Anthem

Medical Policy

Subject: Gene Therapy for Hemophilia
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Description/Scope

This document addresses gene therapy for hemophilia, a congenital medical condition in which the blood does not clot normally due to lack of sufficient blood-clotting proteins known as clotting factors. There are several forms of hemophilia, the most common of which are hemophilia A, which involves a deficiency in clotting factor VIII, and hemophilia B, which involves a deficiency in clotting factor IX. Gene therapy products for hemophilia use a virus vector with a working copy of the missing gene attached (factor VIII and factor IX for hemophilia A and B, respectively).

Position Statement

Medically Necessary:

Etranacogene dezaparvovec-drlb is considered **medically necessary** in individuals who meet **all** of the following criteria:

A. Diagnosis of hemophilia B; **and**
B. Age 18 years or older; **and**
C. Baseline factor IX level is less than 1 international unit (IU)/deciliter (dL) (or 1% endogenous factor IX) **and**
D. No contraindications to infusion (if any of the following are present, treatment is contraindicated):
    1. Active infection; **or**
    2. Immunosuppressive disorder; **or**
    3. Liver cirrhosis; **or**
    4. Active hepatitis B or C; **or**
    5. Alanine transaminase (ALT) greater than 3 times the upper limit of normal; **or**
    6. Bilirubin greater than 3 times the upper limit of normal; **or**
    7. Alkaline phosphatase greater than 3 times the upper limit of normal; **or**
    8. International normalized ratio (INR) greater than1.4.; **or**
    9. Prior infusion of gene therapy for hemophilia B (for example, etranacogene dezaparvovec-drlb or fidanacogene elaparvovec-dzkt);
    and
E. Poor disease control meeting one or more of the following:
    1. One or more episodes of spontaneous bleeding into a joint or the central nervous system while receiving routine prophylaxis factor replacement therapy; **or**
    2. Four or more episodes of soft tissue bleeding in an 8-week period while receiving routine prophylaxis factor replacement therapy; **or**
    3. At least 12 bleeding episodes over the previous year while receiving on-demand therapy.

Fidanacogene elaparvovec-dzkt is considered **medically necessary** in individuals who meet **all** of the following criteria:

A. Diagnosis of hemophilia B; **and**
B. Age 18 years or older; **and**
C. Baseline factor IX level is less than 1 international unit (IU)/deciliter (dL) (or 1% endogenous factor IX) **and**
D. No contraindications to infusion (if any of the following are present, treatment is contraindicated):
    1. Neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid; **or**
    2. Active infection; **or**
    3. Immunosuppressive disorder; **or**
    4. Liver cirrhosis; **or**
    5. Active hepatitis B or C; **or**
    6. Alanine transaminase (ALT) greater than 3 times the upper limit of normal; **or**
    7. Bilirubin greater than 3 times the upper limit of normal; **or**
    8. Alkaline phosphatase greater than 3 times the upper limit of normal; **or**
    9. International normalized ratio (INR) greater than1.4.; **or**
    10. Prior infusion of gene therapy for hemophilia B (for example, etranacogene dezaparvovec-drlb or fidanacogene elaparvovec-dzkt);
    and
E. Poor disease control meeting one or more of the following:
    1. One or more episodes of spontaneous bleeding into a joint or the central nervous system while receiving routine prophylaxis factor replacement therapy; **or**
    2. Four or more episodes of soft tissue bleeding in an 8-week period while receiving routine prophylaxis factor replacement therapy; **or**
    3. At least 12 bleeding episodes over the previous year while receiving on-demand therapy.

Valoctocogene roxaparvovec-rvox is considered **medically necessary** in individuals who meet **all** of the following criteria:

A. Diagnosis of hemophilia A; **and**
B. Age 18 years or older; **and**
C. Baseline factor VIII level is less than 1 international unit (IU)/deciliter (dL) (or 1% endogenous factor VIII) **and**
D. No contraindications to infusion (if any of the following are present, treatment is contraindicated):
    1. Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies; **or**
    2. History of factor VIII inhibitor; **or**
    3. Active infection; **or**
    4. Immunosuppressive disorder; **or**

5. Liver cirrhosis; **or**
6. Active hepatitis B or C; **or**
7. Alanine transaminase (ALT) greater than 3 times the upper limit of normal;**or**
8. Bilirubin greater than 3 times the upper limit of normal;**or**
9. Alkaline phosphatase greater than 3 times the upper limit of normal;**or**
10. International normalized ratio (INR) greater than1.4.; **or**
11. Prior infusion of valoctocogene roxaparvovec-rvox;
    and

E. Poor disease control meeting one or more of the following:
1. One or more episodes of spontaneous bleeding into a joint or the central nervous system while receiving routine prophylaxis factor replacement therapy; **or**
2. Four or more episodes of soft tissue bleeding in an 8-week period while receiving routine prophylaxis factor replacement therapy; **or**
3. At least 12 bleeding episodes over the previous year while receiving on-demand therapy.

Investigational and Not Medically Necessary:

Gene therapy for hemophilia is considered **investigational and not medically necessary** when the criteria above are not met and in all other situations.

Rationale

Hemophilia B

Etranocogene dezaparovec-drlb (Hemgenix®) (CSL Behring)

Etranacogene dezaparvovec-drlb, previously known as AMT-061, is a gene therapy product for hemophilia B that has received approval from the Food and Drug Administration (FDA). It uses an adeno-associated virus serotype 5 (AAV5) vector that carries the Padua gene variant of Factor IX. Etranacogene dezaparvovec-drlb is indicated for the treatment of adults with hemophilia B (congenital Factor IX deficiency) who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or repeated, serious spontaneous bleeding episodes.

In 2019, Von Drygalski and colleagues published data from a Phase IIb trial of 3 adults with moderate to severe hemophilia B (factor IX activity ≤ 2% per year) who received a single dose of etranocogene dezaparvovec-drlb (AMT-061). The trial aimed to collect preliminary data on the safety and efficacy of the 2×10^{13} genome copies (gc)/kilogram (kg) dose of the product prior to further study in the HOPE-B (Health Outcomes With Padua Gene; Evaluation in Hemophilia-B) phase III trial. At week 26, mean factor IX activity was 47% (range, 33% to 57%). There were no reported bleeds during the 26 weeks of follow-up and there were no reported serious adverse events (SAEs).

Von Drygalski and colleagues (2022) reported additional follow-up data from the Phase IIb trial, discussed above. Data were available for participants 1 and 2 at 3 years and participant 2 at 2.5 years. Factor IX activity at follow-up was over 40% (in the non-hemophilic range) for participants 1 and 2 and was 32.3% (in the mild hemophilic range) for participant 3. All 3 participants remained prophylaxis-free. Overall, participants had annualized bleeding rate of 0.22 and 2 of the 3 participants did not experience any bleeds. The publication reported 1 SAE that occurred in the first year after treatment; this was worsening avascular necrosis requiring hip surgery.

The ongoing 5-year Phase III clinical trial, HOPE-B (NCT03569891) is evaluating individuals with severe or moderately severe hemophilia B who received a single intravenous administration of gene therapy. Inclusion criteria include being male, at least 18 years old, having severe or moderately severe congenital hemophilia B, currently on factor IX prophylaxis and exposure to factor IX protein for at least the past 150 days. Key exclusion criteria include a history of factor IX inhibitors or a positive factor IX inhibitor test at screening, select liver screening laboratory test values over 2 times the upper limit of normal or history of hepatitis B or C or active infection (given the risk of potential hepatotoxicity), a positive HIV test that is not controlled with anti-viral therapy, and previous gene therapy treatment. A total of 67 individuals were enrolled in the trial.

FDA approval in November 2022 was based on an 18-month interim analysis of data from the HOPE-B trial. A total of 54 of the 67 enrolled individuals were dosed with etranacogene dezaparvovec-drlb and were included in the analysis. The FDA product label (2022) reported efficacy data up to 18 months post treatment; 53 of the 54 dosed individuals completed the 18-month follow-up. The person who did not complete follow-up died at month 15 after dosing for reasons deemed unrelated to treatment. The primary efficacy outcome was a non-inferiority analysis of the annualized bleeding rate (ABR) from months 7 to 18 after treatment, and this was compared to the ABR during the initial lead-in period. Individuals were permitted to continue their prophylaxis treatment up to 6 months after being dosed with etranacogene dezaparvovec-drlb. The mean ABR during months 7 to 18 were 1.9 bleeds per year (95% confidence interval [CI], 1.0 to 3.4). During the lead-in period, the estimated mean ABR was 4.1 (95% CI, 3.2 to 5.4). The ratio of the ABR in months 7 to 18 post-treatment compared with during the lead-in period was 0.46 (95% CI, 0.26 to 0.81). Two participants were unable to stop routine prophylaxis after gene therapy treatment, and a third individual, who stopped prophylaxis at 6 months per study protocol, received it again during days 396 to 534. Limitations of this analysis include that the study was uncontrolled (no comparison with individuals on factor replacement therapy), conducted in a relatively small number of people and unable to confirm long-term durability of the etranacogene dezaparvovec-drlb, a one-time therapy (efficacy and safety information beyond 18 months is not available at this time). Moreover, in this analysis, not all individuals were able to stop prophylaxis after treatment and 1 of 54 individuals resumed prophylaxis use after stopping for approximately 6 months, suggesting variable efficacy and a possible waning effect of the treatment. Additional long-term data is needed to establish the durability of etranacogene dezaparvovec-drlb in reducing bleeding and long-term complications, particularly as compared to standard of care factor replacement therapy (including Factor IX preparations with longer half-lives).

In a safety analysis combining data from the 2 clinical studies included in the FDA documents (n=3 and n=54), no SAEs were reported. The most common adverse events were alanine aminotransferase (ALT) elevations (42%), aspartate aminotransferase (AST) elevations (42%), blood creatine kinase elevations (42%), infusion-related reactions (33%), headache (18%), flu-like symptoms (14%), fatigue (12%) and malaise (12%). In 1 individual with an infusion-related reaction, infusion was stopped and not resumed. Nine of the 24 individuals with ALT elevations were treated with corticosteroids for a mean duration of 81 days. Nineteen of the 24 individuals with ALT elevations also had AST elevations.

One study participant with preexisting risk factors for developing hepatic cancer developed hepatocellular carcinoma, which was assessed as not likely related to etranacogene dezaparvovec-drlb (based on vector integration site analyses and whole genome sequencing). As noted in FDA prescribing information: “the integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development.” Although AAV is a non-integrating vector, it can integrate into the nuclear genome in small amounts; the clinical significance and risk of malignancy in the long-term is not known.

The 18-month data on the HOPE-B trial were published in 2023 by Pipe and colleagues. As stated above, the analysis included 54 individuals dosed with etranacogene dezaparvovec-drlb. The majority of enrolled individuals,44 individuals (81%), were classified with severe hemophilia B at the time of diagnosis (defined as plasma factor IX activity of <1%), and 10 individuals (19%) were classified with moderately severe hemophilia B (plasma factor IX activity of 1-2%). The article reported updated outcome data, compared with those included in the 2022 FDA product label. Regarding the primary endpoint, the ABR for all bleeding episodes decreased from 4.19 (95% CI, 3.22 to 5.45) during the lead-in period to 1.51 (95% CI, 0.81 to 2.82) post-treatment. The observed ABR ratio post-treatment compared with during lead-in was 0.36 (95% CI, 0.20 to 0.64, p<0.0001). Findings met the pre-specified non-inferiority margin. That is, the upper bound of the 95% CI (0.64) was less than the non-inferiority margin of 1.8. Moreover, the upper bound of the 95% CI was less than 1, thereby meeting the threshold of the secondary endpoint of superiority. A total of 52 participants (96%) discontinued factor IX prophylaxis during the period from day 21 through month 18 after treatment. Of the remaining 2 participants, one received a partial etranacogene dezaparvovec dose (approximately 10% of the dose), and the other had the highest day-of-dosing AAV5 neutralizing antibody titer in the study. Two quality of life measures were included as secondary endpoints. These were the International Physical Activity Questionnaire (iPAQ) and the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) visual analogue scale (VAS). Scores in both of these measures were not found to differ significantly between the lead-in period and month 12 after treatment. There were a total of 364 mild, 87 moderate and 14 SAEs; all participants experienced at least 1 adverse event. None of the SAEs were considered to be treatment-related by the investigators. There was one fatal SAE, a case of cardiogenic shock. As noted by the authors: “it is understood that the use of this primarily nonintegrating viral vector [AAV5], at the doses used in studies in humans, will result in genomic integration events. Many more years of planned follow-up are needed to fully understand any potential long-term risks of genotoxicity.”

The U.K. National Institute for Health and Clinical Excellence (NICE) published draft guidance on etranacogene dezaparvovec for treatment of moderately severe or severe hemophilia B in July 2023. Conclusions in the draft report included the following statement on the HOPE-B trial, based on the Pipe (2023) trial and additional data submitted by the manufacturer:

> Evidence from a clinical trial suggests that etranacogene dezaparvovec reduces the number of bleeding episodes a person has each year. But there is not enough evidence on how well it works in the long term.
>
> An indirect comparison of etranacogene dezaparvovec with FIX prophylaxis treatments suggests that it improves bleeding outcomes. But there are problems with this evidence, such as differences between studies in the methods used, and the definition and measurement of bleeding outcomes. So, the indirect comparison results are highly uncertain.

Coppens and colleagues (2024) reported on a post-hoc analysis of 24-month data from the HOPE-B trial. An analysis of all 54 participants found that the adjusted ABR for all bleeding episodes decreased significantly from 4.18 (95% CI, 3.21 to 5.44) during the lead-in period to 1.51 (95% CI, 0.83 to 2.75, p=0.0002) during months 7 to 24. No new safety signals were identified between the 18- and 24-month follow-ups. Adverse-events were reported in all participants during the course of the study; 38 of 54 (70%) were determined to have gene-therapy-related adverse events. Treatment-related adverse events with at least a 10% incidence included headache, influenza-like illness, and increased alanine aminotransferase. There were 3 new SAEs between months 18 and 24; none of these were considered to be related to treatment. There was one case each of severe blood loss anemia, diverticulitis intestinal hemorrhagic, and peripheral artery aneurysm. All of these individuals recovered, and no new deaths were reported.

Given ongoing unknowns related to the long-term durability and safety of etranacogene dezaparvovec-drlb, and the highly established and robust efficacy of prophylactic therapy in reducing bleeding and long-term complications of bleeding, consideration for treatment should be limited to individuals with poor disease control despite optimal management (in the absence of contraindications to therapy such as presence of factor IX inhibitor, active infection, immunosuppressive disorder or significant liver dysfunction or disease).

Fidanacogene elaparvovec-dzkt (Beqvez™, formerly known as SPK-9001 and PF-06838435.)(Pfizer)

Fidanacogene elaparvovec-dzkt uses a bioengineered AAV capsid and a high-activity variant of the human coagulation FIX gene. In 2018, following a licensing agreement between the two companies, Spark Therapeutics transferred responsibility for the phase III program evaluating this product to Pfizer.

Fidanacogene elaparvovec-dzkt received approval from the FDA on April 26, 2024. The FDA-approved indication for fidanacogene elaparvovec-dzkt is for the treatment of adults with moderate to severe hemophilia B (congenital Factor IX deficiency) who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or repeated, serious spontaneous bleeding episodes, and do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid.

A phase III trial evaluating fidanacogene elaparvovec-dzkt is ongoing; the trial is known as BENEGENE-2 (NCT03861273). The investigators plan to enroll 50 men in the study. The primary study outcome is ABR for total bleeds between week 12 and month 15 after infusion.

BENEGENE-2 eligibility criteria are as follows (Clinicaltrials.gov, 2024):

Inclusion Criteria

- Males who completed 6 months of Factor IX prophylaxis therapy during the lead-in study (C0371004) prior to providing consent at the screening visit for this study
- Documented moderately severe to severe hemophilia B (Factor IX activity < =2%)
- Previous experience with FIX therapy (=>50 documented exposure days to a FIX protein product)
- Suspension of prophylaxis therapy for hemophilia B after administration of the study drug
- Laboratory values (hemoglobin, platelets and creatinine) within study specified limits
- Agree to contraception until components of the drug are eliminated from their body
- Capable of giving signed informed consent

Exclusion Criteria

- Anti-AAVRh74var neutralizing antibodies (nAb) titer above the established threshold (ie, positive for nAb).
- History of inhibitor to Factor IX or inhibitor detected during screening. Clinical signs or symptoms of decreased response to Factor IX
- Hypersensitivity to Factor IX replacement product or IV immunoglobulin administration
- History of chronic infection or other chronic disease
- Any conditions associated with increased thromboembolic risk
- Concurrent clinically significant major disease or condition unsuitable for participation and/or may interfere with the interpretation of study results
- Laboratory values at screening visit that are abnormal or outside acceptable study limits
- Current unstable liver or biliary disease

- Currently on antiviral therapy for hepatitis B or C
- Planned surgical procedure requiring Factor IX surgical prophylactic factor treatment 15 months from screening visit
- Use of restricted therapies (e.g., blood products, acetylsalicylic acid [aspirin] or ibuprofen, other investigational therapy, and by-passing agents)
- Previously dosed in a gene therapy research trial at any time or in an interventional clinical study within 12 weeks of screening visit
- Active hepatitis B or C; hepatitis B surface antigen, hepatitis B virus deoxyribonucleic acid positivity, or hepatitis C virus ribonucleic acid positivity
- Significant liver disease
- Serological evidence of HIV1 or HIV2 infection with either CD4+ cell count <=200 mm3 and/or a viral load >20 copies/mL
- Study and sponsor staff involved in the conduct of the study and their families
- Unable to comply with study procedures
- Sensitivity to heparin or heparin induced thrombocytopenia
- Sensitivity to any of the study interventions, or components thereof, or drug or other allergy

Following completion in BENEGENE-2, participants are eligible to participate in a long-term follow-up study (NCT05568719) in which they will be followed up to 10 years post-infusion.

Previously, a Phase I/II trial (NCT02484092) evaluating SPK-9001 (PF-06838435) enrolled 15 males aged 18 and older with factor IX coagulant activity ≤ 2% of normal. Interim data reporting on 10 of the study participants who received a dose of 5E11 vector genome (vg)/kg were published by George and colleagues (2017a). The primary objective was to assess the safety of gene therapy. Exploratory efficacy endpoints included change from baseline in the ABR, consumption of favor IX replacement therapy and infusions. After a follow-up period ranging from 28-78 weeks, the ABR rate was significantly reduced from pre-infusion (mean rate: 11.1 events per year) to post-infusion (mean rate: 0.4 events per year). At follow-up, 8 of 10 participants (80%) did not use factor IX replacement therapy and 9 of 10 (90%) did not have any bleeds after gene therapy infusion. No SAEs were reported.

The FDA materials report safety data from 60 individuals who enrolled in 1 of 2 clinical trials (45 individuals in NCT03861273 and 15 individuals in NCT02484092. No SAEs were reported. The most common adverse event was transaminase elevation, which occurred in 24 (53.3%) individuals in NCT03861273 and 2 (13.3%) in NCT0248409.

FDA materials also report efficacy data from an interim analysis of the BENEGENE-2 trial (NCT03861273). The analysis included 45 adult males with moderately severe to severe hemophilia B (factor IX activity ≤ 2% IU/dL). The materials did not report the percentage of participants who had factor IX activity of 1% versus less than 2%. Individuals received a gene therapy dose of 5 X 10^{11} vg/kg of body weight. Median follow-up at the time of analysis was 2.0 years (range, 0.4 to 3.2 years) from the time of infusion. The main efficacy outcome reported was a non-inferiority test of ABR from week 12 after infusion (the efficacy evaluation period), compared with baseline ABR during the lead in period. The ABR included both treated and untreated bleeds, but not procedural bleeds. The median ABR was 1.3 during the lead-in period and 0.0 during the efficacy evaluation period. A total of 29% of participants had no bleeds during the lead-in period and 60% had no bleeds during the efficacy evaluation period. The model-derived mean ABR was 4.5 bleeds/year (95% CI, 1.9 to 7.2) during the baseline period and 2.5 bleeds/year (95% CI, 1.0 to 3.9) during the efficacy evaluation period. This was a difference from baseline to follow-up of -2.1 bleeds per year (95% CI, -4.8 to 0.7). The upper bound of the 95% CI in the difference was less than 3.0 bleeds/year, meeting the non-inferiority study success criterion. Six out of 45 individuals (13%) resumed routine factor IX prophylaxis after gene therapy treatment, an additional individual had intermittent exogenous factor IX use.

Verbrinacogene setparvovec (FLT180a) (Freeline Therapeutics)

Verbrinacogene setparvovec, also known as FLT180a, uses an AAVS3 synthetic capsid vector that carries a gain-of-function Padua gene variant (R338L) of Factor IX. It has not been approved by the FDA.

Results of a Phase I/II study evaluating verbrinacogene setparvovec (the B-AMAZE study) were published by Chowdary and colleagues in 2022. The study included 10 males at least 18 years old with hemophilia B that was categorized as severe (factor IX level < 1%) or moderately severe (factor IX level, 1-2%) with a severe bleeding phenotype. Individuals with evidence of inhibitors to factor IX were not eligible to participate. None of the participants had evidence of AAVS3 neutralizing antibodies. Participants were treated with 1 of 4 doses of vector; 3.84E11 (n=2), 6.40E11 (n=2), 8.32E11 (n=4). or 1.23E12 (n=2). All 10 individuals completed the 26-week trial. In the total study population, the mean ABR at baseline was 2.93 events per year (range, 0 to 7.3) and was 0.71 events per year (range, 0 to 1.7) after treatment. Annualized factor IX consumption decreased from a mean at baseline of 226,026 IU per year to a mean of 9723 IU per year after receiving gene therapy. There were 12 SAEs that were thought to be related to gene therapy; 9 of these were an increase in liver aminotransferase levels.

Hemophilia A

Valoctocogene roxaparvovec-rvox (Roctavian™) (Biomarin Pharmaceuticals)

Valoctocogene roxaparvovec-rvox, an AAV5 vector gene therapy product, received FDA approval on June 29, 2023. The FDA-approved indication (FDA, 2023) is “treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test”.

Data from a phase I/II dose-escalation study evaluating valoctocogene roxaparvovec (a previous name) for hemophilia A (NCT02576795) have been published. The study included 15 males aged 18 and older with severe hemophilia A disease (base factor VIII level ≤ 1 IU/dL who had no history of factor VIII inhibitor development. Individuals who used on-demand therapy were required to have had ≥ 12 bleeding episodes in the previous 12 months. Individuals were excluded if they had detectable pre-existing immunity to the AAV5 capsid, evidence of active infection, any immunosuppressive disorder or any bleeding disorder other than hemophilia A, were HIV positive or had significant liver dysfunction. Study participants were required to discontinue using prophylactic factor VIII replacement therapy but were permitted to use factor VIII therapy if they experienced a bleeding episode during the study. Participants received a single intravenous injection of one of four doses of gene therapy: 6E12 vg/kg (n=1), 2E13 vg/kg (n=1), 6E13 vg/kg (n=7) or 4E13 (n=6). The primary aims of the study were to assess the number of participants with treatment-related adverse events over 5 years and to determine the dose of gene therapy needed to achieve expression of factor VIII ≥ 5% of normal activity (> 5 IU/dL) 16 weeks after infusion. Factor VIII activity levels were performed at a central laboratory and were measured in two ways; by a one-stage activated partial thromboplastin time-based clotting assay and a chromogenic factor Xa assay.

Individuals were sequentially enrolled in the study, with those enrolled first receiving the lowest dose of gene therapy. Rangarajan and colleagues (2017) reported 1-year data on the first three cohorts (n=9). In 6 of 7 individuals in the higher-dose cohort (6E13 vg/kg), factor VIII activity increased to a normal level (> 50 IU/dL) and this level was maintained at 1 year. In 6 individuals in the higher-dose cohort who had received factor VIII prophylaxis before trial entry, the median ABR decreased from 16 events per year to 1 event per year. One SAE, progression of chronic arthropathy, was reported.

Pasi and colleagues (2020) reported on all four cohorts (n=15) and up to 3 years of follow-up data. Three years after infusion, the 2 individuals in the lowest-dose cohorts (6E12 vg/kg, n=1 and 2E13 vg/kg, n=1), had factor VIII expression below IU/dL. Three-year data were also available for the 7 individuals in the third cohort, those who received the 6E13 vg/kg dose. At the end of years 1, 2 and 3, the mean factor VIII activity levels as measured by chromogenic assay were 64 IU/dL, 36 IU/dL and 33 IU/dL, respectively. Mean factor VIII values at the same time points using the one-stage assay were 104 IU/dL, 59 IU/dL and 52 IU/dL, respectively. After reaching a peak factor VIII level, the mean factor VIII expression decreased by 43% during year 2 and by 10% during year 3. In the third cohort, the mean annualized rate of bleeding events decreased by 96%, from a mean of 16.3 (standard deviation [SD), 15.7) events per year at baseline to a mean of 0.7 (SD, 1.6) events per year at the end of year 3. At baseline, only 1 of 6 participants who were receiving prophylaxis was free from breakthrough bleeding events. At the end of the third year of follow-up, 6 of 7 participants (86%) were free from bleeding events.

Two-year follow-up data were available on the 6 participants in the fourth cohort who received the highest dose of gene therapy, 4E13. The mean factor VIII activity level, according to the chromogenic assay, was 21.0 IU/dL at the end of year 1 and 15 IU/dL at the end of year 2. Mean factor VIII levels according to the one-stage assay were 31 IU/dL at the end of year 1 and 23 IU/dL at the end of year 2. In this cohort, Factor VIII level decreased by 30% during the second year after infusion. None of the individuals in the third or fourth cohorts were using prophylactic factor replacement at the end of year 3. In cohort 4, the annualized rate of bleeding events decreased by 92%, from a mean of 12.2 (SD, 5.4) events per year in the year before study entry to a mean of 1.2 (SD, 2.4) events per year at the end of year 2. All 6 individuals in cohort 4 were using prophylactic replacement therapy at baseline. In the year before study entry, 1 of these 6 individuals (17%) was free from breakthrough bleeding events. At the 2-year follow-up, 4 of 6 individuals (67%) were free from bleeding events.

All of the study participants had at least 1 adverse event. The most common AE was elevation of the alanine aminotransferase level with 14 events; 13 were grade 1 and 1 was a grade 2 event. The elevations in the alanine aminotransferase level were managed with glucocorticoid treatment. Three participants experienced SAEs at some point during the study. These included 1 case of grade 2 pyrexia, along with myalgia and headache that occurred within 24 hours of gene therapy infusion. Symptoms resolved within 48 hours. Two participants had SAEs associated with pre-existing hemophilic arthropathies; these were determined by investigators to be unrelated to treatment.

Six-year data were reported by Symington and colleagues in 2024. Data were available for all 7 participants in the 6E13 cohort and the 6 participants in the 4E13 cohort. No new treatment-related SAEs were reported after the first year of follow-up. Two SAEs determined to be unrelated to treatment emerged in the final year of follow-up. These included grade 2 parotid gland acinar cell carcinoma (6E13 dose) and an exacerbation of Crohn's disease (4E13 cohort). Regarding efficacy, there was a sustained reduction from baseline in ABR. Over the entire study period, mean ABR was 0.7 treated bleeds per year (median 0.0) in the 6E13 cohort and 1.1 treated bleeds per year (median, 0.6) in the 4E14 cohort. Over this same time period, the mean FVIII infusion rate was 4.5 infusions per year (median 1.5) in the 6E13 cohort and 9.6 infusions per year in the 4E13 cohort.

Data from a phase III trial (NCT03370913) evaluating a single 6E13 vg/kg dose of valoctocogene roxaparvovec were published in 2022 by Ozelo and colleagues. Eligibility included being at least 18 years old with severe congenital hemophilia A (factor VIII activity level ≤ 1 IU/dL), having received prophylaxis with factor VIII concentrates for at least 1 year prior to enrollment and being negative for factor VIII inhibitors. Key exclusion criteria were the presence of anti-AAV5 capsid antibodies, HIV infection, and substantial liver dysfunction, fibrosis or cirrhosis. The primary efficacy outcome was change from baseline in factor VIII activity at 1 year. A total of 181 men were screened, 144 were enrolled in the study and 134 were dosed with 6E13 vg/kg of valoctocogene roxaparvovec and completed the week 49-52 visit. Anti-AAV5 capsid antibodies were present in most (26 of 37) of the men who were ineligible after screening. Of the 134 individuals who received a dose of gene therapy, 132 were HIV-negative and were included in a modified intention-to-treat (ITT) population. In the modified ITT analysis, the mean change from baseline in the factor VIII activity level at 1 year was 41.9 IU (95% CI, 34.1 to 49.7) per deciliter. The median change was 22.9 IU per deciliter. There were 17 participants who had at least 2 years of follow-up. This group had mean factor VIII activity levels of 42.2 IU per deciliter at week 49-52 and 24.2 IU per deciliter at week 104. Median factor VIII activity levels in this group were 23.9 IU per deciliter at week 49-52 and 14.7 IU per deciliter at week 104. In the modified ITT population, the mean and median annualized rates of treated bleeding episodes were 4.8 per year and 2.8 per year, respectively, at baseline and 0.8 bleeds per year and 0 bleeds per year, respectively, after week 4. In terms of safety, all 134 participants had at least one adverse event; most were grade 1 or grade 2. A total of 22 participants (16.4%) reported any SAE; five SAEs were determined by the investigators to be related to the study drug. All of the SAEs resolved and there were no reported deaths and none of the participants withdrew due to adverse events or developed factor VIII inhibitors.

Mahlangu (2023) reported 2-year findings of the Phase III trial. After a median follow-up of 110.9 weeks (range 66 to 194 weeks), the mean change in the annualized bleeding rate, compared with baseline (when the participants were receiving prophylaxis), was -4.1 bleeding events per year (95% CI, -5.3 to -4.1). The annualized rate of factor VIII use decreased by 98.2% from baseline. The Factor VIII activity increased from baseline by a mean of 22.0 IU per deciliter (95% CI, 26.9 to 43.). Nine individuals had an adverse event in Year 2, none of which were SAEs.

The FDA product insert (2023) reported data in individuals in the Phase III study who were followed for at least 3 years. The primary efficacy outcome for the analysis was a non-inferiority evaluation of the difference in ABR during the post-treatment evaluation period compared with baseline. The investigators established a non-inferiority margin of 3.5 bleeds per year. The mean ABR was 2.6 bleeds per year post-treatment, compared to a mean baseline ABR of 5.4 bleeds per year. The mean difference pre- and post-treatment was -2.8 bleeds per year (95% CI, -4.3 to -1.2), meeting the pre-specified non-inferiority margin.

The rollover population (n=122) consisted of individuals with at least 6 months of prospectively collected data on factor VIII prophylaxis prior to receiving Roctavian, In this group (n=122), a total of 5 participants (4%) did not respond to treatment with Roctavian and 17 participants (15%) lost response to treatment over a median time of 2.3 years (range: 1.0 to 3.3 years). Among the remaining study participants with a longer follow-up (n=22), a total of 1 participant (5%) did not respond to treatment with Roctavian and 6 participants (27%) lost response to treatment over a median time of 3.6 years (range: 1.2 to 4.3 years).

Given ongoing unknowns related to the long-term durability and safety of valoctocogene roxaparvovec-rvox, and the highly established and robust efficacy of prophylactic therapy in reducing bleeding and long-term complications of bleeding, consideration for treatment should be limited to individuals with poor disease control despite optimal management (in the absence of contraindications to therapy such as presence of factor VIII inhibitor, active infection, immunosuppressive disorder or significant liver dysfunction or disease).

SPK-8011 (Spark Therapeutics)

In 2021, George and colleagues published results of a Phase I/II dose escalation trial evaluating a single dose of SPK-8011. Participants received 1 of 4 doses of gene therapy, ranging rom a low dose of 5E11vg/kg to 2E12 vg/kg. Participants were males at least 18 years old with congenital hemophilia A and baseline factor VIII activity 2% or less of normal value, no history of factor VIII inhibitory antibodies and SPK200 neutralizing antibody titers of 1:5 or less. A total of 18 men met inclusion criteria and were dosed. At baseline, 13 of the 18 were receiving factor VIII prophylaxis and the others received factor VIII on demand. After a median efficacy

follow-up of 33.4 months, the median annualized rate of bleeding events decreased from 8.5 (range, 0 to 43) before SPK-8011 administration to 0.3 events per year (range, 0 to 6.5) after administration. The annualized number of factor VIII administrations decreased from a median of 57.5 infusions (range, 24 to 245) per year at baseline to 0.6 (range, 0 to 28.6) after administration. One drug-related SAE was reported, elevated liver aminotransferase level.

An ongoing trial, NCT03432520, involves long-term follow-up of individuals with hemophilia A who have previously received SPK-8011 in a Spark-sponsored trial, with an estimated enrollment of 40 individuals.

A 2020 Cochrane review searched for and did not identify any randomized controlled trials (RCTs) or quasi-RCTs comparing gene therapy for hemophilia A or B to standard treatment or a different potentially curative treatment (such as stem cell transplant) (Sharma, 2020).

Giroctocogene fitelparvovec (SB-525) Pfizer (under license from Sangamo)

Giroctocogene fitelparvovec has not received approval from the FDA.

Data from a Phase I/II dose-ranging study (NCT03061201) were published in 2024 (Leavitt). The study included males aged at least 18 years with severe hemophilia A (FVIII activity < 1% of normal). In addition, eligibility including having at least 150 prior treatment or exposure days to FVIII concentrates or cryoprecipitate and, if using on-demand treatment, having at least 12 bleeding episodes during the year before screening. The study used escalating doses of giroctocogene fitelparvovec, starting at 9E11, to achieve a FVIII activity of 40% to 100% of normal. The primary efficacy endpoint was change in circulating FVIII activity. Eleven of the 37 screened candidates were enrolled and dosed in 1 of 4 cohorts. In the 12 months prior to enrollment, study participants had a mean of 7.5 (SD, 8.8) bleeding episodes. Ten of the 11 participants were receiving FVIII prophylaxis. A total of 103 treatment-emergent AEs were reported; 26 of these were considered to be related to treatment. All of the participants reported at least 1 treatment-related AE. The most common of these were increase in ALT levels (13 events in 5 participants), increase in aspartate aminotransferase levels (5 events in 3 participants). A total of 4 SAEs were reported in 3 participants. Two of the SAEs were considered related to treatment and occurred in a participant who received the highest dose (3E13 vg/kg); these were grade 3 hypotension and grade 2 pyrexia that occurred 2 hours after dosing and resolved within 24 hours of treatment. Circulating FVIII activity increased as dose increased. All 5 participants in the highest dose cohort achieved peak FVIII in the normal range (> 50%) by week 9. The mean FVIII activity level in this cohort (using the chromogenic assay) were 52.6% at week 52 and 25.4% at week 104. In cohort 4, the mean total ABR was 8.8 (SD, 8.3) in the year before dosing versus 0.7 (SD, 1.4) after dosing.

A Phase III single-arm trial known as AFFINE (NCT04370054) is underway. The first participant was dosed in October 2020 and the estimated enrollment is 63 individuals. The primary outcome of the study is ABR at 12 months.

Background/Overview

Hemophilia is an inherited bleeding disorder that impairs the blood clotting process. The disease results in prolonged bleeding after an injury or surgery, easy bruising, and an increased risk of bleeding, including inside joints, muscles and/or the brain.

Hemophilia A, the most common type, involves a deficiency in blood clotting factor VIII and is caused by mutations in the F8 gene whereas hemophilia B (also called Christmas disease) involves a deficiency in factor IX and is caused by mutations in the F9 gene. The F8 and F9 genes provide instructions for making proteins called coagulation factor VIII and IX, respectively, which are necessary for the blood clotting process. Mutations in the F8 or F9 genes lead to reduction in the level of these coagulation factors, or production of abnormal versions of these proteins.

Both hemophilia A and B are x-linked recessive genetic disorders; that is, the genes associated with the conditions are located on the X-chromosome. Hemophilia more commonly affects males because they have only one copy of the X-chromosome. Females have two copies of the X-chromosome; when they have a single altered copy of the F8 or F9 gene, the mutation results in about half the normal level of coagulation factor VIII or IX, which is generally not sufficient to cause hemophilia. Most females (about 90%) with a single altered copy of the F8 or F9 gene are asymptomatic carriers who have a 50% chance of passing on the disease to their sons. It is possible for females to have two altered copies of the gene causing hemophilia, but this occurs very rarely (Genetics Home Reference, 2012; GeneReviews, 2017a and 2017b).

The age at diagnosis and severity of symptoms of hemophilia A and B depend on the level of factor VIII or IX clotting activity (GeneReviews, 2017a and 2017b). Severity is categorized as follows:

- **Severe hemophilia** (factor clotting activity level < 1%): Usually diagnosed within the first two years of life. Without prophylactic treatment with factor replacement, individuals with severe hemophilia A or B may average 2 to 5 spontaneous bleeds per month. Spontaneous bleeding can occur into the joints, can lead to joint destruction, as well as into the brain, a dangerous and life-threatening event. Delayed bleeding after trauma is also common in individuals with severe hemophilia. Bleeding can be massive or persist as continuous oozing for days or weeks.
- **Moderate hemophilia** (factor clotting activity level 1-5%): Usually diagnosed before age five to six years. These individuals rarely have spontaneous bleeding, but do have prolonged bleeding or delayed oozing after relatively minor trauma. Frequency of bleeding episodes varies but generally occur between once a month and once a year.
- **Mild hemophilia** (factor clotting activity level 5-40%): Mild disease is often not diagnosed until later in life, depending on the individual's exposure to surgical procedures or serious injury. Individuals with mild hemophilia do not have spontaneous bleeding episodes. Abnormal bleeding occurs with surgery or tooth extractions. The frequency of bleeding varies from once a year to once every 10 years.

Baseline factor level is often determined at the time of diagnosis (preceding factor replacement therapy). Assessment of baseline factor activity during therapeutic management with factor replacement therapy may pose laboratory challenges (ref). For purposes of applying this document, baseline factor level measurement can be based on a previously documented test result, for example, at the time of diagnosis (Nardi, 2019).

The prevalence of hemophilia B is about one-fifth that of hemophilia A. In the United States, the birth prevalence of hemophilia A is approximately 1 in 6500 live male births and the birth prevalence of hemophilia B is about 1 in 30,000 live male births (GeneReviews, 2017a and 2017b). For both hemophilia A and B, approximately 60% of individuals have severe disease, 15% have moderate disease and 25% have mild disease (National Hemophilia Foundation).

According to guidelines from the World Federation of Hemophilia (WFH) (2020), hemophilia is best managed in a comprehensive care setting. Comprehensive care is defined as care that "promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality". Comprehensive care involves a multidisciplinary team of healthcare professionals and, when available, uses accepted protocols and national treatment guidelines. The functions of a comprehensive care program are to provide or coordinate

inpatient and outpatient care and services to individuals with hemophilia their families. Key tenets include:

- Patients should be seen by all core team members at least yearly (children every six months) for a complete hematologic, musculoskeletal, and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan.
- To initiate, provide training for, and supervise home therapy with clotting factor concentrates where available.
- To educate patients, family members and other caregivers to ensure that the needs of the patient are met.
- To collect data on sites of bleeds, types and doses of treatment given, assessment of long-term outcomes (particularly with reference to musculoskeletal function), complications from treatment, and surgical procedures.

The current medical management strategy for hemophilia is prevention and treatment of bleeding with infusions of replacement blood clotting factors. A variety of replacement products are available. All of the available prophylaxis products are considered effective, but may vary by patient response, safety profile (e.g., risk of inhibitor development), and product characteristic (e.g., product half-life, effects on monitoring). Prophylactic use of factor replacement therapy is recommended for individuals with severe hemophilia due to the high risk of spontaneous bleeding. Even a small increase in factor clotting activity can significantly reduce clinical bleeding rates. For moderate or mild hemophilia, recommendations regarding prophylactic use of factor replacement therapy are individualized depending on the person's clinical situation and preferences. Repeated intravenous infusions can be burdensome and involve risks such as infection from a central venous catheter. Other hemophilia management strategies include avoiding activities likely to cause trauma, exercising regularly to stimulate normal psychomotor development and improve fitness, practicing good oral hygiene and avoiding medications that increase bleeding risk.

Various gene therapy products for hemophilia A and hemophilia B are currently being investigated. These products use a virus vector with a working copy of the missing gene attached (factor VIII and factor IX for hemophilia A and B, respectively). The virus vector is the outer structure (capsid) of an adeno-associated virus (AAV) which is incapable of replicating and thus unlikely to cause disease (Chuah 2013). The gene therapy is infused intravenously where it selectively targets hepatocytes (liver cells), the site where factor VIII and factor IX production primarily takes place. Several hemophilia B gene therapy products use AAVs that carry the Padua gene variant of Factor IX. The Padua variant is a naturally occurring missense mutation in the factor IX gene that increases its activity approximately 4- to 40-fold. This can potentially increase the efficacy of the treatment without using higher doses of vector (VandenDriessche, 2018) and may have implications for treatment durability. AAV vector-based gene therapy is intended to be a one-time treatment.

Pre-existing AAV neutralizing antibodies (NAbs) are a contraindication to receiving gene therapy as it is currently formulated, limiting the number of individuals potentially eligible for treatment. A review article identified found prevalences of anti-AAV NAbs ranging from 3% to 50% in individual studies (Louis Jeune, 2013). Pre-clinical studies have been conducted to evaluate gene therapy for inducing immune tolerance in individuals with hemophilia, but to date, clinical data are lacking (Arruda, 2016; Borsotti, 2018).

Some individuals with hemophilia may develop an inhibitor (an antibody directed against infused factor that inhibits the function of the factor). Individuals who develop inhibitors can often no longer use standard factor replacement to treat bleeding or to provide prophylaxis against bleeding. Individuals who have developed an inhibitor to factor have been excluded from gene therapy trials due to concerns about reduced efficacy.

There are a number of unanswered questions concerning gene therapy for hemophilia. It is unclear how certain characteristics, such as age at treatment, duration of disease and severity of disease, affect the likelihood that individuals with hemophilia would benefit from gene therapy. It is also unknown whether gene therapy for hemophilia will provide durable long- term benefit in individuals who initially benefit. Hepatocytes, the target of hemophilia gene therapy, have the capability to undergo cell division (Miyaoka, 2013). However, the scope and rate of hepatocellular turnover is variable, and in the context of gene therapy, it is unclear whether long-term liver regeneration will dilute the therapeutic effect of gene therapy (particularly in children, where ongoing proliferation of liver cells may dilute the number of viral genomes). Given this, current vectors are designed to target adult postmitotic hepatocytes (George, 2017b).

Long-term safety of gene therapy for hemophilia remains unknown. Theoretical safety concerns include inflammatory reaction to AAV proteins in other tissues or organs, unintended DNA insertion causing mutagenesis (i.e., possibility for cancer) or genotoxicity (cellular death), protein overexpression (causing for example, an amyloidosis-like condition), and virus transmission to other individuals including family, or into the environment. Insertional mutagenesis in reproductive cells could lead to infertility or, indirectly, to birth defects. In addition, use of the Padua variant of factor IX in hemophilia B gene therapy has uncertain safety issues; for example, a clinical trial evaluating verbrinacogene setparvovec found an SAE of arteriovenous fistula thrombosis in an individual with high factor IX levels after gene therapy using the Padua variant.

The first FDA approval for a gene therapy product for hemophilia B was for etranacogene dezaparvovec-drlb (Hemgenix) in November 2022. According to the FDA:

> HEMGENIX is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

The product is approved for single-dose administration. The following warnings and precautions were included in the product label:

- Infusion reactions: Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved.
- Hepatotoxicity: Closely monitor transaminase levels once per week for 3 months after HEMGENIX administration to mitigate the risk of potential hepatotoxicity. Continue to monitor transaminases in all patients who developed liver enzyme elevations until liver enzymes return to baseline. Consider corticosteroid treatment should elevations occur.
- Hepatocellular carcinogenicity: For patients with preexisting risk factors (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease (NAFLD), chronic alcohol consumption, non-alcoholic steatohepatitis (NASH), and advanced age), perform regular (e.g., annual) liver ultrasound and alpha-fetoprotein testing following administration.
- Monitoring Laboratory tests: Monitor for Factor IX activity and Factor IX inhibitors.

A second gene therapy for hemophilia B, fidanacogene elaparvovec-dzkt (BEQVEZ), was approved by the FDA in April 2024. The FDA-approved indication is as follows:

> BEQVEZ is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who:

- Currently use factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes, and,
- Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.

Of note, on April 29, 2024, the FDA approved the AbCyte™ Anti-AAVRh74var HB-FE Assay (Labcorp) as a companion diagnostic test to determine eligibility for treatment with fidanacogene elaparvovec-dzkt. If individuals are found to have neutralizing antibodies to adeno-associated virus serotype Rh74var using this test, they are not eligible for treatment with fidanacogene elaparvovec-dzkt.

BEQVEZ is approved for single-dose administration. The following contraindications, warnings and precautions were included in the product label:

> Warnings and Precautions

- Hepatotoxicity: Monitor transaminases and factor IX activity levels once or twice weekly for at least 4 months after BEQVEZ administration to mitigate the risk of potential hepatotoxicity. Consider corticosteroid treatment for transaminase elevation or a decline in factor IX activity. (2.3, 5.1)
- Infusion Reactions: Monitor during administration and for at least 3hours after end of infusion. If symptoms occur, slow or stop administration. Restart infusion at a slower rate once reaction has resolved. (5.2)
- Malignancy: Monitor patients with risk factors for hepatocellular carcinoma (e.g., hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, advanced age) with regular liver ultrasound (e.g., annually) and alpha-fetoprotein testing for 5 years following administration. In the event that a malignancy occurs after treatment with BEQVEZ, contact Pfizer Inc.at1-800-438-1985. (5.3)
- Monitoring laboratory tests: Monitor for factor IX activity and factor IX inhibitors. (5.4)

In June 2023, the FDA granted approval for valoctocogene roxaparvovec-rvox (Roctavian) for hemophilia A. According to the FDA:

> ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.

The product is approved for single-dose administration. The following contraindications, warnings and precautions were included in the product label:

Contraindications:

- Active infections, either acute or uncontrolled chronic. (4)
- Known significant hepatic fibrosis (stage 3 or 4), or cirrhosis. (4)
- Known hypersensitivity to mannitol. (4)

Warnings and Precautions:

- Infusion-related reactions: Infusion reactions, including hypersensitivity reactions and anaphylaxis, have occurred. Monitor during and for at least 3 hours after ROCTAVIAN administration. If symptoms occur, slow or interrupt administration and give appropriate treatment. Restart infusion at slower rate once symptoms resolve. Discontinue infusion for anaphylaxis. (2.3, 5.1)
- Hepatotoxicity: Monitor alanine aminotransferase (ALT) weekly for at least 26 weeks and institute corticosteroid treatment in response to ALT elevations as required. Continue to monitor ALT until it returns to baseline. Monitor factor VIII activity levels since ALT elevation may be accompanied by a decrease in factor VIII activity. Monitor for and manage adverse reactions from corticosteroid use. (5.2)
- Thromboembolic events: Thromboembolic events may occur in the setting of elevated factor VIII activity above the upper limit of normal (ULN). Factor VIII activity above ULN has been reported following ROCTAVIAN infusion. Evaluate for risk factors for thrombosis including cardiovascular risk factors prior to and after ROCTAVIAN use and advise patients accordingly. (5.3)
- Monitoring laboratory tests: Monitor for factor VIII activity and factor VIII inhibitors. (5.4)
- Malignancy: Monitor for hepatocellular malignancy in patients with risk factors for hepatocellular carcinoma (e.g., hepatitis B or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, advanced age). Perform regular liver ultrasound (e.g., annually) and alpha-fetoprotein testing following administration.

Definitions

Adeno-associated virus (AAV): A small virus that infects humans and is not known to cause disease. Modified (non-replicating) AAVs are frequently used as viral vectors for gene therapy.

Comprehensive care: Coordinated delivery of care that “promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality”, generally conducted by “a multidisciplinary team of healthcare professionals, in accordance with accepted protocols that are practical and national treatment guidelines, if available” (Srivastava, 2013). Comprehensive care represents optimal management of the severe form of hemophilia.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

Phenotype: Observable traits or characteristics in an individual that result from having particular genes (i.e., genotype) and from the interaction of the genotype with the environment.

X-linked recessive trait: A mutation in the gene on the X-chromosome. The phenotype is always expressed in males (who have only one X chromosome) and in females who have mutations in both of their X chromosomes.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Hemophilia B gene therapy

When services may be Medically Necessary when criteria are met:

HCPCS

J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose (Hemgenix)
	For the following codes **when specified as fidanacogene elaparvovec-dzkt (Beqvez)**:
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Diagnosis

D67	Hereditary factor IX deficiency

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Hemophilia A gene therapy
When services may be Medically Necessary when criteria are met:

HCPCS

J1412	Injection, valoctocogene roxaparvovec-rvox, per mL, containing nominal 2 × 10^13 vector genomes (Roctavian)

ICD-10 Diagnosis

D66	Hereditary factor VIII deficiency

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Other therapies
When services are also Investigational and Not Medically Necessary:
When the code describes any other gene therapy product for hemophilia.

HCPCS

	For the following unlisted codes **when specified as a gene therapy for hemophilia other than Hemgenix, Beqvez, or Roctavian:**
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Diagnosis

	All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	05/09/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Added MN statement on fidanacogene elaparvovec-dzkt. Revised MN statement on etranacogene dezaparvovec-drlb. Updated Background/Overview, Rationale, Coding, References, and Index sections.
	12/28/2023	Updated Coding section with 01/01/2024 HCPCS changes, added J1412 replacing NOC codes for Roctavian.
	08/16/2023	Updated Rationale and References sections.
Revised	07/10/2023	MPTAC review. Revised MN statement on etranacogene dezaparvovec-drlb. Added MN statement on valoctocogene roxaparvovec-rvox. Revised first INV&NMN statement and deleted second INV&NMN statement. Updated Rationale, Background/Overview, Coding, References and Index sections.
Reviewed	02/16/2023	MPTAC review. Updated Rationale and References sections. Updated Coding section with 04/01/2023 HCPCS changes; added J1411 replacing NOC codes for Hemgenix.
New	12/01/2022	MPTAC review. Initial document development.
Preliminary Discussion	11/10/2022	MPTAC Pre-FDA Approval Review.
Preliminary Discussion	08/13/2020	MPTAC Pre-FDA Approval Review.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update

Medical Policy periodically.