MediCom Worldwide, Inc.

Hemophilia Gene Therapy Resource Guide

Gene therapy will become a powerful approach in the management of hemophilia and could offer a definitive cure.

Clinical trials of gene therapy have:

- Resulted in long term therapeutic levels of factor expression with normal FIX and FVIII levels
- Resulted in extraordinary reduction of bleeding events
- Allowed patients freedom from being tethered to prophylactic factor therapy

Below is a summary of:

- Pending and recent gene therapy drug approvals in hemophilia
- Safety considerations for administering approved gene therapies
- Emerging data from long-term follow-up of gene therapy in hemophilia
- Ongoing hemophilia A and B gene therapy trials

Abbreviations

AAV	Adeno-associated virus
AAV5	Adeno-associated viral vector of serotype 5
ABR	Annualized bleeding rate
AE	Adverse event
AFP	Alpha-fetoprotein
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BLA	Biologics License Application
cDNA	Complementary deoxyribonucleic acid
CPK	Creatinine phosphokinase
FDA	US Food and Drug Administration
FIX	Factor IX
FVIII	Factor VIII
Gc	Genome copies
HCCC	Hemophilia Comprehensive Care Center
HTC	Hemophilia treatment center
IV	Intravenous
Kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver function test
Nabs	Naturalizing antibodies
SAE	Serious adverse event
Vg	Vector genomes

Newly Approved Gene Therapies in Hemophilia

Valoctocogene roxaparvovec-rvox

The FDA has approved BioMarin's valoctocogene roxaparvovec; the first and only gene therapy for adults with severe **hemophilia A**. This one-time, single-dose therapy was shown to be effective in controlling bleeding for at least 3 years in the largest and longest phase 3 study of a gene therapy for hemophilia to date.

- **Approval date**: June 29, 2023
- **Indication**: Treatment of severe hemophilia A in adults with FVIII activity <1 U/dL without pre-existing antibodies to adeno-associated virus serotype 5
- **Dosage**: One-time, single-dose infusion of 6 x 10^{13} vg per kg of body weight

Clinical Trial Findings	Safety
In the Phase 3 GENEr8-1 study, valoctocogene roxaparvovec conferred an ABR reduction of 52% and an 83% reduction in treated bleeds	Common adverse reactions include fatigue, headache, abdominal pain, nausea, vomiting, and infusion-related reactions Adverse reactions were also seen with the use of corticosteroids Monitoring of liver enzymes is required

Ongoing trials of valoctocogene roxaparvovec-rvox:

Clinical Trial ID	Title	Summary
NCT02576795	Gene Therapy Study in Severe Haemophilia A Patients (270-201)	This study is being conducted as an open label, dose escalation study in order to determine the safety and efficacy of valoctocogene roxaparvovec, an AAV-based gene therapy vector in participants with severe hemophilia A
NCT03392974	Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients at a Dose of 4E13 vg/kg (BMN270-302)	This phase 3 clinical study will assess the efficacy of BMN 270, defined as FVIII activity, during weeks 49-52 following intravenous infusion of BMN 270 and assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy and the number of bleeding episodes from week 5 to week 52
NCT03370913	Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients (BMN 270-301) (BMN 270-301)	This phase 3 clinical study will assess the efficacy of BMN 270, defined as FVIII activity, during weeks 49-52 following intravenous infusion of BMN 270 and assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy and the number of bleeding episodes from week 5 to last visit by data cutoff
NCT05768386	A Long-Term Follow-Up Study in Severe Hemophilia A Subjects Who Received BMN 270 in a Prior BioMarin Clinical Trial (270-401)	The BMN 270 clinical development program consists of multiple interventional studies designed to assess the safety and efficacy of a single infusion of BMN 270 for at least 5 years post-infusion. This long-term follow-up study is needed to help further understand the long-term safety of BMN 270 beyond 5 years and to assess the durability of efficacy

Clinical Trial ID	Title	Summary
NCT03520712	Gene Therapy Study in Severe Hemophilia A Patients With Antibodies Against AAV5 (270-203)	This study is being conducted as an open label, single dose study to determine the safety of valoctocogene roxaparvovec (an AAV-based gene therapy vector) in severe hemophilia A patients with pre-existing antibodies against AAV5
NCT04323098	Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in Hemophilia A (GENEr8-3)	This phase 3 clinical study will evaluate the safety and effectiveness of valoctocogene roxaparvovec in combination with prophylactic corticosteroids in patients with severe hemophilia A
NCT04684940	Safety, Tolerability, and Efficacy Study of Valoctocogene Roxaparvovec in Hemophilia A With Active or Prior Inhibitors	This Phase 1/2 clinical study will evaluate the safety and efficacy of valoctocogene roxaparvovec in patients with severe hemophilia A and inhibitors to FVIII. Part A of the study will involve subjects who have active inhibitors to FVIII, and Part B involving subjects with a prior history of inhibitors

Resources:
Approval announcement
Package Insert

Etranacogene dezaparvovec-drlb

The FDA has approved CSL Behring's etranacogene dezaparvovec, an AAV-based gene therapy for the treatment of adults with **hemophilia B** who currently use FIX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. This one-time gene therapy product has been shown to be safe and effective for reducing ABR with an acceptable safety profile.

- **Approval date**: November 22, 2022
- **Indication**: Adults with hemophilia B (congenital FIX deficiency) who currently use FIX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes
- **Dosage**: Intravenous infusion of 2 x 10^{13} gc per kg of body weight

Drug description	Drug effects	Safety
Etranacogene dezaparvovec-drlb is an AAV-based gene therapy approved for the treatment of hemophilia B in adults who are: • Currently using FIX prophylaxis therapy • Have current or historical life-threatening hemorrhage, or • Have repeated, serious spontaneous bleeding episodes	In an open-label, phase 3 trial, treatment resulted in: • Increased FIX activity levels • Decreased need for routine FIX replacement prophylaxis, and • A 54% reduction in ABR compared to baseline	Common adverse reactions include liver enzyme elevations, headache, mild infusion-related reactions, and flu-like symptoms. Patients should be monitored for adverse infusion reactions and liver enzyme elevations (transaminitis) in their blood.

Ongoing trials of etranacogene dezaparvovec-drlb:

Clinical Trial ID	Title	Summary
NCT05962398	Long-term Follow-up Study of Male Adults With Hemophilia B Previously Treated With Etranacogene Dezaparvovec (CSL222)	The primary purpose of this study is to assess the long-term safety in male adults with hemophilia B who were treated with CSL222 in studies CSL222_2001 (NCT03489291) or CSL222_3001 (NCT03569891)
NCT06003387	Efficacy and Safety of CSL222 (Etranacogene Dezaparvovec) Gene Therapy in Adults With Hemophilia B With Pretreatment Adeno-associated Virus Serotype 5 (AAV5) Neutralizing Antibodies (Nabs)	The purpose of this study is to assess the risk of bleeding due to failure of expected pharmacological action of CSL222 in adults with severe or moderately severe hemophilia B with detectable pretreatment AAV5 Nabs
NCT06008938	An Observational Cohort Study to Characterize the Effectiveness and Safety of HEMGENIX® in Patients With Hemophilia B (IX-TEND 4001)	This observational, post-authorization, long-term follow-up study aims to investigate the short and long-term effectiveness and safety of the study drug in patients with hemophilia B. The study will also include a cohort of patients with hemophilia B treated with FIX prophylaxis to enable interpretation of relevant efficacy and safety findings

Clinical Trial ID	Title	Summary
NCT03569891	HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients	This is an open-label, single-dose, multi-center, multinational trial to demonstrate the efficacy of AMT-061 and to further describe its safety profile. The study drug is identified as AAV5-hFIXco-Padua (AMT- 061). AMT-061 is a recombinant AAV5-containing the Padua variant of a codon-optimized human FIX cDNA under the control of a liver-specific promoter. The pharmaceutical form of AMT-061 is a solution for intravenous infusion administered at a dose of 2 x 10^{13} gc/kg

Resources:
Approval announcement
Package Insert

Pending Approvals

Fidanacogene elaparvovec

The FDA has accepted Pfizer's BLA for fidanacogene elaparvovec for the treatment of adults with hemophilia B. Fidanacogene elaparvovec is a novel, investigational gene therapy that contains a bio-engineered AAV capsid (protein shell) and a high-activity variant of human coagulation FIX gene. For people living with hemophilia B, the goal of this gene therapy is to enable them to produce FIX themselves via this one-time treatment rather than needing regular intravenous infusions of FIX, as is the current standard of care.

The submissions for fidanacogene elaparvovec are based on efficacy and safety data from the Phase 3 BENEGENE-2 study (NCT03861273), which met and surpassed its primary endpoint of non-inferiority regarding the ABR of total bleeds post-treatment versus a standard prophylaxis regimen with FIX. Fidanacogene elaparvovec was generally well-tolerated, with a safety profile consistent with Phase 1/2 results.

Clinical Trial Findings	Safety
In the Phase 3 BENEGENE-2 study, fidanacogene elaparvovec demonstrated superiority to standard prophylaxis, with the treatment groups experiencing a mean ABR of 1.3 over 12 months compared to an ABR of 4.43 during the lead-in pre-treatment period; this represents a 71% reduction in ABR. Fidanacogene elaparvovec also produced a 92% reduction in annualized infusion rate.	The safety profile is consistent with Phase 1/2 trial results. In the BENEGENE-2 study, 14 SAEs were reported in seven (16%) patients, including one case with two events assessed as related to treatment: a duodenal ulcer hemorrhage and anemia occurring in the setting of corticosteroid use. No deaths, SAEs associated with infusion reactions, thrombotic events, or FIX inhibitors were reported.

Safety Considerations for Administration of Gene Therapy

Valoctocogene roxaparvovec
Package Insert

The most common adverse reactions in patients treated with valoctocogene roxaparvovec include **headache** (7%), **nausea** (31%), **vomiting** (6%), **abdominal pain** (6%), **fatigue** (16%), and **infusion-related reactions** (7%, Grade ≥3 1%)

Laboratory abnormalities in patients treated with valoctocogene roxaparvovec include increases in **ALT** (81%), **AST** (69%), **LDH** (57%), **CPK** (45%), **GGT** (18%), and **bilirubin** (13%)

Adverse Event	Monitoring	Minimization	Treatment Strategies
Infusion reactions	Monitor for at least 3 hours after infusion	Do not infuse the product faster than 4 mL/min Slow or interrupt administration	Restart administration at a slower infusion once resolved Discontinue infusion for anaphylaxis Consider treatment with corticosteroid, antihistamine, and other means of infusion reaction management
Elevation in liver transaminases, particularly ALT elevation	Monitor ALT and institute corticosteroid treatment in response to ALT elevations, as required Monitor ALT and FVIII activity levels weekly and during corticosteroid therapy	Avoid medications and substances that can cause or exacerbate hepatotoxicity	Consider corticosteroids when transaminases elevate
Thromboembolic events	Evaluate patients for risk of thrombosis including general cardiovascular risk factors before and after administration	N/A	Refer for guideline-directed medical treatment
Hepatocellular carcinogenicity	Monitor patients for risk factors such as: • Hepatitis B or C • Non-alcoholic fatty liver disease • Chronic alcohol consumption • Non-alcoholic steatohepatitis • Advanced age	N/A	Refer for guideline-directed medical treatment Contact BioMarin Pharmaceutical Inc. at 1-866-906-6100 to obtain instructions on collecting patient samples for testing

Etranacogene dezaparvovec
Package Insert

The most common adverse reactions in patients treated with etranacogene dezaparvovec include **ALT increase** (42%), **headache** (18%), **blood creatine kinase increase** (42%), **flu-like symptoms** (14%), **infusion-related reactions** (33%), **hypersensitivity** (4%), **fatigue** (12%), **AST increase** (42%), **nausea** (7%), and **malaise** (12%)

Adverse Event	Monitoring	Minimization	Treatment Strategies
Infusion reactions	Monitor for at least 3 hours after infusion	Slow or interrupt administration	Restart administration at a slower infusion once resolved
Elevation in liver transaminases (≥5%)	Closely monitor transaminases once a week for three months	Continue to monitor transaminases in all patients until LFTs return to baseline	Consider corticosteroids when transaminases elevate Review and update National HTC
Development of inhibitors	Monitor for FIX activity and FIX inhibitors	Consult HCCC	Consult HCCC
Hepatocellular carcinogenicity	Assess patients for pre-existing risk factors such as: • Cirrhosis • Advanced hepatic fibrosis • Hepatitis B or C • Nonalcoholic steatohepatitis • Chronic alcohol consumption • Advanced age	Monitor liver ultrasound annually Monitor AFP regularly following administration	Consult HCCC if abnormal studies ensue and immediately involve appropriate oncologic specialists
Loss of transgene expression	Monitor FIX activity	Consult HCCC	Consult HCCC

Emerging data from long-term follow-up of gene therapy in hemophilia

Study	Agent	Phase	Result
Hemophilia A			
Croteau SE, et al ASH 2022 Annual Meeting	SPK-8011	1/2	At 5 years of follow-up, a single infusion of SPK-8011 resulted in durable year-to-year reduction in ABRs and FVIII infusion rates for 16/18 patients.
Visweshwar N, et al Updated results of the ALTA study ASH 2021 Annual Meeting	Giroctocogene fitelparvovec (PF-07055408/SB-525)	1/2	A single infusion of giroctocogene fitelparvovec in patients with hemophilia A was 'generally well-tolerated' with increases in FVIII and minimal bleeding observed in the high-dose cohort.
Hemophilia B			
Escobar M, et al ASH 2022 Annual Meeting	BAX 335	1/2	No additional BAX 335-related AEs, malignancy or thrombosis were reported in this long-term follow-up analysis of a phase 1/2 study. One participant achieved persistent FIX transgene activity in the circulation for 7.2 years and currently remains free from bleeding and the need for FIX replacement therapy.
Pipe SW, et al HOPE-B clinical trial 24-month follow-up	Etranacogene dezaparvovec	3	Patients experienced a 64% reduction in ABR, a 73% reduction in treated bleeds, and a 75% reduction in annual spontaneous bleeding rate. Patients also demonstrated ability to maintain FIX activity regardless of the presence of neutralizing antibodies to AAV.

Ongoing Hemophilia A Gene Therapy Trials

Sponsor/ Program	Therapy	Study title	Phase	Brief description	Status
Pfizer AFFINE NCT04370054	PF-07055480 / Giroctocogene fitelparvovec	Study to Evaluate the Efficacy and Safety of PF-07055480 / Giroctocogene Fitelparvovec Gene Therapy in Moderately Severe to Severe Hemophilia A Adults (AFFINE)	3	C3731003 is a pivotal Phase 3 study to evaluate the clinical efficacy and safety of a single IV infusion of PF-07055480/ giroctocogene fitelparvovec (Recombinant AAV2/6 Human FVIII Gene Therapy) in adult male participants with moderately severe or severe hemophilia A (FVIII:C≤1%) for the study duration of 5 years. The study will enroll eligible participants who have been followed on routine prophylaxis with FVIII products in the Lead-In study C0371004.	Recruiting
Pfizer NCT03061201	SB-525 (PF-07055480)	A Study of Recombinant AAV2/6 Human Factor 8 Gene Therapy SB-525 (PF-07055480) in Subjects With Severe Hemophilia A	2	The purpose of the study is to evaluate the safety, tolerability, and time-course profile of FVIII activity after dosing with SB-525 (PF-07055480). The constant production of FVIII after a single SB-525 (PF-07055480) administration may provide potential benefit in durable protection against bleeding and the complications thereof without lifelong repetitive IV factor replacement administration.	Active, not recruiting
Spark Therapeutics NCT03003533	SPK-8011	A Gene Transfer Study for Hemophilia A	1/2	This clinical research study is being conducted to determine the safety and efficacy of the FVIII gene transfer treatment with SPK-8011 in individuals with hemophilia A. The approach being tested uses a further modified novel AAV vector (with a stronger attraction to the human liver) to deliver the human FVIII gene into liver cells so that they can produce FVIII protein.	Active, not recruiting
University College, London GO-8 NCT03001830	Serotype 8 Capsid Pseudotyped Adeno-associated Viral Vector Encoding Factor VIII-V3	Gene Therapy for Haemophilia A (GO-8)	1/2	This is an open label, Phase 1/2 dose escalation study entailing a single systemic administration of AAV2/8-HLP-FVIII-V3 in adults (>18 years of age) with severe hemophilia A who have baseline FVIII levels of <1% of normal that has been designed to establish safety and efficacy of the approach.	Recruiting

Sponsor/ Program	Therapy	Study title	Phase	Brief description	Status
Bayer/Ultragenix NCT03588299	BAY 2599023 (DTX 201)	Study to Test the Safety and How Well Patients With Severe Hemophilia A Respond to Treatment With BAY 2599023 (DTX 201), a Drug Therapy That Delivers a Healthy Version of the Defective Factor VIII Gene Into the Nucleus of Liver Cells Using an Altered, Non-infectious Virus (AAV) as a "Shuttle".	1/2	In this study, researchers want to gather more information about safety and effectiveness of BAY 2599023 (DTX201), a drug therapy that delivers the human FVIII gene into the human body by use of a viral vector to treat the disease. Researcher want to find the optimal dose of BAY 2599023 (DTX201) so that the body may produce enough clotting factor on its own.	Active, not recruiting
Baxalta/Shire NCT03370172	BAX 888	A Study of BAX 888 in Male Adults With Severe Hemophilia A	1/2	The main aim of this study is to check if there are side effects from BAX 888 and to determine the dose of BAX 888 for treating severe hemophilia A in male adults.	Active, not recruiting
Spark Therapeutics NCT03432520	SPK-8011 and SPK-8016	Long-Term Safety and Efficacy of Spark-Sponsored Gene Therapies in Males With Hemophilia A	N/A	This long-term follow-up study will continue to evaluate the long-term safety and efficacy of SPK-8011 and SPK-8016 in males with hemophilia A who have received a single IV administration of SPK-8011 or SPK-8016 in any Spark-sponsored SPK-8011 or SPK-8016 study.	Enrolling by invitation

Ongoing Hemophilia B Gene Therapy Trials

Sponsor/ Program	Therapy	Study title	Phase	Brief description	Status
Pfizer BENEGENE-2 NCT03861273	PF-06838435	A Study to Evaluate the Efficacy and Safety of Factor IX Gene Therapy With PF-06838435 in Adult Males With Moderately Severe to Severe Hemophilia B (BENEGENE-2)	3	This study will evaluate the efficacy and safety of PF-06838435 (a gene therapy drug) in adult male participants with moderately severe to severe hemophilia B (participants that have a Factor IX circulating activity of 2% or less). The gene therapy is designed to introduce genetic material into cells to compensate for missing or non-functioning FIX. Eligible study participants will have completed a minimum 6 months of routine FIX prophylaxis therapy during the lead in study (C0371004).	Recruiting PENDING APPROVAL (see details in pending approval section)
Pfizer NCT02484092	SPK-9001	A Gene Therapy Study for Hemophilia B	2	This study uses a novel recombinant AAV, which in nature causes no disease, to deliver the human FIX gene to the liver cells where FIX is normally made. This study will seek to determine the safety and kinetics of a single IV infusion of SPK-9001 (a novel AAV vector carrying a high specific activity FIX variant).	Active, not recruiting
Pfizer NCT03307980	PF 06838435	Long-term Safety and Efficacy Study and Dose-Escalation Sub-study of PF 06838435 in Individuals With Hemophilia B	2	This is a long-term safety and efficacy follow-up for participants with hemophilia B who were previously treated in the C0371005 (formerly SPK-9001-101) study, and a dose-escalation sub-study evaluating safety, tolerability, and kinetics of a higher dose with long-term safety and efficacy follow-up. Participants in the sub-study do not need to have participated in C0371005.	Active, not recruiting

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