity at 49 to 52 weeks after infusion, as measured in a central laboratory with a chromogenic substrate assay (lower limit of quantitation, 3.0 IU per deciliter). The secondary efficacy end points were the changes from baseline in annualized use of factor VIII concentrate and the annualized number of treated bleeding episodes after week 4 (from week 5 to the last visit before data cutoff). Additional reported end points included factor VIII activity as measured with a one-stage assay (lower limit of quantitation, 1.0 IU per deciliter), efficacy in participants who received an infusion at least 2 years before the data cutoff, and changes in types of bleeding and reasons for factor VIII use.

Safety was assessed through recording of adverse events (graded with the use of the Common Terminology Criteria for Adverse Events, version 4.03), laboratory testing, and physical examination. The definitions of elevations in alanine aminotransferase levels as adverse events are provided in the Supplementary Appendix.

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OVERSIGHT

The sponsor, BioMarin Pharmaceutical, designed this study with input from the authors. Authors who are employees of the sponsor contributed to the study design, and authors who are not employees of the sponsor provided consultation on the design and conduct of the study. Employees of the sponsor oversaw the collection and analysis of the data. The first draft of the manuscript was written by a medical writer contracted by the sponsor, under the direction of the authors; all the authors critically reviewed the manuscript and provided substantive input during drafting. All the authors contributed to data interpretation and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. The study was conducted in accordance with Good Clinical Practice guidelines and local regulations. Independent ethics committees or institutional review boards at each study site approved the protocol. Participants provided written informed consent before enrollment. An independent data and safety monitoring committee oversaw the safety of the participants and the ethics of the study conduct. A data-access plan minimizing bias and preserving the scientific and business integrity of this single-group, open-label study strictly limited sponsor access to efficacy data before protocol-specified analyses were performed.

STATISTICAL ANALYSIS

The primary efficacy end point of the change from baseline in factor VIII activity was analyzed in HIV-negative participants who received valoctocogene roxaparvovec (modified intention-to-treat population). The baseline factor VIII activity level was imputed as 1 IU per deciliter, since no factor VIII washout period was required. The change from baseline in median factor VIII activity during weeks 49 through 52 was evaluated with a one-sided significance level of 0.05 against the null hypothesis that the change from baseline was zero. For missing data, the last observation was carried forward.

The secondary end points of the change from baseline in annualized factor VIII concentrate use and treated bleeding rate were analyzed in the subgroup of participants in the modified intention-to-treat population who had at least 6 months of prospectively collected bleeding and factor VIII usage data from the 270-902 study (rollover population from the noninterventional study). Both end points were assessed with the use of two-sided one-sample t-tests against the null hypothesis that the change from baseline was zero. The annualized rate of treated bleeding episodes was tested first for noninferiority as compared with prophylaxis (margin, 3.5 episodes per year) and then, if significant, was tested for superiority as compared with prophylaxis. The primary and secondary efficacy end points were tested hierarchically to control overall type I error.[13] The planned sample size provided at least 90% power for testing the superiority of the efficacy end points (see the Supplementary Appendix).

RESULTS

PARTICIPANTS

Overall, 181 men with severe hemophilia A were screened; 144 were enrolled at 48 sites in 13 countries worldwide between December 19, 2017, and November 15, 2019 (Fig. S1 in the Supplementary Appendix). Most of the participants who were ineligible after screening (26 of 37) were excluded from the study because of positivity for anti-AAV5 capsid antibodies (Fig. S2). Overall, 134 participants received one valoctocogene roxaparvovec infusion (6×10^{13} vg per kilogram of body weight) and completed week 49–52 visits. As of the November 16, 2020, data cutoff, one participant had been lost to follow-up, at week 66. Median follow-up was 60.2 weeks (range, 51.1 to 150.4).

The intention-to-treat population included all 134 participants who received an infusion. The modified intention-to-treat population included the 132 HIV-negative participants, 17 of whom received an infusion at least 2 years before the data cutoff. The rollover population included 112 participants from the modified intention-to-treat population who had at least 6 months of data from the 270-902 study. The baseline characteristics of the participants in the different study populations were generally similar (Table 1); in the subgroup of participants in the modified intention-to-treat population who received the infusion 2 or more years before the data cutoff, both the percentage of participants who had problem joints (defined as joints with chronic pain, chronic synovitis, arthropathy, limited motion, or recurrent bleeding) and the median annualized rate of factor VIII use were higher than they were in the full study population. At base-

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Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	Modified Intention-to-Treat Population, ≥2-Year Subgroup (N=17)†	Rollover Population (N=112)‡	Modified Intention-to-Treat Population (N=132)	Intention-to-Treat Population (N=134)§
Age at enrollment — yr				
Mean	29.5±6.0	31.8±10.6	31.4±10.1	31.7±10.3
Median (range)	29.0 (19–43)	30.0 (19–70)	30.0 (18–70)	30.0 (18–70)
Male sex — no. (%)	17 (100)	112 (100)	132 (100)	134 (100)
Race or ethnic group — no. (%)¶				
White	14 (82)	78 (69.6)	94 (71.2)	96 (71.6)
Asian	1 (6)	17 (15.2)	19 (14.4)	19 (14.2)
Black	1 (6)	14 (12.5)	15 (11.4)	15 (11.2)
Hawaiian or Pacific Islander	0	1 (0.9)	1 (0.8)	1 (0.7)
Not provided‖	1 (6)	2 (1.8)	3 (2.3)	3 (2.2)
Hispanic or Latino	1 (6)	5 (4.5)	7 (5.3)	7 (5.2)
Body-mass index**	26.4±3.8	25.2±4.7	25.3±4.6	25.3±4.6
Medical history — no. (%)				
Hepatitis B	1 (6)	17 (15.2)	18 (13.6)	20 (14.9)
Hepatitis C	6 (35)	33 (29.5)	39 (29.5)	41 (30.6)
HIV infection	0	0	0	2 (1.5)
Positive factor VIII inhibitor test††	0	1 (0.9)‡‡	1 (0.8)‡‡	1 (0.7)‡‡
Number of problem joints at study initiation — no. (%)§§				
0	10 (59)	82 (73.2)	95 (72.0)	97 (72.4)
1	4 (24)	13 (11.6)	17 (12.9)	17 (12.7)
2	0	9 (8.0)	9 (6.8)	9 (6.7)
3	2 (12)	6 (5.4)	8 (6.1)	8 (6.0)
>3	1 (6)	2 (1.8)	3 (2.3)	3 (2.2)
Receipt of factor VIII prophylaxis for hemophilia A — no. (%)	17 (100)	112 (100)	132 (100)	134 (100)
SHL products	10 (59)	69 (61.6)	81 (61.4)	83 (61.9)
EHL products	7 (41)	28 (25.0)	36 (27.3)	37 (27.6)
Plasma-derived products	1 (6)	23 (20.5)	24 (18.2)	24 (17.9)
Missing data	1 (6)	0	1 (0.8)	1 (0.7)
Duration of baseline collection period — mo	13.1±0.4	8.4±2.2	9.1±2.6	9.2±2.6
Prestudy annualized factor VIII usage — IU/kg/yr				
Mean	4830.0±1578.1	3961.2±1751.5	4111.3±1747.8	4113.5±1739.0
Median (range)	4635.0 (2550.9–7885.0)	3754.4 (1296.4–11251.1)	3860.3 (1296.4–11251.1)	3860.3 (1296.4–11251.1)
Prestudy annualized factor VIII infusions — infusions/yr				
Mean	152.9±86.6	135.9±52.0	138.1±57.2	137.5±57.0
Median (range)	119.7 (49.3–358.7)	128.6 (39.5–363.8)	125.1 (39.5–363.8)	121.1 (39.5–363.8)
Annualized rate of treated bleeds — bleeds/yr				
Mean	9.5±22.5	4.8±6.5	5.4±10.0	5.4±10.0
Median (range)	0.9 (0–91.5)	2.8 (0–33.1)	2.0 (0–91.5)	2.3 (0–91.5)

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Table 1. (Continued.)

* Plus–minus values are means ±SD. EHL denotes extended half-life, and SHL standard half-life.
† This subgroup included participants in the modified intention-to-treat population (human immunodeficiency virus [HIV]–negative participants who received valoctocogene roxaparvovec) who received the infusion 2 or more years before data cutoff date.
‡ The rollover population included participants from the modified intention-to-treat population for whom at least 6 months of data were available from their participation in the noninterventional 270-902 study.
§ The intention-to-treat population included all participants who received an infusion.
¶ Race and ethnic group were reported by the participants.
‖ Information is not provided because of patient privacy laws.
** Body-mass index is the weight in kilograms divided by the square of the height in meters.
†† Positivity for factor VIII inhibitors was defined as a result of at least 0.6 Bethesda units (BU) on a Bethesda assay or a Bethesda assay with Nijmegen modification or at least 1.0 BU for laboratories with a historical lower sensitivity cutoff for inhibitor detection of 1.0 BU.
‡‡ This participant's factor VIII inhibitor test result was determined to be a false positive.
§§ Problem joints were identified by the investigators at baseline and were defined as joints with any of the following symptoms: chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.

line, 61.9% of the participants were receiving factor VIII prophylaxis with standard half-life products, 27.6% with extended half-life products, and 17.9% with plasma-derived products. No participants were receiving emicizumab.

PRIMARY AND SECONDARY EFFICACY END POINTS

In the modified intention-to-treat population (132 participants), the mean (±SD) and median chromogenic substrate factor VIII activity levels during weeks 49 through 52 were 42.9±45.5 IU per deciliter and 23.9 IU per deciliter (interquartile range, 11.9 to 62.3), respectively (Figs. 1A and S3A). Factor VIII data were imputed for 2 participants at this time point; results were similar without imputation (Figs. S3B and S4A). The baseline factor VIII activity level was imputed as 1 IU per deciliter; the mean and median changes from baseline were 41.9 IU per deciliter (95% confidence interval [CI], 34.1 to 49.7; P<0.001) and 22.9 IU per deciliter (interquartile range, 10.9 to 61.3), respectively. At weeks 49 through 52, the median factor VIII activity level was 40 IU per deciliter or greater (i.e., nonhemophilic) in 50 participants (37.9%), at least 5 and less than 40 IU per deciliter (mild hemophilia) in 66 participants (50.0%), and less than 5 IU per deciliter in 16 participants (12.1%); 12 participants (9.1%) had a median factor VIII activity level of less than 3 IU per deciliter (additional details and one-stage assay results are provided in Table S1). Inter- and intraparticipant variation in factor VIII activity was observed (Fig. S5).

In the rollover population (112 participants), baseline mean and median annualized factor VIII use was 3961.2 and 3754.4 IU per kilogram per year, respectively (Fig. 2A). After week 4, mean and median annualized factor VIII concentrate use was 56.9 IU per kilogram per year (a 98.6% reduction; P<0.001) and 0 IU per kilogram per year, respectively. The mean and median annualized factor VIII infusion rates were 135.9 and 128.6 infusions per year, respectively, at baseline, and 2.0 (a 98.6% reduction) and 0 infusions per year, respectively, after week 4 (Fig. 2B).

The mean and median annualized rates of treated bleeding episodes at baseline were 4.8 and 2.8 bleeds per year, respectively (Fig. 2C), and declined to 0.8 and 0 bleeds per year, respectively, after week 4 in the rollover population. The mean change from baseline was −4.1 bleeds per year (95% CI, −5.3 to −2.8) — an 83.8% reduction, which met the criteria for superiority to factor VIII prophylaxis (P<0.001).

ADDITIONAL END POINTS

Among the 17 participants who had received infusions at least 2 years before the data cutoff, the mean and median factor VIII activity levels were 42.2±50.9 IU per deciliter and 23.9 IU per deciliter (interquartile range, 11.2 to 55.0), respectively, at weeks 49 through 52 after infusion and were 24.4±29.2 IU per deciliter and 14.7 IU per deciliter (interquartile range, 6.4 to 28.6), respectively, at week 104 (Figs. 1B, S3C, S3D, and S4B). At week 104, the median factor VIII activity level was at least 40 IU per deciliter in 3 participants (18%), at least 5 and lower than 40 IU per deciliter in 10 participants (59%), and less than 5 IU per deciliter in 4 participants (24%); 3 participants (18%) had a median factor VIII activity level of less than 3 IU per deciliter. (Additional details and one-stage assay results are provided in Table S2 and Fig. S6.)

Among the 112 participants in the rollover population, the mean annualized rates of factor VIII concentrate use after week 4 for usual prophylaxis, treatment of bleeding, surgery or other

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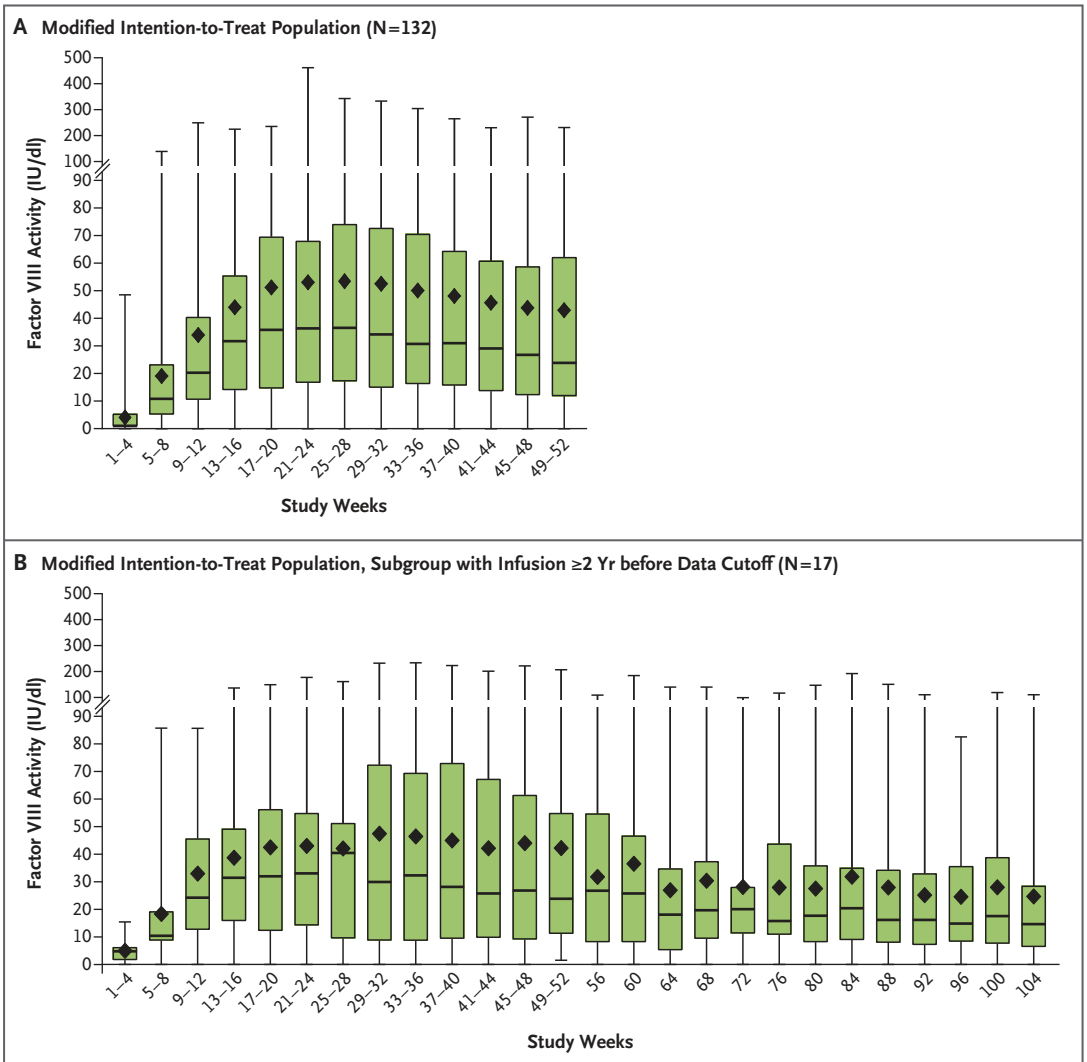

Figure 1. Median Factor VIII Activity Levels over Time.

A chromogenic substrate assay was used to measure factor VIII activity, shown here in 4-week windows in the modified intention-to-treat population (human immunodeficiency virus [HIV]–negative participants who received valoctocogene roxaparvovec; 132 participants) up to weeks 49–52 (Panel A) and in the subgroup of participants in the modified intention-to-treat population who received the infusion 2 or more years before the data cutoff date (17 participants) up to week 104 (Panel B). At weeks 49–52 in the modified intention-to-treat population, the mean and median changes from baseline in factor VIII activity (with the baseline value imputed as 1 IU per deciliter) were 41.9 IU per deciliter (95% confidence interval [CI], 34.1 to 49.7; P<0.001) and 22.9 IU per deciliter (interquartile range, 10.9 to 61.3), respectively. Missing data were imputed with the use of the last-observation-carried-forward approach. Values for factor VIII activity were excluded if they were obtained within 72 hours (or 3 calendar days, if the time was not available) after the last infusion of exogenous factor VIII replacement therapy. Values below the lower limit of quantitation of the chromogenic assay (3 IU per deciliter) were imputed as 0 IU per deciliter. Baseline values were imputed as 1 IU per deciliter, since no washout of factor VIII concentrates was required before infusion with valoctocogene roxaparvovec. Boxes represent the interquartile range, whiskers represent the range, horizontal lines represent the median, and diamonds represent the mean.

procedure, and one-time prophylaxis decreased from baseline by 99.6%, 85.5%, 88.0%, and 30.2%, respectively (Table S3); similar reductions occurred in the annualized infusion rates. Factor VIII was used by 7 participants (6.2%) for surgery or another procedure and by 9 participants (8.0%) as one-time prophylaxis. The mean annualized bleeding rate decreased by 84.2% for

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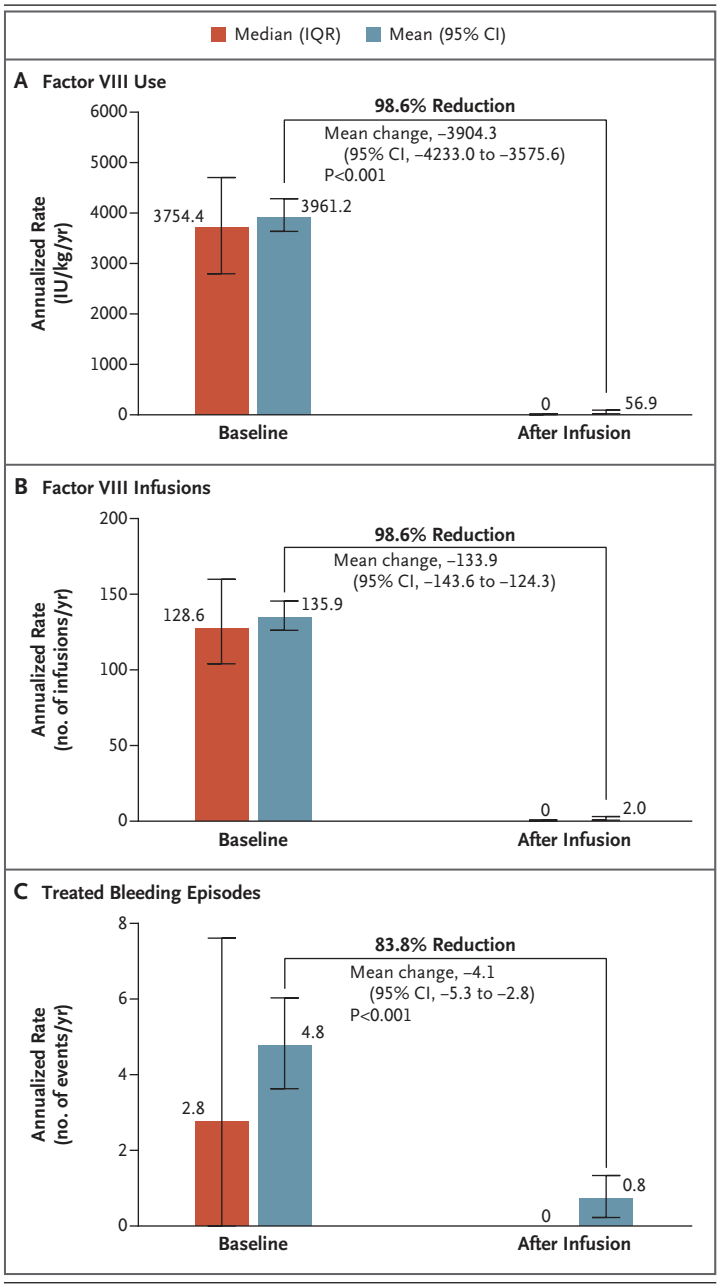

Figure 2. Changes from Baseline in Annualized Factor VIII Use and Infusion Rates and Annualized Treated Bleeding Rate after Infusion (Rollover Population).

The rollover population included 112 participants from the modified intention-to-treat population (HIV-negative participants who received valoctocogene roxaparvovec) who had at least 6 months of data from their participation in the noninterventional 270-902 study. The period after infusion started after week 4. The P values in Panels A and C are from two-sided one-sample t-tests against the null hypothesis that the change from baseline would be zero. The annualized factor VIII use rate was defined as (IU of factor VIII used per kilogram of body weight ÷ total number of days) × 365.25. The annualized factor VIII infusion rate was defined as (number of exogenous factor VIII infusions ÷ total number of days) × 365.25. The annualized treated bleeding rate was defined as (number of treated bleeding episodes ÷ total number of days) × 365.25. The 95% confidence interval for the annualized factor VIII infusion rate should not be used to infer significance, since it was not adjusted for multiplicity. IQR denotes interquartile range.

treated joint bleeds, by 85.0% for treated problem joint bleeds, by 81.3% for treated spontaneous bleeds, and by 85.4% for treated traumatic bleeds (Table S4).

Of the 134 participants in the intention-to-treat population, 35 (26.1%) had no treated bleeds either while receiving prophylaxis or after week 4 (Figs. 3 and S7), and 66 (49.3%) had treated bleeds during the baseline period while receiving prophylaxis but not after week 4. Of the 33 participants (24.6%) with treated bleeds after week 4, the annualized bleeding rate after infusion decreased for 20 participants (14.9%) and increased for 13 (9.7%). The 13 participants with increases in bleeding after infusion included 6 who had bleeds only within 30 days after stopping prophylaxis, 3 who reported only traumatic bleeds, and 4 participants (2 of whom had low factor VIII levels throughout the study) who reported both spontaneous and traumatic bleeds, including those in preexisting problem joints. Overall, 121 of 134 participants (90.3%) had no treated bleeds or fewer treated bleeds after infusion. Participants in each of these categories had a wide range of factor VIII activity values at weeks 49 through 52.

SAFETY

All 134 participants had at least one adverse event (Table 2). Most events were of grade 1 or 2; an increase in alanine aminotransferase level (in 85.8% of the participants), headache (in 38.1%), nausea (in 37.3%), and an increase in aspartate aminotransferase level (in 35.1%) were the most common adverse events. A total of 22 participants (16.4%) reported serious adverse events (Table S5); 5 (3.7%) reported serious adverse events that were determined by the investigators to be related to the study drug. All serious adverse events resolved. No participants died, withdrew because of adverse events, or had development of factor VIII inhibitors. At weeks 49 through 52, factor VIII activity levels greater than 150 IU per deciliter were found in 7 of 134

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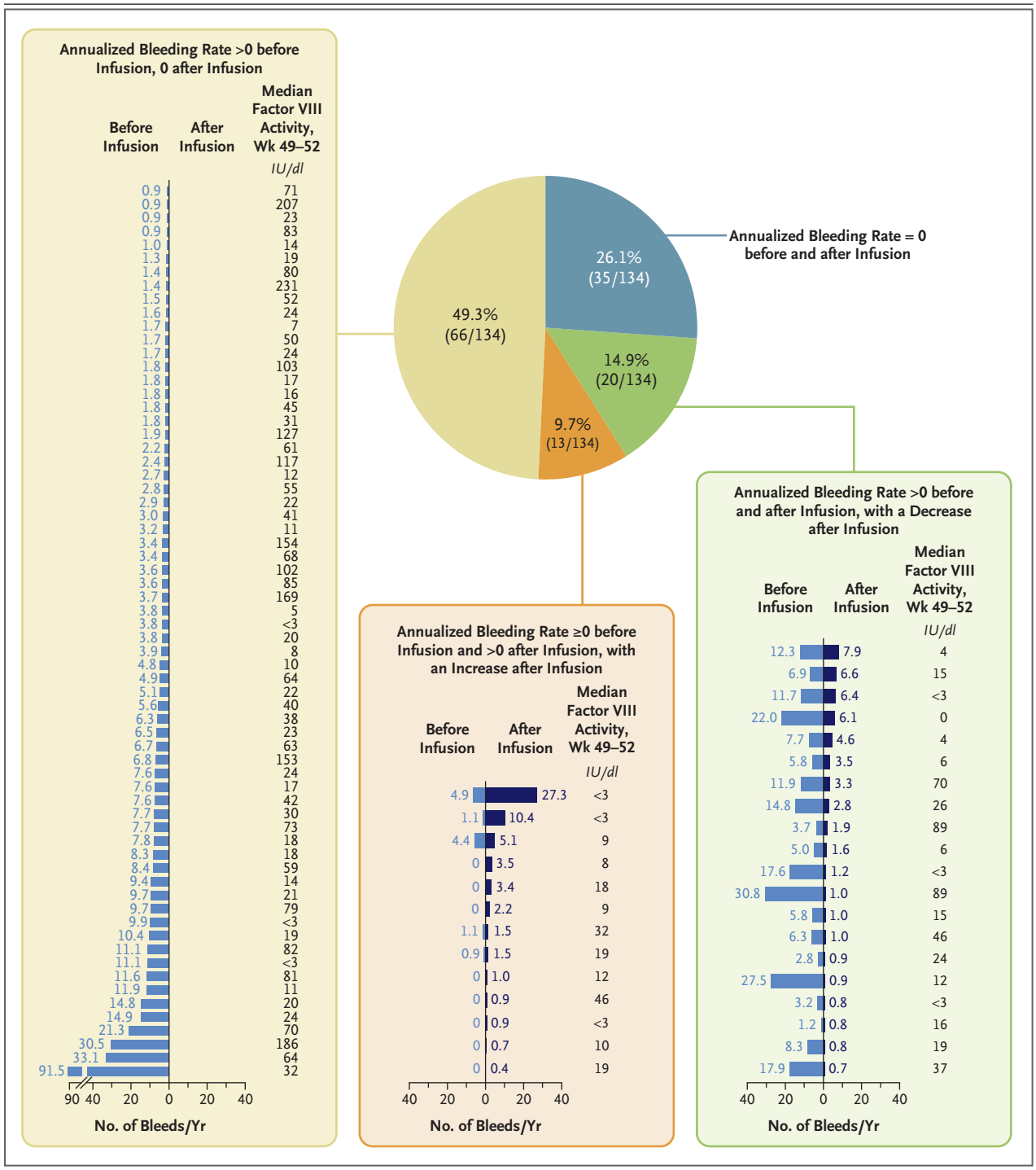

participants (5.2%); no participants reported thromboembolism (see the Supplementary Appendix).

During or shortly after infusion, 7 participants (5.2%) had systemic hypersensitivity; 3 (2.2%) reported serious infusion-related reactions (1 reported maculopapular rash and presyncope, 1 reported an anaphylactic reaction, and 1 reported a hypersensitivity reaction). Infusion reactions were effectively mitigated by slowing or pausing the infusion and administering treatment with supportive medications (e.g., antihistamines, anti-

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Figure 3 (facing page). Annualized Treated Bleeding Rates before and after Infusion in Individual Participants (Intention-to-Treat Population).

Participants were classified as having an annualized treated bleeding rate of 0 before and after infusion (35 participants); a rate of greater than 0 before infusion and a rate of 0 after infusion (66 participants); a rate of greater than 0 before and after infusion, with the rate decreased after infusion (20 participants); or a rate of 0 or greater before infusion and greater than 0 after infusion, with an increase after infusion (13 participants). In the bar graphs, each line represents an individual participant, ordered according to postinfusion annualized bleeding rate. Bars on the left of the vertical axis indicate annualized treated bleeding rates at baseline, and bars on the right indicate annualized treated bleeding rates in the postinfusion period (after week 4). Factor VIII activity was measured with a chromogenic substrate assay. The lower limit of quantitation of the chromogenic substrate assay was 3.0 IU per deciliter. Of the 13 participants with more frequent bleeding after the infusion than before the infusion, 6 had bleeds only within 30 days after stopping prophylaxis, 3 reported only traumatic bleeds, and 4, two of whom had low factor VIII levels throughout the study, reported both spontaneous and traumatic bleeds, including bleeds in preexisting problem joints. An alternative view of this figure with participants ordered according to preinfusion annualized bleeding rate is shown in Figure S7.

pyretics, or glucocorticoids), as indicated. All participants completed the infusion; 4 participants (3.0%) completed the infusion after having it paused.

Overall, 115 participants (85.8%) had an adverse event of an elevation in the alanine aminotransferase level (Table S6). Glucocorticoids were administered as treatment; as of the data cutoff, 96.2% of the events had resolved. The median time to the first elevation in alanine aminotransferase level after infusion was 8.0 weeks. The median duration of elevation was 15 days. In total, 11 participants (8.2%) had grade 3 elevations in alanine aminotransferase level (>5 to 20 times the upper limit of the normal range); one of these participants had two events. Of these 12 events, 2 (in 2 participants [1.5%]) were serious adverse events leading to intervention with intravenous methylprednisolone (see the Supplementary Appendix). None of these events met Hy's law criteria for drug-induced liver injury (elevation in alanine aminotransferase level to >3 times the upper limit of the normal range with elevation in total bilirubin level to >2 times the upper limit of the normal range without findings of obstruction, cancer, or impaired glucuronidation capacity).[14] Of the 12 grade 3 events, 9 occurred within 26 weeks after infusion and 3 occurred during weeks 26 through 36; all were managed with glucocorticoids and resolved. No grade 4 or higher elevations in alanine aminotransferase level occurred.

A total of 106 participants (79.1%) received glucocorticoids in accordance with the protocol (Table S7). The median time to initiation of glucocorticoid treatment was 8.1 weeks, and the median treatment duration was 230 days (range, 22 to 551). Adverse events attributed to glucocorticoid treatment were reported by 79 of the 110 participants (71.8%) who received any glucocorticoids; the most common events were acne, insomnia, Cushing's syndrome, and weight increase. Serious adverse events attributed to glucocorticoids occurred in 3 of the 110 participants (2.7%) (Table S8). Other immunosuppressants were used by 39 participants (29.1%) (Table S9) because of contraindications, side effects, or a poor or no response to glucocorticoid treatment (Table S10).

DISCUSSION

Valoctocogene roxaparvovec substantially increased factor VIII activity and reduced the annualized rates of factor VIII use and bleeding as compared with factor VIII prophylaxis. At weeks 49 through 52, a median factor VIII activity level of 5 IU per deciliter or higher was found in 88.1% of participants. The annualized rates of factor VIII use and treated bleeding declined by 98.6% and 83.8%, respectively, after infusion.

Both intra- and interindividual variability in factor VIII activity after gene transfer were notable. In the modified intention-to-treat population at weeks 49 through 52, 7 participants (5.3%) had a median factor VIII activity level greater than 150 IU per deciliter. During the same interval, 12 participants (9.1%) had a median factor VIII activity level of less than 3 IU per deciliter as measured with a chromogenic assay; as measured with a one-stage assay, 2 participants (1.5%) had a factor VIII activity level of less than 1 IU per deciliter. The causes of this variability are not fully understood, but many biologic variables[15-17] and molecular events related to gene transfer and expression (e.g., hepatocyte transduction, vector-encoded factor VIII sequence transcription, factor VIII protein fold-

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Table 2. Adverse Events (Intention-to-Treat Population).*

Event	Intention-to-Treat Population (N = 134)
	no. (%)
Any adverse event	134 (100)
Grade 1	133 (99.3)
Grade 2	113 (84.3)
Grade 3	35 (26.1)
Grade 4	1 (0.7)
Adverse events occurring in ≥20% of participants	
Alanine aminotransferase increase	115 (85.8)
Headache	51 (38.1)
Nausea	50 (37.3)
Aspartate aminotransferase increase	47 (35.1)
Arthralgia	39 (29.1)
Fatigue	37 (27.6)
Acne	36 (26.9)
Insomnia	28 (20.9)
Upper respiratory tract infection	27 (20.1)
Any serious adverse event	22 (16.4)
Serious adverse events occurring in ≥2 participants	
Alanine aminotransferase increase	2 (1.5)
Diarrhea	2 (1.5)
Gastroenteritis	2 (1.5)
Rectal hemorrhage	2 (1.5)
Any treatment-related adverse event	123 (91.8)
Treatment-related adverse events occurring in ≥20% of participants	
Alanine aminotransferase increase	108 (80.6)
Aspartate aminotransferase increase	39 (29.1)
Nausea	31 (23.1)
Any treatment-related serious adverse event	5 (3.7)
Alanine aminotransferase increase	2 (1.5)
Anaphylactic reaction	1 (0.7)
Hypersensitivity	1 (0.7)
Maculopapular rash†	1 (0.7)
Presyncope†	1 (0.7)
Any adverse event related to glucocorticoids	81 (60.4)
Any adverse event related to nonsteroidal immunosuppressants	14 (10.4)
Adverse events of special interest	
Alanine aminotransferase increase	115 (85.8)
Potential Hy's law case‡	0
Infusion-related reaction§	50 (37.3)
Systemic hypersensitivity	7 (5.2)
Anaphylactic or anaphylactoid reaction	3 (2.2)¶
Thromboembolic event	0
Development of factor VIII inhibitors	0

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Table 2. (Continued.)

* Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 23.0, and were graded for severity with the use of Common Terminology Criteria for Adverse Events, version 4.03. The determination of whether an event was related to the study drug was made by the investigator. Additional details on adverse events are provided in the Supplementary Appendix.
† Maculopapular rash and presyncope occurred in the same participant.
‡ Hy's law cases have three components: elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level to greater than 3 times the upper limit of the normal range (ULN), often much greater (to >5 times or >10 times the ULN); total bilirubin elevations to greater than 2 times the ULN, without findings of obstruction (e.g., an elevated alkaline phosphatase level), cancer, or impaired glucuronidation capacity; and absence of another explanation for the combination of increased ALT or AST and total bilirubin levels (e.g., viral hepatitis or preexisting liver disease).[14]
§ Infusion-related reactions were defined as adverse events occurring within 48 hours after infusion; commonly reported events were nausea (19 participants, 14.2%), fatigue (10 participants, 7.5%), and headache (8 participants, 6.0%). Most events were mild to moderate.
¶ One anaphylactic reaction was considered to be a treatment-related serious adverse event.

ing and secretion, and host immune response against the AAV5 capsid[11,18-24]) may influence endogenous factor VIII production.

Overall, 90.3% of the participants in our study had either no treated bleeds or fewer treated bleeds after infusion than with factor VIII prophylaxis: 26.1% of the participants had no treated bleeds during the baseline period and no treated bleeds after the infusion, 49.3% had treated bleeds while receiving prophylaxis but none after the infusion, and 14.9% had fewer treated bleeds after the infusion than while receiving prophylaxis. Increased bleeding after the infusion was observed in 9.7% of the participants. Some participants with a factor VIII activity level of less than 5 IU per deciliter at weeks 49 through 52 had no bleeds after the infusion, whereas some participants with higher factor VIII activity levels did have bleeds. Previous modeling with epidemiologic data suggests that a factor VIII activity level of greater than 15 IU per deciliter is protective against joint bleeding,[25] but even low levels of clotting factors reduce bleeding.[25-29] Preliminary analyses correlating endogenous factor VIII activity with bleeding in this study suggest that a similar relationship exists (data not shown); analyses are ongoing.

In the phase 1–2 study of valoctocogene roxaparvovec, seven participants who received 6×10^{13} vg per kilogram had a median factor VIII activity level (as measured with a chromogenic assay) of 60.3, 26.2, 19.9, 16.4, and 8.2 IU per deciliter after 1, 2, 3, 4, and 5 years, respectively, and six participants who received 4×10^{13} vg per kilogram had a median factor VIII activity level of 22.9, 13.1, 7.9, and 4.8 IU per deciliter after 1, 2, 3, and 4 years, respectively.[8-10] Few adverse events related to treatment occurred after year 1; no participants chose to resume prophylaxis.[8-10] In this phase 3 study of the dose of 6×10^{13} vg per kilogram, the median factor VIII activity level was 23.9 IU per deciliter at weeks 49 through 52; among the participants who received the infusion 2 years before, the median factor VIII activity level was 14.7 IU per deciliter at week 104. Median factor VIII levels in this study were lower than those with the same dose in the phase 1–2 study. Differences in glucocorticoid use between the studies[8-10] and potential unidentified differences introduced by scaling up the vector-manufacturing process may have contributed to this finding. The decline in factor VIII activity between years 1 and 2 was similar in both studies. Additional follow-up of the participants in the phase 3 study will be required in order to determine the durability of clinical benefit with respect to reduced bleeding and the cessation of prophylaxis resulting from endogenous factor VIII production.

The valoctocogene roxaparvovec infusion was associated mainly with low-grade toxic effects. Systemic hypersensitivity of unknown cause occurred after infusion in 5% of participants. Effective mitigation strategies included slowing the initial infusion rate, pausing the infusion when necessary, providing supportive care, and extending observation after the infusion. All participants completed the infusion.

The most common adverse events were elevations in alanine aminotransferase levels and side effects from the glucocorticoids used to manage them. Although the exact causes of elevations in alanine aminotransferase level after gene transfer are unknown, some, particularly those occurring early after the infusion, may be partially due to inflammatory or immune responses to AAV

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gene transfer.[26,27,30,31] Glucocorticoids reduce that response and were used here reactively to preserve transgene expression and manage elevations in alanine aminotransferase levels.[8,9,26,27,31] Although 29.1% of the participants received other immunosuppressants, most participants also received glucocorticoids (usually first), making it difficult to compare the efficacy of other immunosuppressants with that of glucocorticoids alone. Research on the relationships between elevations in alanine aminotransferase levels, factor VIII expression, and glucocorticoid use is ongoing. A phase 3 study evaluating the efficacy and safety of valoctocogene roxaparvovec with prophylactic glucocorticoids in patients with hemophilia A is currently under way (GENEr8-3; ClinicalTrials.gov number, NCT04323098).

In this study, we did not assess potential vector genome integration into the host nuclear genome, which may pose a risk of insertional mutagenesis and cannot be excluded as a long-term persistence mechanism.[32] Liver-biopsy specimens from participants in this study have not yet been obtained, and therefore we cannot comment on results of histologic assessment, vector distribution, or DNA structures contributing to long-term expression. Although factor VIII activity levels measured within 72 hours after factor VIII therapy were excluded, the use of extended-half-life products may have increased the factor VIII activity in some participants. Because the two participants with HIV infection were excluded from the primary analysis, the clinical applicability of results to persons with HIV infection is limited. Enrollment in the 270-902 study may have been biased because participants and investigators knew that potential participants without AAV5 antibodies who met all other criteria could enter screening for this study; enrollment may have also been biased toward younger people. As in many clinical studies, the generalizability of these results to the general population of patients with severe hemophilia A is difficult to assess, particularly given the low levels of hemophilia A diagnosis and treatment in many parts of the world (Table S11).[33] Although the efficacy of valoctocogene roxaparvovec cannot be directly compared with that of emicizumab because participants in this study had previously been using factor VIII concentrates, the annualized rates of treated bleeding here were similar to those reported with long-term emicizumab prophylaxis.[7]

Gene therapy for hemophilia A may enable maintenance of steady, endogenous factor VIII activity without regular prophylaxis. The expression of the transferred gene appears to decline over time; further study is needed to address whether repeat treatment will be necessary or possible. Valoctocogene roxaparvovec gene transfer for severe hemophilia A provided significant increases in factor VIII activity with reduced bleeding and factor VIII use for most participants over a period of up to 2 years. The most common adverse event was an elevation in alanine aminotransferase level. Overall, the risk–benefit profile appears favorable; we look forward to learning more about the long-term durability and safety of the treatment as we continue to follow the participants in this study.

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APPENDIX

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