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REVIEW ARTICLE

Evaluating Gene Therapy as a Potential Paradigm Shift in Treating Severe Hemophilia

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Abstract

Hemophilia is characterized by a deficiency in coagulation factors VIII or IX. The general standard of care for severe hemophilia is frequent intravenous recombinant or plasma-derived factor replacement to prevent bleeding. While this treatment is effective in preventing bleeding, frequent infusions are burdensome for patients. Nonadherence to the therapeutic regimen leaves people with hemophilia at risk for spontaneous and traumatic bleeds into joints as well as life-threatening bleeds such as intracranial hemorrhage. The chronicity of the disorder often leads to the formation of target joints, causing long-term pain and impairing mobility. As a monogenic disorder with well-understood genetics, hemophilia is an ideal disorder for implementing innovations in gene therapies. Indeed, recent approvals of two gene therapy products have the potential to shift the hemophilia treatment paradigm. Valoctocogene roxaparvovec and etranacogene dezaparvovec-drlb are gene therapies for hemophilia A and B, respectively. These therapies, given as a single intravenous infusion, may improve patients' quality of life, decreasing treatment burden and resulting in factor expression that virtually eliminates the need for factor replacement. Since both treatments involve viral vectors targeted to the liver, short- and long-term safety and efficacy monitoring involves monitoring liver enzymes to track liver health. Long-term monitoring of efficacy, durability of gene expression, and safety are ongoing. Gene therapy presents a promising new therapeutic option for patients with hemophilia and warrants continued innovation and investigation.

Key Points

Gene therapy products valoctocogene roxaparvovec (for hemophilia A) and etranacogene dezaparvovec-drlb (for hemophilia B) have the potential to shift the paradigm in treating severe hemophilia. However, several uncertainties remain, including the need for potential immunosuppression, the unpredictability of response, long-term efficacy, and safety.

Here, we review Phase 3 efficacy and safety data in detail (including differences between hemophilia A and B) and propose criteria to determine if a patient may be a suitable candidate for gene therapy.

1 Introduction

Hemophilia A and B are rare, X-linked inherited bleeding disorders due to deficiency of coagulation factors VIII and IX respectively [1–3].

In the USA, the estimated prevalence of hemophilia A is 12 per 100,000 males, and the prevalence of hemophilia B is 3.7 per 100,000 males [4]. For people living with hemophilia (PwH), the high burden of disease is related to treatment burden, breakthrough bleeding, and chronic joint disease [5].

Clotting factor replacement therapies are used to treat and prevent bleeding [2]. These factor replacement therapies differ in half-life length and approved indications. All factor replacement therapies for hemophilia are administered by intravenous (IV) infusions one to four times per week, which can be challenging and negatively impact treatment adherence. Since 2014, bioengineered clotting factors with extended half-lives have been approved [6], and a new-in-class agent providing high, sustained FVIII activity by overcoming the von Willebrand factor-imposed half-life ceiling (efanesoctocog alfa, Sanofi)

Extended author information available on the last page of the article

received approval from the US Food and Drug Administration (FDA) in February 2023 [7]. Effectively, this allows patients to increase the number of days between infusions and tends to increase adherence [2]. The major complication of factor replacement is the development of neutralizing inhibitors to the coagulation factor in previously untreated and minimally untreated patients [2, 5, 8]. It has been reported that about 30% with severe hemophilia A [9] and 3–10% with hemophilia B develop inhibitors within the first 50 days of exposure to recombinant replacement therapies.

Non-replacement therapies have been developed as another option for prophylaxis for PwH. Hemostatic rebalancing agents result in hemostatic rebalancing by antagonizing the natural anticoagulant system with reduction in antithrombin, tissue factor pathway inhibitor, or protein C. As such, they may be used to prevent bleeding in PwH A and B with and without inhibitors of inhibitors [2, 5]. Three hemostatic rebalancing agents currently under investigation are fitusiran (Sanofi), marstacimab (Pfizer), and concizumab (NovoNordisk), all of which are administered subcutaneously. Fitusiran is a small interfering RNA therapy that targets antithrombin, thereby allowing thrombin generation and effective coagulation [3, 5, 8]. Marstacimab is a monoclonal antibody that promotes coagulation by targeting the tissue factor pathway inhibitor (TFPI) [10]. Concizumab (NovoNordisk) works by binding the Kunitz-2 domain of the TFPI, thus inhibiting TFPI from blocking the coagulation factor Xa (FXa) active site. This modulation allows for sufficient FXa production, resulting in a rebalancing of hemostasis [5, 8]. In March 2023, concizumab was approved in Canada for PwH 12 years and older with hemophilia B and inhibitors, but in May 2023, NovoNordisk received a Complete Response letter from the FDA requesting additional information about monitoring and dosing [11, 12]. In addition to these treatments, emicizumab, a therapeutic bispecific antibody that mimics the function of FVIII (created by Chugai Pharmaceutical Co., Ltd. and co-developed by Chugai, Genentech, and Roche) is approved for prophylaxis for people of all ages with hemophilia A with and without FVIII inhibitors [5, 8]. PwH using non-replacement therapies for prophylaxis may still require factor replacement for breakthrough bleeding, trauma, and surgery.

Challenges associated with the use of these therapeutic agents leave room for a new type of therapy that could improve upon these unmet needs: gene therapy. The most advanced type of gene therapy for hemophilia is gene transfer, in which functional *F8* or *F9* genetic information is transferred into a patient's cells and endogenously expressed. In this context, a successful gene therapy would result in long-term, sustained endogenous production of the FVIII or FIX proteins at concentrations sufficient to restore normal hemostasis [2]. Here, we review how gene therapies may become an important treatment strategy for PwH to consider, and we examine the clinical feasibility of such therapies. Specifically, this review focuses on two recently approved gene therapies, Valoctocogene roxaparvovec (BioMarin Pharmaceutical Inc.) and etranacogene dezaparvovec-drlb (CSL Behring).

2 Gene Therapy for Hemophilia

Gene addition for hemophilia gene therapy involves adeno-associated viral (AAV) vectors, small viruses that target the liver for endogenous factor expression. AAV vectors are advantageous because they are non-pathogenic. They transduce dividing and non-dividing cells but have low integration rates. They are administered by IV infusion.

Following a single IV infusion over 1–3 h, the vector particles are picked up by liver cell receptors, and taken up into the cell, where the vector particle uncoats and delivers the DNA to the nucleus of the cell. Vector DNA forms stable extrachromosomal episomes, which form concatemeric episomes in cell nuclei. Genetic elements that accompany the gene allow for efficient expression and ultimate secretion of FVIII or FIX protein into the plasma, ultimately reaching a steady state between secretion and clearance that is represented by a measurable factor level [13].

Current gene therapies for hemophilia use AAV vectors to target their transgene to hepatocytes. Specifically, both valoctocogene roxaparvovec and etranacogene dezaparvovec-drlb use the AAV serotype 5 (AAV5) [14, 15]. AAV5 was selected from AAV serotypes 1–10 because it is immunologically distinct from other serotypes, has low seroprevalence, provokes minimal cross-reactivity against common pre-existing AAV2 neutralizing antibodies, and efficiently transduces hepatocytes [2, 16]. One disadvantage of AAV is that naturally occurring immunity, in the form of neutralizing antibodies, is common among the general population and can hamper the efficacy of gene therapies. The relatively low seroprevalence and cross-reactivity of AAV5 compared to other AAVs help circumvent this potential challenge [2, 17].

2.1 Select Phase 3 Gene Therapy Trials for Hemophilia

2.1.1 Valctocogene Roxaparvovec GENEr8-1 Phase 3 Trial for Hemophilia A

Two gene therapies for hemophilia received approval for clinical use in 2022. Valoctocogene roxaparvovec was approved in Europe in August 2022. Etranacogene dezaparvovec-drlb received FDA approval in the USA in November 2022 and European approval in February 2023 [14, 15, 18].

Valoctocogene roxaparvovec was developed by BioMarin Pharmaceutical Inc. and is indicated for the treatment of severe hemophilia A in adult patients without a history of FVIII inhibitors and without detectable antibodies to AAV5 (Table 1) [14]. The GENEr8-1 Phase 3 clinical trial (NCT03370913) leading to this approval is part of an ongoing, open-label, single-arm trial. The study population included adult males with severe hemophilia A (FVIII ≤ 1 IU/dL) who had been on prophylactic FVIII replacement for at least 12 months prior to enrollment. Participants had at least 150 exposure days of treatment with FVIII concentrates or cryoprecipitate and could not have a history of FVIII inhibitors (Table 1) [14, 19]. Participants were excluded if they had detectable levels of antibodies to the AAV5 capsid, significant liver dysfunction, an additional bleeding disorder, a platelet count below 100 x 10^9/L, or creatinine levels ≥ 1.5 mg/dL (Table 1) [14, 19]. After a study amendment, participants with human immunodeficiency virus (HIV) were excluded. Upon recommendation from the FDA, the primary endpoint for the GENEr8-1 trial was changed from FVIII activity levels (by chromogenic substrate assay) to annualized bleed rate (ABR) at year 1 after infusion of the AAV5-hFVIII-SQ vector.

The total intention-to-treat (ITT) population included 134 participants. The modified intention-to-treat (mITT) population included 132 HIV-negative participants. A rollover population included 112 HIV-negative participants with pre-infusion bleed and treatment data collected for comparison to post-infusion data. One- and 2-year data have been published [19, 20]. At the time of the 2-year data cut-off, one participant was lost to follow-up and one participant with a history of depression died of suicide [20]. Seventeen participants had 3-year data available.

At year 1, mean FVIII activity was 42.9 IU/dL, reflecting a substantial increase from baseline (Table 2) [19]. Median FVIII activity at year 1 was 23.9 IU/dL (Table 2) [19]. FVIII activity trended down over time (Table 2) [20]. Statistical modeling predicted a transgene half-life of 123 weeks, projecting mean and median FVIII activity levels to remain in the mild hemophilia range over 5 years.

Overall, there was a substantial decrease in ABR and all bleeding events, and based on the year 1 analysis of ABR in

Table 1 Phase 3 trials for approved multinational gene therapies in hemophilia

	Valoctocogene roxaparvovec [14, 19, 24]	Etranacogene dezaparvovec-drlb [15, 18, 25]
Sponsor	BioMarin Pharmaceutical Inc.	CSL Behring
Vector (alternative name)	AAV5-hFVIII-SQ (BMN 270)	AAV5-hFIXco-Padua (AMT-061)
Approval status	Approved in Europe: 24 August 2022 FDA granted RMAT designation in March 2021	Approved in USA: 22 November 2022 Approved in Europe: 20 February 2023
Indication	Valoctocogene roxaparvovec is indicated for the treatment of severe hemophilia A in adult patients without a history of FVIII inhibitors and without detectable antibodies to AAV5	Etranacogene dezaparvovec-drlb is an AAV vector-based gene therapy indicated for treatment of adults with hemophilia B who[a]: Currently use FIX prophylaxis therapy, or Have current or historical life-threatening hemorrhage, or Have repeated, serious spontaneous bleeding episodes
Trial status	GENEr8-1 (NCT03370913) Ongoing, multinational, open-label, single-arm trial	HOPE-B (NCT03569891) Ongoing, multinational, open-label, single-arm trial
Inclusion criteria	Adult males Severe hemophilia A (FVIII ≤1 IU/dL) On prophylactic FVIII replacement for ≥12 months prior to enrollment 150 or more exposure days of treatment with FVIII concentrates or cryoprecipitate No history of FVIII inhibitors	Adult males Severe or moderately severe hemophilia B (FIX ≤ 2 IU/dL) Currently on FIX prophylaxis > 150 previous exposure days of treatment with FIX protein With or without pre-existing neutralizing antibodies to AAV5
Select exclusion criteria	FVIII inhibitors prior to or at screening Detectable pre-existing antibodies to AAV5 capsid Significant liver dysfunction, fibrosis, or cirrhosis, or malignancy Infection or HIV Additional bleeding disorder Platelet count of < 100 × 10^9/L Creatinine ≥1.5 mg/dL	FIX inhibitors prior to or at screening Uncontrolled HIV infection Advanced liver fibrosis

AAV5 adeno-associated virus serotype 5, *FIX* factor IX, *FDA* US Food and Drug Administration, *FVIII* factor VIII, *hFVIII* human factor VIII, *hFIXco* human factor XI cogene, *HIV* human immunodeficiency virus, *RMAT* Regenerative Medicine Advanced Therapy

[a]Etranacogene dezaparvovec is not intended for administration in women

the rollover population, gene therapy was superior to FVIII prophylaxis ($p < 0.001$). Low bleeding rates were maintained at 2 years post infusion [20], though, as expected, lower mean FVIII activity was associated with more treated spontaneous bleeding and traumatic bleeding events. Modeling of bleeding events and FVIII activity suggested that participants with FVIII 3–5% (moderate range) had a bleeding phenotype more consistent with hemophilia (Table 2) [20].

Factor consumption decreased due to discontinuation of prophylaxis and reduction in bleeding. In the rollover population at week 5 and beyond, the use of factor VIII for usual prophylaxis decreased by 99.6% (Table 2) [20]. At year 2, 128 of 134 participants in the ITT group did not resume prophylaxis, whereas six participants resumed prophylaxis (five used FVIII clotting factor and one used emicizumab), including five participants with FVIII activity < 5 IU/dL by chromogenic substrate assay (CSA) [20]. Overall, participants had lower bleeding rates compared to baseline both before and after resuming prophylaxis.

Safety outcomes were measured in the ITT population ($n = 134$) (Table 2) [14, 19]. Twenty-two participants (16.4%) reported serious adverse events, and 3.7% reported treatment-related serious adverse events [19, 20]. The most common treatment-related adverse events were increased alanine aminotransferase (ALT) [85.8%], elevated aspartate aminotransferase (AST) (29.1%), and nausea (23.1%) (Table 2) [19, 20]. Treatment-related serious adverse events at year 1 included ALT increase, anaphylactic reaction, hypersensitivity, maculopapular rash, and presyncope. No treatment-related serious adverse events emerged at year 2, and no new safety signals were reported [20]. At year 2, ALT increase was reported as an adverse event of special interest in 29.1% of participants [20]. No participants developed FVIII inhibitors during this trial. Two participants developed malignancies, but both were determined to be unrelated to the treatment [21–23]. There were no deaths or withdrawals due to adverse events at year 1, but at year 2 there was one death from suicide that was determined to be unrelated to the treatment [19, 20].

Of all participants who experienced elevated ALT (85.8%), the median time to first elevation was 8.0 weeks, and the median elevation duration was 15 days (Table 2) [20]. ALT elevations grade 3 or higher occurred in 8.2% of patients at year 1 and 0.7% of participants at year 2 [20]. Increases in ALT were managed primarily with glucocorticoids. All were resolved without escalating to grade 4 elevations or drug-induced liver injury (DILI) [19]. Of the participants, 79.1% received glucocorticoids, and the median treatment duration with glucocorticoids was 230 days. At the 2-year data cutoff, 96.2% of ALT elevation events were resolved, two were still resolving, nine were unresolved, and one was unknown [20]. In addition, 29.1% of participants were administered other types of immunosuppressants due to contraindications, adverse effects of glucocorticoids, or a poor response to glucocorticoid management (Table 2) [19, 20]. These patients received budesonide, tacrolimus, mycophenolate, or methylprednisolone [20]. The ongoing GENEr8-3 trial (NCT04323098) will further explore relationships between ALT elevations, FVIII expression, and the use of glucocorticoids and/or other immunosuppressants (Table 2) [14, 19].

In summary, challenges of valoctocogene roxaparvovec treatment include waning of gene expression over years and the need for prolonged use of immunosuppression with corticosteroids for many patients [8]. Data continue to accrue regarding predictability and durability of response and these data will be important to guide patient decision making about gene therapy. Control over bleeding remained strong at 2 years post-treatment, but longer-term data will inform about durability of gene expression and bleeding phenotype [20]. Since some participants had low expression levels, and others had high expression levels, it has become clear that it is not possible to predict expression level, which is a significant drawback that impacts the decision to pursue gene therapy. Additionally, protocols to minimize elevated liver enzymes and loss of gene expression should be optimized. Patients with pre-existing neutralizing antibodies were excluded from this study. This study excluded female patients, children, and males who had a history of FVIII inhibitors [19]. Future studies may improve this therapeutic option by exploring attempts to fill these gaps.

In March 2021, the FDA granted valoctocogene roxaparvovec a Regenerative Medicine Advanced Therapy (RMAT) designation by the FDA [24]. RMAT is a program that seeks to accelerate development and review of regenerative therapies. It received conditional approval by the European Medicines Agency in 2022 and is pending regulatory review in the USA.

2.1.2 Etranacogene Dezaparvovec-drlb HOPE-B Phase 3 Trial for Hemophilia B

For hemophilia B, the gene therapy etranacogene dezaparvovec-drlb was developed by uniQure and CSL Behring. The AAV vector-based gene therapy with a hyperfunctional F9 variant (AAV5-hFIXco-Padua) is indicated for the treatment of adults with hemophilia B who currently use FIX prophylaxis therapy, have current or prior life-threatening hemorrhage, or have repeated, serious spontaneous bleeds (Table 1) [15, 25]. The HOPE-B Phase 3 clinical trial (NCT03569891) is an ongoing multinational, open-label single-arm trial with 54 participants. The trial included adult males with severe or moderately severe hemophilia B, defined as a FIX activity level of ≤ 2 IU/dL. Participants must have been on FIX prophylaxis with at least 150

Table 2 Efficacy and safety in Phase 3 trials for gene therapies in hemophilia

	Valoctocogene roxaparvovec [14, 19, 20]	Etranacogene dezaparvovec-drlb [15, 25]
Primary efficacy endpoint	***Year 1*** Change from baseline in FVIII activity at Weeks 49–52 after infusion: Mean (SD): 42.9 IU/dL (± 45.5 IU/dL); $p < 0.001$[a] Median (IQR): 23.9 IU/dL (11.9–62.3 IU/dL) ***Year 2*** Change from baseline in ABR at week 104: -84.5%; $p < 0.001$ Original primary endpoint: Change from baseline in FVIII activity at Week 104, Mean (95% CI): 22.0 IU/dL (16.4–27.7)	Non-inferiority of annualized bleed rate during months 7–18 compared with lead-in period ABR (95% CI)[i]: Lead-in: 4.19 (3.22, 5.45) Month 7–18: 1.51 (0.81, 2.82) Adjusted ABR ratio: 0.36 (0.20, 0.64)[j]
Select secondary efficacy endpoints	***Year 1*** After week 4[a]: Annualized FVIII concentrate use: -98.6%; p < 0.001 ABR: – 83.8%; $p < 0.001$ Additional outcome measure: Percentage of patients with treatment-related serious AEs: 3.7%[b] ***Year 2*** Change from baseline in: Annualized FVIII utilization rate for usual prophylaxis to week 104 (mean): – 99.6%[c] ABR (mean treated bleeds): – 83.8%[c] Additional outcome measure: Model-estimated half-life of transgene-derived FVIII (weeks, 95% CI): (123, 84–232)	Change from baseline in FIX activity level at 6, 12, and 18 months after dosing[i,k] LSM value (95% CI) 6 months: 36.18 (31.41, 40.95); $p < 0.001$ 12 months: 38.81 (34.01, 43.60); $p < 0.001$ 18 months: 34.31 (29.52, 39.11); $p < 0.001$ Change from baseline measurement during lead-in period vs. months 7-18 post-treatment[i] Annualized consumption of FIX replacement therapy [adjusted mean difference in IU (95% CI)]: – 248,825.0 (– 291,149,9; – 206,500.1); $p < 0.001$[l] Annualized infusion rate of FIX replacement therapy [adjusted infusion rate ratio (95% CI)]: 0.03 (0.01, 0.10); $p < 0.001$[l] Adjusted ABR ratio for spontaneous bleeding episodes [ratio (95% CI)]: 0.29 (0.12, 0.71); $p = 0.007$ Adjusted ABR ratio for joint bleeding episodes [ratio (95% CI)]: 0.22 (0.10, 0.46); $p < 0.001$ Odds ratio for one-stage aPTT-based FIX activity < 12% of normal at baseline vs. months 6–18 [odds ratio (95% CI)]: 0.036 (0.014, 0.093); $p < 0.001$[i,n]
Adverse events	***Year 1*** Treatment-related AEs in ≥20% of participants (n, %): ALT increase: (115, 85.8%)[e] Median time to first ALT elevation: 8.0 weeks[e] Median length of ALT elevation: 15 days[e] Patients with grade 3 ALT elevations: (11, 8.2%)[e] AST increase: (39, 29.1%)[b] Nausea: (31, 23.1%)[b] Any treatment-related serious AEs (n, %)[b]: ALT increase: (2, 1.5%) Anaphylactic reaction: (1, 0.7%) Hypersensitivity: (1, 0.7%) Maculopapular rash: (1, 0.7%)[d] Presyncope: (1, 0.7%)[d] No participants developed FVIII inhibitors[b] ***Year 2*** Any treatment-related AE (*n*, %): (28, 20.9%)[e] Any treatment-related serious AE (*n*, %): (0, 0%)[e] No new treatment-related serious AEs occurred[e] AE of special interest >1% (*n*, %)[e]: ALT increase: (39, 29.1%) ALT increase grade ≥ 3: (1, 0.7%) AE related to liver function: (39, 29.1%) No new safety signals emerged[e]	Treatment-related AEs in ≥5% of participants (*n*, %)[o]: ALT increase: (9, 17%) Headache: (8, 15%) Influenza-like illness: (7, 13%) AST increase: (5, 9%) Fatigue: (4, 7%) Blood creatinine kinase increase: (4, 7%) Nausea: (4, 7%) Arthralgia: (3, 6%) No treatment-related serious AEs occurred

Table 2 (continued)

	Valoctocogene roxaparvovec [14, 19, 20]	Etranacogene dezaparvovec-drlb [15, 25]
Immunosuppression	***Year 1*** Management of ALT with glucocorticoid (n, %)[b]: Received glucocorticoids: (106, 79.1%) Median duration of glucocorticoid use: 230 days Any AE related to glucocorticoid use: (81, 60.4%) Most common AEs related to steroid use: acne, insomnia, Cushing's syndrome, weight increase Management of ALT with other immunosuppressants (*n*, %)[b]: Received other types of immunosuppressants: (39, 29.1%) AE related to non-steroidal immunosuppressants: (14, 10.4%) ***Year 2*** Management of ALT with glucocorticoid (*n*, %)[e]: Received glucocorticoids: (106, 79.1%) Median duration of glucocorticoid use: 230 days Any AE related to glucocorticoid use: (79, 71.8%)[f] Most common AEs related to steroid use: acne, insomnia, Cushingoid, weight increase[f] Participants with any use of other immunosuppressant (*n*, %)[e,g]: Received immunosuppressant: (39, 29.1%) Any AE related to use of immunosuppressants: (14, 42.4%)[h] Most common AEs related to use of immunosuppressants: hypomagnesemia, diarrhea, hypophosphatemia[h]	Management of ALT with glucocorticoid[n]: Received glucocorticoids (*n*, %): (9, 17%) Duration of glucocorticoid use (mean±SD): 79.8 ± 26.6 days No glucocorticoid-related AEs were reported

[a]Modified intention-to-treat population ($n = 132$) includes HIV-negative participants

[b]Intention-to-treat population ($n = 134$) includes 132 HIV-negative participants and two patients with a history of HIV

[c]Rollover population ($n = 112$) includes participants in the modified intention-to-treat population who were negative for HIV and had been enrolled in the 270-902 study

[d]Maculopapular rash and presyncope occurred in the same participant

[e]Year 2 intention-to-treat population includes all patients who received valoctocogene roxaparvovec ($n = 134$)

[f]Includes participants who received any glucocorticoids ($n = 110$)

[g]Participants who received other immunosuppressants ($n = 39$) including budesonide, tacrolimus, mycophenolate, and/or methylprednisolone

[h]Includes participants who received mycophenolate mofetil, mycophenolate sodium, fujimycin, tacrolimus, or tacrolimus monohydrate ($n = 33$)

[i]Full analysis population included all participants who were enrolled, entered the lead-in phase, received etranacogene dezaparvovec-drlb, and had at least one efficacy endpoint assessment after receipt of etranacogene dezaparvovec-drlb

[j]The upper limit of the CI of the ABR ratio was compared with the noninferiority margin of 1/8. If the upper limit was less than 1.8, then noninferiority was declared

[k]The value is the LSM from a repeated-measures linear mixed model with visit as a categorical covariate. Two-sided *P* value of ≤ 0.05 was considered statistically significant

[l]*P* value was calculated with a paired *t*-test. Two-sided *P* value of ≤ 0.05 was considered statistically significant

[m]Rate ratio calculated as the value for the post-treatment period divided by the value in the lead-in period. Two-sided *P* value of ≤ 0.05 was considered statistically significant

[n]Odds ratio is from a generalized linear mixed logistic regression model with visit as a categorical covariate. Two-sided *P* value of ≤ 0.05 was considered statistically significant

[o]Safety population included all participants who were enrolled and received etranacogene dezaparvovec-drlb

ABR annualized bleeding rate, *AE* adverse event, *ALT* alanine aminotransferase, *aPTT* activated partial thromboplastin time, *AST* aspartate aminotransferase, *CI* confidence interval, *FIX* factor IX, *FVIII* factor VIII, *HIV* human immunodeficiency virus, *IQR* interquartile range, *LSM* Least-squares mean, *SD* standard deviation

prior days of exposure to FIX treatment. Participants with or without pre-existing neutralizing antibodies to AAV5 were included. Patients with FIX inhibitors prior to or at screening were excluded (Table 1) [15, 25].

The primary efficacy endpoint in the HOPE-B trial was non-inferiority of the ABR during months 7–18 after infusion compared with the 26-week lead-in period. The ABR during the lead-in period was 4.19 (95% confidence interval (CI) 3.22, 5.45) and the ABR during months 7–18 decreased to 1.51 (95% CI 0.81, 2.82) consistent with non-inferiority of gene therapy to factor replacement prophylaxis (Table 2) [25]. Overall, all bleeding events decreased and this decrease was sustained over time.

At baseline 81% of participants had FIX activity less than 1 IU/dL. Six months post-treatment, FIX activity (least squares mean) increased to 39.0 ± 18.7 IU/dL, and the increased level of FIX activity was sustained at 12 and 18 months. In most gene therapy trials, participants are excluded if they have pre-existing AAV neutralizing antibodies as it is anticipated that the antibodies will block transgene efficacy. However, in HOPE-B, antibodies were measured but not used as a trial exclusion. At month 18, mean FIX levels were 31.1 IU/dL for participants with neutralizing antibodies against AAV5 ($n = 21$) and 39.9% for those without ($n = 33$). No correlation between neutralizing antibody titer and FIX level was observed [25].

Factor consumption decreased due to reduction in prophylaxis and treated bleeds. Ninety-six percent of participants discontinued their use of FIX replacement prophylaxis between post-treatment day 21 and month 18 [25]. During the lead-in period, participants used a mean of 257,339 ± 149,013 IU of FIX per year. Between the lead-in period and the post-treatment period, FIX use decreased by a mean of 248,825 IU/year per participant (Table 2).

Quality of life was examined as an exploratory endpoint using the International Physical Activity Questionnaire (iPAQ) and the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L), and at 12 months post-treatment, participants demonstrated improved QoL compared to baseline based on the Hem-A-QoL total scores [25].

Safety outcomes from the HOPE-B trial included adverse events that occurred or worsened during or after treatment, abnormalities in liver function, vector shedding, and an immune reaction to the AAV5 vector or transgene. All participants experienced adverse events that occurred or worsened during or after treatment. The most common treatment-related adverse events were ALT elevation (17%), headache (15%), influenza-like illness (13%), and AST elevation (9%) (Table 2) [25]. Seventeen percent of participants received glucocorticoid treatment for elevated ALT. The mean duration of glucocorticoid treatment for elevated ALT was 79.8 ± 26.6 days, and no adverse events related to the use of corticosteroids were reported (Table 2).

One participant developed hepatocellular carcinoma that was determined to be unrelated to the AAV5 vector. At 18 months post-treatment, clearance of vector DNA was observed in semen specimens from 61% of participants and blood specimens from 46% of participants. No patients developed FIX inhibitors during the trial [25]. Adverse events were similar among participants with or without AAV5 neutralizing antibodies.

2.1.3 Comparison of Hemophilia A versus Hemophilia B Gene Therapy

Compared to the GENEr8-1 study for hemophilia A, the HOPE-B study for hemophilia B showed etranacogene dezaparvovec-drlb provides a more sustained response with less hepatotoxicity. While FVIII levels decrease over time after treatment with valoctocogene roxaparvovec, results from the Phase 2b etranacogene dezaparvovec-drlb trial showed stable and durable FIX levels 3 years post-treatment [26], and gene therapy recipients in other hemophilia B gene therapy trials have maintained their response for nearly a decade [8, 19, 27]. Difficulty in predicting expression levels is an important consideration for patients considering therapy, but if there is lack or loss of response, patients may safely resume prophylactic therapy [19, 25].

Valoctocogene roxaparvovec is associated with higher rates of transaminitis and consequently associated immunosuppressive treatments than etranacogene dezaparvovec-drlb. This is an important point when balancing risks and benefits of gene therapy. Therefore, liver health is essential for all AAV gene therapy and patients must understand key liver health exclusions and precautions, including avoiding alcohol in excess and hepatotoxic medications.

The HOPE-B trial included patients with pre-existing neutralizing antibodies to AAV5, while the GENEr8-1 trial did not [19, 25]. Patients with hemophilia A who are considering gene therapy must understand that they may be excluded due to pre-existing antibodies and all patients should understand that with current strategies re-dosing will not be possible since everyone mounts an antibody response to AAV after treatment.

2.2 Remaining Questions for Gene Therapies in Hemophilia

Many of the questions about gene therapies for hemophilia focus on long-term efficacy. Although the expectation is a single infusion with durable efficacy, the actual duration of treatment effectiveness is largely unknown [3, 28]. Notably, the durability of valoctocogene roxaparvovec therapy is shorter than the durability of etranacogene dezaparvovec-drlb therapy [19, 20, 25, 26]. Reasons are unclear but may be inherent to the fact that the native site of FIX production is the hepatocyte, which coincides with the AAV vector target cell. In contrast, the native site for FVIII production is liver

sinusoidal endothelial cells, which is different from the AAV target cell. The difference in cell type for FVIII could lead to stress on the endoplasmic reticulum, potentially reducing the protein expression over time [29, 30]. As the trials are still ongoing, the continued collection of efficacy data will be important to increase knowledge about how to use these gene therapies to provide maximum benefit for patients. Long-term follow-up is essential for all gene therapy recipients, including those who receive commercial product, and patients will be enrolled into gene therapy registries.

In addition to examining questions about efficacy over time, it is critical to consider concerns about long-term safety, especially with regard to liver health [3, 28]. Prolonged immunosuppression with corticosteroids and other immunosuppressants causes undesirable side effects but is an important tool for managing ALT elevations. Long-term effects on liver health are currently unknown, and it is unclear if risks will be different in patients with HIV or other immunodeficiency. Clearly, patients undergoing gene therapy for hemophilia will need to actively maintain their liver health by avoiding excessive alcohol intake and hepatotoxic medications. Maintaining liver health will be necessary to maintain gene expression [3, 28].

There are further questions surrounding the use of immunosuppressants. Specifically, it would be beneficial to gain knowledge about when to initiate immunosuppressants. Would a patient benefit most from immunosuppressant initiation during prophylaxis, immediately before beginning gene therapy, immediately after the gene therapy infusion, or later? Answers to these questions will optimize the treatment protocol to help ease the burden of undergoing gene therapy [3].

Further, cancer was reported at rates seen in the general population in both Phase 3 trials, and the cases were determined by investigators to be unrelated to the gene therapy [19, 20, 25, 26]. Nonetheless, gene therapy that uses liver-targeted AAV vectors must be carefully considered for patients with pre-existing risk factors for hepatocellular carcinoma.

Additional potential safety concerns include thrombosis with supraphysiologic factor levels and genotoxicity [25].

Overall, when discussing gene therapy with patients, clinicians should be transparent about these remaining questions and potential implications.

2.3 Determining Patient Eligibility for Gene Therapy

It is paramount to consider which patients may be eligible for gene therapy for hemophilia [3, 27]. The criteria will be defined in the prescribing information as each therapy is approved and may be different to clinical trial criteria and/or expand over time. PwH will need to understand that even if they are interested in gene therapy, they may not be eligible.

For example, a history of inhibitors is a current exclusion criterion. While it seems reasonable that a patient who had FVIII inhibitors as a child, and was successfully tolerized and maintained with factor VIII replacement therapy, would not be at very high risk for inhibitor risk with gene therapy, suitability of gene therapy in the context of inhibitors is currently being investigated (ClinicalTrials.gov Identifier: NCT04684940). Pre-existing neutralizing antibodies to AAV5 are an exclusion criterion for valoctocogene roxaparvovec but not etranacogene dezaparvovec-drlb.

HIV was an exclusion criterion in Phase 3 clinical trials for valoctocogene roxaparvovec but not etranacogene dezaparvovec-drlb [19, 25]. It is discussed more as a consideration for valoctocogene roxaparvovec and not addressed in etranacogene dezaparvovec-drlb labelling [15]. These gene therapies have not been widely evaluated in patients who have HIV or are otherwise immunocompromised.

In addition to the biologic characteristics that qualify or disqualify an individual for gene therapy, the importance of considering a patient's own perspectives, quality of life, and willingness to undergo gene therapy cannot be overemphasized [31, 32]. Given these considerations, we propose a three-pronged stratification of patients to determine an individual's suitability for gene therapy. Under our model, a PwH may be categorized as an unlikely candidate, a potential candidate, or a good candidate for gene therapy. Factors contributing to this classification include hemophilia severity, liver health, the presence of neutralizing antibodies to AAV5, a history of inhibitors, immune status, and importantly, an individual patient's willingness to undergo gene therapy and the presence of strong emotional and logistical support for the patient to travel for treatment and follow-up appointments (Table 3).

A good candidate for gene therapy may be unable to self-infuse, may experience a high ABR or frequent spontaneous bleeds, and may have worsening target joints that cause chronic pain. Since gene therapy requires commitment to intensive short- and long-term monitoring, it is associated with a different side-effect profile than current treatments, and it creates the potential need for immunosuppressant therapy with its own set of adverse effects, it is critical that a patient undergoing gene therapy agrees with their provider that this treatment could improve their quality of life. Finally, a good candidate for gene therapy must be able to travel to the local or regional treatment center where the infusion will be administered, as well as frequent follow-up appointments during the first few years,

and must have strong mental health support (Table 3). In weighing the benefit-to-risk ratio here, it is also important to consider the implications of potentially needing to return to regular self-infusions after several years since the long-term durability of gene therapy remains unknown. While additional infusion or subcutaneous options may be available in the future, patients may experience frustration, anxiety, or depression associated with resuming prophylaxis after undergoing gene therapy. On the other hand, patients may appreciate being infusion-free for several years only, if informed appropriately at the outset, avoiding expectations of a "one-and-done cure".

For PwH who manage their current prophylaxis well and feel comfortable with their therapeutic strategy, the adverse events and frequent follow-up appointments associated with gene therapy may be a disincentive. In addition, a PwH who is unable to undergo frequent monitoring during the first year after a gene therapy infusion, is unreliable, or does not have the support to travel to regular appointments, would not likely be a good candidate for gene therapy (Table 3). Since long-term survival is expected with prophylaxis, it is important to focus the discussion of the benefits of gene therapy to a consideration of whether the treatment will improve a patient's quality of life and reduce their treatment burden [31].

Children (aged < 18 years) have not been part of the Phase 3 clinical trials to date. There is an expected lower age limit to achieve efficacy and durability given higher hepatocyte turnover throughout childhood, with loss of episomal gene expression over time. It is possible that this therapy will be effective in adolescents though, and that eligibility could be expanded in the future. Lastly, there is much discussion among experts regarding unresolved questions pertaining to liver health, and to what extent conditions like fatty liver, steatohepatitis, various degrees of fibrosis or cirrhosis may influence the efficacy and safety of gene therapy at the time of treatment and over a patient's lifetime.

3 Discussion

Gene therapy entering into the clinical arena after decades of research clearly has opened a new and exciting era for the management of hemophilia. However, many new questions and uncertainties have arisen in that realm, which can only be answered as time and experience with this novel treatment modality progress. Perhaps the most important questions at this juncture relate to the identification of patients deemed good candidates for gene therapy. Based on real-world experience survey data and the expectations and requirements along the gene therapy journey, we feel that it is critical to partner with the PwH to align on individual benefits, risks, and required logistics [33, 34]. Bringing patients into the discussion early allows them to advocate for their own health, feel empowered in their choice, and understand risks pertaining to non-adherence of a rather burdensome monitoring schedule throughout at least the first year after gene therapy infusion. Conversely, it is also important to consider what patients expect of their care team, and that by and large PwH place a high value on shared decision-making about treatment strategies [35]. Prominent factors that could influence a patient's decision to receive gene therapy include the burden of administration of factor and non-factor products, personal experiences with previous hemostatic regimens, improved efficacy in preventing bleeds, and the prospect of a more active life with sustained clotting factor activity levels. On the other hand, factors such as fearing the unknown long-term safety effects and fear of being an early adopter of a new treatment could be barriers [35]. Some participants may wish to wait to see how gene transfer technology improves over time or to wait for other developing gene therapy strategies such as gene editing, since gene therapy is likely to remain a "once-in-a-lifetime treatment."

An important component of gene therapy administration is the need for frequent monitoring, especially in the first year after the initial infusion. One way to facilitate long-term monitoring of PwH who receive gene therapy is to enable patients who undergo treatment at an experienced hemophilia treatment center to receive follow-up care at their local center ("Hub and Spoke Model"). Such a collaboration would reduce the burdensome and expensive requirement on patients to travel to a specialized treatment center more than once. Patients should also be enrolled in long-term follow-up registries that collect a core dataset on the safety, efficacy, and durability of gene expression. This dataset will be useful in caring for the individual PwH as well as for guiding future innovation. Currently, the World Federation of Hemophilia is collecting long-term data as part of the WFH Gene Therapy Registry (The World Federation of Hemophilia Gene Therapy Registry-Informational Webinar-eLearning Platform (elearning.wfh.org)); in the USA the American Thrombosis and Hemostasis Network will collect data as part of Hemophilia Gene Therapy Outcomes Study (NCT04398628), and data will feed into the WFH registry.

With any new therapeutic, it is prudent to balance the discussion of innovation with an acknowledgement of its limitations. For example, gene therapy for hemophilia may be able to prevent further progression of chronic joint disease, but it may not correct existing joint damage. Additionally, gene expression may wane over years, and many patients require prolonged immunosuppression with corticosteroids [8]. Furthermore, gene therapy may not be suitable for children because of episomal expression and anticipated reduction of

Table 3 Determining candidacy of individual patients for gene therapy in hemophilia

Determinant	Not likely a candidate for gene therapy	Potentially a candidate for gene therapy	Good candidate for gene therapy
Disease severity	Mild	Moderate	Moderate to severe; severe
Liver health	History of liver dysfunction, fibrosis, cirrhosis, or malignancy are of concern, especially for gene therapy with valoctocogene roxaparvovec History of HIV for gene therapy with valoctocogene roxaparvovec	No history of liver pathology	No history of liver pathology
Presence of neutralizing antibodies to AAV5	Detectable neutralizing antibodies to AAV5 disqualify a patient from receiving valoctocogene roxaparvovec	Detectable neutralizing antibodies to AAV5 may be permissible for therapy with etranacogene dezaparvovec for hemophilia B	No history of neutralizing antibodies to AAV5
History of inhibitors to FVIII or FIX for patients with Hemophilia A or B, respectively	History of inhibitors of FVIII or FIX in patients with hemophilia A or B, respectively	No history of inhibitors	No history of inhibitors
Patient willingness to undergo gene therapy	Patient manages disease well with current method of prophylaxis Patient is uninterested in changing treatment strategies Patient feels their quality of life will not improve or could worsen because of gene therapy Patient is not willing to undergo gene therapy and experience the potential side effects Patient unable to undergo frequent monitoring during the first year after gene therapy Patient's use of current method of prophylaxis is unreliable, suggesting they may not adhere to attending follow-up monitoring appointments Unwillingness to disengage from alcohol use or other liver-toxic behavior	Patient is mostly adherent to current prophylaxis, but experiences a high ABR or has complications with target joints Patient expresses interest in learning more about new therapeutic approaches for their condition	Patient is unable to self-infuse Patient experiences high ABR, frequent spontaneous bleeds, and/or worsening target joints Patient agrees their quality of life could be improved by gene therapy and is willing to undergo the treatment Patient does not have a condition excluding the potential use of immunosuppressive drugs
Emotional and logistical support to travel for treatment and follow-up appointments	Patient is unable to travel to a treatment center providing the gene therapy infusion Patient does not have a support network or plan to facilitate attending frequent follow-up appointments	Patient has moderate support of family/friends and can travel to the treatment center, though not easily	Patient can easily travel to treatment center and is supported emotionally by family and/or friends Willingness for frequent monitoring during the first few years

AAV5 adeno-associated virus serotype 5, *ABR* annualized bleed rate, *FIX* factor IX, *FVIII* factor VIII, *HIV* human immunodeficiency virus

plasma levels with growing livers. The current gene therapies available are non-integrating, meaning that they would not be passed on to new hepatocytes during cell division.

Future advances in gene therapy through continued investigations will be important to increase patient eligibility, achieve durable factor expression (especially for hemophilia A), and minimize hepatoxicity and the need for prolonged immunosuppression. Such updates will have the potential to improve the benefit-to-risk ratio of undergoing gene therapy. Other potential advancements, such as gene therapies suitable for children whose livers are still developing, may provide benefit early in life before target joints develop.

At present, gene therapy has the potential to offer an additional treatment option to carefully selected PwH. We believe gene therapy is a valuable therapeutic option, which will undoubtedly benefit from further investigation. Going forward, delving into the world of gene therapy has the potential to revolutionize how we think about treating genetic disorders.

Declarations

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Conflict of Interest Courtney D. Thornburg has had institutional grant funding from BioMarin Pharmaceuticals. Courtney D. Thornburg has received honoraria for participating in scientific advisory panels, consulting, and speaking engagements for CSL Behring, HemaBiologics, Genentech, Pfizer, Sanofi Genzyme, and Spark Therapeutics. Courtney D. Thornburg has received fees for participation in data monitoring board from BlueBird Bio. Dana H. Simmons declares that she has no conflict of interest. Annette von Drygalski has received honoraria for participating in scientific advisory board panels, consulting, and speaking engagements for BioMarin, Regeneron, Pfizer, Bioverativ/Sanofi, CSL Behring, NovoNordisk, Spark Therapeutics, Genentech and UniQure. Annette von Drygalski is a co-founder and member of the Board of Directors of Hematherix LLC., a biotechnology company that is developing ^{super}FVa therapy for bleeding complications.

Ethics Approval, Patient Consent None required, this work represents a review of available evidence.

Availability of Data and Materials Not applicable, this work represents a review of available evidence.

Code Availability Not applicable.

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